Venous thromboembolism:

reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital

METHODS, EVIDENCE & GUIDANCE

Produced by the National Clinical Guideline Centre – Acute and Chronic Conditions (formerly the National Collaborating Centre for Acute Care)

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Foreword

The second report of session 2004-5 of The House of Commons Health Committee 'The Prevention of Venous Thromboembolism in Hospitalised Patients' opens with these worrying statistics: Each year 25,000 people in the UK die from venous thromboembolism. This figure includes both patients admitted for medical care of serious illnesses, as well as, those admitted for surgery. The report goes on to state that this is a larger number of deaths than are attributable to breast cancer, AIDS and road traffic accidents combined. It is 25 times the number of people who die as a result of MRSA infection [286].

The sudden killer is pulmonary embolism (PE). That is a thrombus (or blood clot) which forms in the lower limb or pelvic veins and then comes loose and is carried in the blood to lodge in the lungs. Acute massive pulmonary embolism often kills immediately. If the patient survives the immediate haemodynamic consequences, death may still ensue in the days or weeks that follow. Survivors of the initial event may eventually recover after a protracted hospital course including some time in intensive care.

Deep vein thrombosis (DVT) is in itself a cause of substantial morbidity and may lead to the development of post thrombotic syndrome (PTS) with chronic swelling and ulceration of the legs amongst its manifestations. Add this burden of morbidity to the estimated 25,000 deaths and it becomes a massive health problem. This is the perception of the situation as presented to the Health Committee, the CMO by expert advisors and patient representatives.

Many of these deaths are in patients admitted for medical care but some have gone into hospital for a planned surgical operation such as joint replacement, gynaecological surgery or gall bladder removal intended to improve their quality of life, or for a cancer operation with the hope of cure. Characteristically it is several weeks after surgery, when recovery is in sight that this tragedy strikes. Our guideline covers all patients admitted to hospital and includes patients having surgery in day-case facilities. The magnitude of risk of venous thromboembolism (VTE) is dependent upon factors inherent in the operation and factors related to the individual patient. It is the combination of these factors which defines certain patients as at increased risk of VTE. A key part of this guidance is systematic risk assessment of all patients either on admission in the case of emergencies or prior to admission for planned surgery. This evaluation must be repeated regularly during a hospital stay because the balance of risks of bleeding and of VTE change as the condition of the patient changes. The part of our work relating to risk assessment has been done in close collaboration with the Department of Health and the Chief Medical Officer's VTE Working Group as part of the national VTE prevention strategy.

Surgeons have been acutely aware of the dangers of VTE and have been central to research from the 1970s and 1980s[642]. Physical methods (such as graduated compression/anti-embolism stockings, foot impulse and intermittent pneumatic compression devices) and pharmacological treatments (such as heparin and warfarin) have been studied in a plethora of randomised trials. Both physical and pharmacological treatments have been shown to reduce the incidence of DVT under study conditions. The difficulty is knowing how to implement prophylaxis in practice. Will reduction of DVTs translate into reduced death rates from PE?

There is a question over whether the incidence of PE bears a reasonably consistent numerical relationship to the more frequent clinical event of DVT. We have not simply accepted this as an assumption but, where data sets allow both to be counted, we have tested the hypothesis. There appears to be a reasonably consistent association. However, this putative relationship between detectable lower limb DVT and fatal PE may break down in special cases such as knee replacement. The next question is whether reducing the incidence of DVT (the more numerous and more readily studied outcome) will result in a proportionate reduction in potentially fatal PE. Again we have tried to test this extrapolation against the data. We have conducted analyses where data are sufficient such as in studies of unfractionated heparin versus no prophylaxis: and found a similar reduction in fatal PEs[473]. A note of caution must remain however. We generally lack evidence for reduction in all-cause mortality which would require very large trials.

The pharmacological methods introduce another consideration. They carry with them a new risk - that of bleeding. It is major bleeding events which are counted in the RCTs. We have to give guidance concerning the method of VTE prophylaxis which steers the safest course between the competing risks posed by thrombosis on the one hand and bleeding on the other.

Major bleeding is clearly a threat to life but under some circumstances, a low volume bleed can be a very major complication. A few millilitres of bleeding into the brain, or compressing the spinal cord within the vertebral canal can cause death or permanent neurological damage. Small volumes of bleeding into a joint can cause the operation to fail and the patient will be worse off than before.

It is a clinical problem which requires a meticulously researched and analysed evidence base. The potential health gains for the optimal strategy are great. An individual team will have patients who suffer PE and patients whose recovery is complicated by a treatment related bleed. The clinical difficulty is that both fatal pulmonary embolism and major bleeding have low event rates affecting fewer than one in a hundred patients. We cannot emphasise too strongly that it is evidence from the best available randomised controlled trials that we must use to quantify these competing risks. Clinical impressions cannot adequately capture the trade off between risk and benefit, particularly where both relate to infrequent clinical events or where the manefestations are delayed. It has been well shown that if clinicians base decisions for future patients on a recent adverse event in their own experience, those decisions are not likely to be in the best interest of future patients [108].

The impossibility of basing a policy on clinical experience makes it essential to rely on evidence based guidance. It is appropriate that this guidance is made available for individual clinicians and their teams to use in framing locally implemented prophylactic policies. Hence VTE prophylaxis is an ideal subject for an evidence based guideline. The complex task has been undertaken in collaboration between the scientific staff at the NCC-AC, and the medical professionals of the Guideline Development Group (GDG).

There are important changes expected in anticoagulation if the oral agents recently licensed or currently undergoing evaluation prove to be safe and consistently effective. We have been cautious in our recommendations, but if during the lifetime of this guideline they fulfill the hope that many doctors have for them, they will simplify practice that at present relies on daily injections of an anticoagulant, although there will need to be consideration of their drug interactions.

A summary of our recommendations:

Mechanical methods have been proven to be effective in surgical patients and do not to add the risk of bleeding. We have recommended these methods for patients at risk of bleeding and in combination with pharmacological methods for many groups of patients. However during our work on this guidance a large study in stroke patients did not show any beneficial effect of stockings in stroke patients but did show an increase in skin complications associated with their use. This influenced our recommendations [158].

In patients at higher risk of VTE, the use of pharmacological methods is cost effective. In surgical patients these are often to be used in combination with mechanical prophylaxis such as stockings as this was the case in many of the RCTs on which we rely.

There will be patients who are already on antiplatelet medication; there will also be some for whom aspirin may be recommended in the perioperative period for the reduction of risk of heart attack and stroke. This may present a therapeutic conflict: clinicians will be concerned about the risk of bleeding. It should be noted that while aspirin does reduce the risk of VTE to some extent, we have not recommended it as a form of VTE prophylaxis. Aspirin has an important role in cardiovascular perioperative risk reduction, but this is outside our scope. It might be tempting to see antiplatelet therapy as a convenient prophylactic "two for one". To use this as a clinical justification for omitting recommended VTE pharmacological prophylaxis risks is not recommended because the protective effective of aspirin against VTE is insufficient

Although there are many trials, we still found ourselves with uncertainties. For example, the true present day rate of DVT and PE is very hard to ascertain. Many more patients have less invasive surgery. Surgical patients get out of bed sooner. High emphasis is placed on early mobilisation and early discharge from hospital. Prophylaxis (both mechanical and pharmacological) is widely used, but practice varies and implementation is probably patchy. There is a strong sense that DVT and PE are less of a problem than they used to be in surgical patients but maybe it is hidden from the view of clinicians by early discharge rather than being truly reduced because 80% of DVT are subclinical and the average DVT occurs on the 7th postoperative day, long after the patient has left hospital.

High quality monitoring of adverse events will be needed to ensure that these recommendations are as safe as they can be and we emphasise strongly the need to implement the research recommendations. These research recommendations specifically target the area where we found the biggest potential consequence from uncertainty. We also welcome the recommendation of the House of Commons Health Committee: "Systems must be put in place to ensure that the NICE VTE guidelines are implemented" [286]. Once implemented, we need to monitor adverse events, both bleeding and venous thromboembolism to ensure that guidance is steering the safest course between those competing risks to all patients admitted to hospital.

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Guideline review panel

The Guideline Review Panel is an independent panel that overseas the development of the guideline and takes responsibility for monitoring its quality. The panel includes members from the following perspectives.

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Bayer HealthCare
Boehringer Ingelheim Ltd
Bristol-Myers Squibb Pharmaceuticals Limited
British Association of Day Surgery
British Association of Knee Surgery
British Association of Spine Surgeons (BASS)
British Association Of Stroke Physicians (BASP)
British Cardiovascular Society
British Elbow and Shoulder Society (BESS)
British Hip Society
British Orthopaedic Association
British Society for Haematology
British Society for Surgery of the Hand
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Christie Hospital NHS Foundation Trust
Colchester Hospital University NHS Foundation Trust
Cornwall Isles of Scilly Community Health Services
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Royal College of Midwives
Royal College of Nursing
Royal College of Obstetricians & Gynaecologists
Royal College of Pathologists
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St. Helens & Knowsley Teaching Hospitals NHS Trust
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Vascular Society of Great Britain and Ireland
Whittington Hospital
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Abbreviations

ACS	Acute Coronary Syndrome
AES	Anti-embolism stockings
BMI	Body mass index
BNF	British National Formulary
CCA	Cost-consequences analysis
CCT	Controlled clinical trial
CEA	Cost-effectiveness analysis
CI	Confidence interval
CPM	Continuous passive motion
CRT	Catheter related thrombosis
CTEPH	Chronic thromboembolic pulmonary hypertension
CUA	Cost-utility analysis
CVC	Central venous catheters
DH	Department of Health
DVT	Deep-vein thrombosis
FID	Foot impulse devices
FP	Forest Plot
GCS	Graduated compression stocking
GDG	Guideline Development Group
GP	General Practitioner
GPRD	General Practice Research Database
GRADE	Guidelines Recommendations Assessment Development Evaluation
GRP	Guideline Review Panel
HD	High dose
HES	Hospital Episode Statistics
HIT	Heparin-induced thrombocytopenia
HRQL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICU	Intensive Care Unit
IPCD	Intermittent pneumatic compression devices
INB	Incremental net benefit
INR	International normalized ratio
IPCD	Intermittent pneumatic compression devices
IV	Intravenous
LD	Low dose
LMWH	Low molecular weight heparin

LOS	Length of stay
LY	Life-year
MB	Major Bleeding
MHRA	Medicines and Healthcare Products Regulatory Agency
NCC-AC	National Collaborating Centre for Acute Care
NCGC	National Clinical Guideline Centre for Acute and Chronic Conditions (Formerly known as the National Collaborating Centre for Acute Care)
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NMA	Network meta-analysis
NNT	Number needed to treat
OAC	Oral anticoagulants
OR	Odds ratio
PASA	NHS Purchasing and Supply Agency
PE	Pulmonary embolism
PHT	Chronic thromboembolic pulmonary hypertension
PICO	Framework incorporating patients, interventions, comparisons, outcomes
PPIP	Patient and Public Involvement Programme
PSA	Probabilistic sensitivity analysis
PTS	Post-thrombotic syndrome
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RR	Relative risk
SC	Subcutaneous
SR	Systematic review
UKOSS	United Kingdom Obstetric Surveillance System
UFH	Unfractionated heparin
VKA	Vitamin K antagonist
VS	Versus
VTE	Venous thromboembolism

Glossary of terms

Absolute effect	The difference in the risk of an event between two groups (one subtracted from the other) in a comparative study.
Absolute risk reduction (Risk difference)	See absolute effect
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Acute medical admission	A medical admission concerned with the immediate and early specialist management of adult patients suffering from a wide range of medical conditions who present to, or from within, hospitals, requiring urgent or emergency care
Adherence	The extent to which the patient's behaviour matches the prescriber's recommendations. Adherence emphasises the need for agreement and that the patient is free to decide whether or not to adhere to the doctor's recommendation. [472]
Adjustment	A statistical procedure in which the effects of differences in composition of the populations being compared (or treatment given at the same time) have been minimised by statistical methods.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in a RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Anticoagulants	Any agent used to prevent the formation of blood clots. These include oral agents, such as warfarin, and others which are injected into a vein or under the skin, such as heparin.
Anti-embolism stockings	Hosiery which, when worn on the leg, exerts graduated compression on the leg surface and is intended to reduce the incidence of deep vein thrombosis. These should not be confused with "graduated compression stockings" which have a different pressure profile and are not used for the prevention of venous thromboembolism.
Applicability	The degree to which the results of an observation, study or review

	are likely to hold true in a particular clinical practice setting.
Appraisal of Guidelines, Research and Evaluation (AGREE)	An international collaboration of researchers and policy makers whose aim is to improve the quality and effectiveness of clinical practice guidelines (http://www.agreecollaboration.org). The AGREE instrument, developed by the group, is designed to assess the quality of clinical guidelines.
Arm (of a clinical study)	Sub-section of individuals within a study who receive one particular intervention, for example placebo arm.
Association	Statistical relationship between two or more events, characteristics or other variables. The relationship may or may not be causal.
Audit	See 'Clinical audit'.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results that is caused by the way the study is designed or conducted.
Blinding (masking)	Keeping the study participants, caregivers, researchers and outcome assessors unaware about the interventions to which the participants have been allocated in a study.
Capital costs	Costs of purchasing major capital assets (usually land, buildings or equipment). Capital costs represent investments at one point in time.
Carer (caregiver)	Someone other than a health professional who is involved in caring for a person with a medical condition.
Case-control study	Comparative observational study in which the investigator selects individuals who have experienced an event (For example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Chronic thrombembolic pulmonary hypertension	Abnormally elevated blood pressure within the pulmonary circuit (pulmonary artery).
Clinical audit	A quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	The extent to which an intervention produces an overall health benefit in routine clinical practice.

Clinical impact	The effect that a guideline recommendation is likely to have on the treatment or treatment outcomes, of the target population.
Clinical question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Clinician	A healthcare professional providing direct patient care, for example doctor, nurse or physiotherapist.
Cluster	A closely grouped series of events or cases of a disease or other related health phenomena with well-defined distribution patterns, in relation to time or place or both. Alternatively, a grouped unit for randomisation.
Cochrane Library	A regularly updated electronic collection of evidence-based medicine databases, including the Cochrane Database of Systematic Reviews.
Cochrane Review	A systematic review of the evidence from randomised controlled trials relating to a particular health problem or healthcare intervention, produced by the Cochrane Collaboration. Available electronically as part of the Cochrane Library.
Cohort study	A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.
Comorbidity	Co-existence of more than one disease or an additional disease (other than that being studied or treated) in an individual.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Compliance	The extent to which a person adheres to the health advice agreed with healthcare professionals. May also be referred to as 'adherence' or 'concordance'.
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which prescriber and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine-taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence[472]
Conference proceedings	Compilation of papers presented at a conference.
Confidence interval (CI)	A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value.

Confounding	In a study, confounding occurs when the effect of an intervention on an outcome is distorted as a result of an association between the population or intervention or outcome and another factor (the 'confounding variable') that can influence the outcome independently of the intervention under study.
Consensus methods	Techniques that aim to reach an agreement on a particular issue. Formal consensus methods include Delphi and nominal group techniques, and consensus development conferences. In the development of clinical guidelines, consensus methods may be used where there is a lack of strong research evidence on a particular topic. Expert consensus methods will aim to reach agreement between experts in a particular field.
Control group	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) – in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Controlled clinical trial (CCT)	A study testing a specific drug or other treatment involving two (or more) groups of patients with the same disease. One (the experimental group) receives the treatment that is being tested, and the other (the comparison or control group) receives an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. A CCT where patients are randomly allocated to treatment and comparison groups is called a randomised controlled trial.
Cost benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost-consequences analysis (CCA)	A type of economic evaluation where various health outcomes are reported in addition to cost for each intervention, but there is no overall measure of health gain.
Cost-effectiveness analysis (CEA)	An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (For example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost-utility analysis (CUA)	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).
Continuous passive motion	Where a joint is moved continuously, either by another person bending it or by a machine.
Credible interval	The Bayesian equivalent of a confidence interval.

Decision analysis	A systematic way of reaching decisions, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Decision analytic techniques	A way of reaching decisions, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees that direct the clinician through a succession of possible scenarios, actions and outcomes.
Decision problem	A clear specification of the interventions, patient populations and outcome measures and perspective adopted in an evaluation, with an explicit justification, relating these to the decision which the analysis is to inform.
Deep-vein thrombosis (DVT)	Venous thrombosis that occurs in the "deep veins" in the legs, thighs, or pelvis.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Distal	Refers to a part of the body that is farther away from the centre of the body than another part.
Dominance	An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective.
Dosage	The prescribed amount of a drug to be taken, including the size and timing of the doses.
Double blind/masked study	A study in which neither the subject (patient) nor the observer (investigator/clinician) is aware of which treatment nor intervention the subject is receiving. The purpose of blinding is to protect against bias.
DVT	See 'Deep-vein thrombosis'.
Drop-out	A participant who withdraws from a clinical trial before the end.
Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association.
Effectiveness	See 'Clinical effectiveness'.
Efficacy	See 'Clinical efficacy'.
Elective	Name for clinical procedures that are regarded as advantageous to the patient but not urgent.
Electrical stimulation	Designed to increase venous blood flow velocity out of the leg to

	reduce the incidence of post-surgical venous thrombosis.
Emergency admission	When admission is unpredictable and at short notice because of clinical need.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (For example, infection, diet) and interventions.
Equity	Fair distribution of resources or benefits.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals and/or patients).
Evidence table	A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Expert consensus	See 'Consensus methods'.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore more efficient and should be preferred, other things remaining equal.
Extrapolation	In data analysis, predicting the value of a parameter outside the range of observed values.
Follow up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Foot impulse devices(FID)	The foot impulse device is designed to stimulate the leg veins (venous pump) artificially by compressing the venous plexus and mimicking normal walking and reducing stasis in immobilised patients.
Generalisability	The extent to which the results of a study based on measurement in a particular patient population and/or a specific context hold true for another population and/or in a different context. In this instance, this is the degree to which the guideline recommendation is applicable across both geographical and contextual settings. For instance, guidelines that suggest substituting one form of labour for another should acknowledge that these costs might vary across the country.
Gold standard	See 'Reference standard'.
Goodness-of-fit	How well a statistical model or distribution compares with the

	observed data.
Graduated compression stockings (GCS)	Stockings manufactured to provide compression around legs at gradually increasing pressures. There are two different standards for graduated compression stockings, the British Standard and the European Standard. These are different to anti-embolism stockings which are used for the prevention of venous thromboembolism.
Grey literature	Reports that are unpublished or have limited distribution, and are not included in the common bibliographic retrieval systems.
Harms	Adverse effects of an intervention.
Health economics	The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.
Health-related quality of life (HRQL)	A combination of an individual's physical, mental and social well-being; not merely the absence of disease.
Heparin-induced thrombocytopenia (HIT)	Low blood platelet count resulting from the administration of heparin (or heparin-like agents). Despite having a low platelet count, patients with this condition are at high risk of their blood clotting.
Heterogeneity	Or lack of homogeneity. The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.
HIT	See 'Heparin-induced thrombocytopenia'.
Homogeneity	This means that the results of studies included in a systematic review or meta-analysis are similar and there is no evidence of heterogeneity. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance.
Hypothesis	A supposition made as a starting point for further investigation.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention
Incremental cost effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest.
Incremental net	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be

benefit (INB)	calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.
Index	In epidemiology and related sciences, this word usually means a rating scale, for example, a set of numbers derived from a series of observations of specified variables. Examples include the various health status indices, and scoring systems for severity or stage of cancer.
Indication (specific)	The defined use of a technology as licensed by the Medicines and Healthcare products Regulatory Agency (MHRA).
Intention-to-treat analysis (ITT analysis)	An analysis of the results of a clinical study in which the data are analysed for all study participants as if they had remained in the group to which they were randomised, regardless of whether or not they remained in the study until the end, crossed over to another treatment or received an alternative intervention.
Intermediate outcomes	Outcomes that are related to the outcome of interest but may be more easily assessed within the context of a clinical study: for example, blood pressure reduction is related to the risk of a stroke.
Intermittent pneumatic compression devices (IPCD)	A method of prophylaxis that comprises the use of inflatable garments wrapped around the legs, inflated by a pneumatic pump. The pump provides intermittent cycles of compressed air which alternately inflates and deflates the chamber garments, enhancing venous return.
Internal validity	The degree to which the results of a study are likely to approximate the 'truth' for the participants recruited in a study (that is, are the results free of bias?). It refers to the integrity of the design and is a prerequisite for applicability (external validity) of a study's findings. See 'External validity'.
Intervention	Healthcare action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy.
Intraoperative	The period of time during a surgical procedure.
Length of stay (LOS)	The total number of days a participant stays in hospital.
Licence	See 'Product licence'.
Life year (LY)	A measure of health outcome which shows the number of years of remaining life expectancy.
Life-years gained	Average years of life gained per person as a result of the intervention.
Mechanical	Physical (as opposed to chemical) agent used, in this context, to reduce likelihood of thrombosis. Mechanical methods of DVT prophylaxis work to combat venous stasis and include: anti-embolism stockings/ Graduated compression stockings (GCS), intermittent pneumatic compression devices (IPCD), foot impulse devices, also known as foot pumps (FID)

Medical devices	All products, except medicines, used in healthcare for the diagnosis, prevention, monitoring or treatment of illness or handicap.
Medicines and Healthcare Products Regulatory Agency (MHRA)	The Executive Agency of the Department of Health protecting and promoting public health and patient safety by ensuring that medicines, healthcare products and medical equipment meet appropriate standards of safety, quality, performance and effectiveness, and are used safely.
Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.
Multivariate model	A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable.
Narrative summary	Summary of findings given as a written description.
Network Meta-analysis (NMA)	Statistical technique for combining all direct and indirect evidence into one analysis (see Section 3.10 for details on methods)
Number needed to treat (NNT)	The number of patients that who on average must be treated to prevent a single occurrence of the outcome of interest.
Observational study	Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example, cohort studies and case–control studies.
Odds ratio (OR)	A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The 'odds' is the ratio of events to non-events.
Off-label	A drug or device used treat a condition or disease for which it is not specifically licensed.
Older people	People over the age of 65 years.
Operating costs	Ongoing costs of carrying out an intervention, excluding capital costs.
Opportunity cost	The opportunity cost of investing in a healthcare intervention is the loss of other healthcare programmes that are displaced by its introduction. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	Measure of the possible results that may stem from exposure to a preventive or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints. See 'Intermediate outcome'.
P values	The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference

	between the means of the observations. If the probability is less than 1 in 20, the P value is less than 0.05; a result with a P value of less than 0.05 is conventionally considered to be 'statistically significant'.
PE	See 'Pulmonary embolism'.
Peer review	A process where research is scrutinised by experts that have not been involved in the design or execution of the studies.
Perioperative	The period from admission through surgery until discharge, encompassing pre-operative and post-operative periods.
Placebo	An inactive and physically identical medication or procedure used as a comparator in controlled clinical trials.
Placebo effect	A beneficial (or adverse) effect produced by a placebo and not due to any property of the placebo itself.
Post-thrombotic (Post-phlebitic) Syndrome	Chronic pain, swelling, and occasional ulceration of the skin of the leg that occur as a consequence of previous venous thrombosis.
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.
Preoperative	Pertaining to the period before surgery commences.
Primary care	Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by GPs, nurses and other healthcare professionals, dentists, pharmacists and opticians.
Primary research	Study generating original data rather than analysing data from existing studies (which is called secondary research).
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prophylaxis	A measure taken for the prevention of a disease.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective.
Proximal	Refers to a part of the body that is closer to the centre of the body than another part.
Pulmonary embolism (PE)	A blood clot that breaks off from the deep veins and travels round the circulation to block the pulmonary arteries (arteries in the lung). Most deaths arising from DVT are caused by PE.
Pulmonary hypertension	See 'Chronic thromboembolic pulmonary hypertension'.
Qualitative research	Research concerned with subjective outcomes relating to social,

	emotional and experiential phenomena in health and social care.
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life-year (QALY)	An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis. The QALYs gained are the mean QALYs associated with one treatment minus the mean QALYs associated with an alternative treatment.
Quantitative research	Research that generates numerical data or data that can be converted into numbers, for example clinical trials or the national Census which counts people and households.
Quick Reference Guide	An abridged version of NICE guidance, which presents the key priorities for implementation and summarises the recommendations for the core clinical audience.
Randomisation	Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias.
Randomised controlled trial (RCT)	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.
RCT	See 'Randomised controlled trial'.
Relative risk (RR)	The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B).
Remit	The brief given by the Department of Health and Welsh Assembly Government at the beginning of the guideline development process. This defines core areas of care that the guideline needs to address.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A retrospective study deals with the present/ past and does not involve studying future events. This contrasts with studies that are prospective.
Review of the literature	An article that summarises the evidence contained in a number of different individual studies and draws conclusions about their findings. It may or may not be systematically researched and developed.
Secondary benefits	Benefits resulting from a treatment in addition to the primary, intended outcome.
Selection bias (also allocation bias)	A systematic bias in selecting participants for study groups, so that the groups have differences in prognosis and/or therapeutic sensitivities at baseline. Randomisation (with concealed allocation) of

	patients protects against this bias.
Selection criteria	Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.
Sensitivity (of a search)	The proportion of relevant studies identified by a search strategy expressed as a percentage of all relevant studies on a given topic. It describes the comprehensiveness of a search method (that is, its ability to identify all relevant studies on a given topic). Highly sensitive strategies tend to have low levels of specificity and vice versa.
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): two or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (For example, Monte Carlo simulation).
Significantly Reduced Mobility	Defined by the GDG as: 'patients who are bed bound, unable to walk unaided or likely to spend a substantial proportion of their day in bed or in a chair'
Stakeholder	Those with an interest in the use of a technology under appraisal or a guideline under development. Stakeholders include manufacturers, sponsors, healthcare professionals, and patient and carer groups.
Statistical power	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Synthesis of evidence	A generic term to describe methods used for summarising (comparing and contrasting) evidence into a clinically meaningful conclusion in order to answer a defined clinical question. This can include systematic review (with or without meta-analysis), qualitative and narrative summaries.

Systematic review	Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.
Thrombophilia	The genetic or acquired prothrombotic states that increase the tendency to venous thromboembolism. It is a condition which leads to a tendency for a person's blood to clot inappropriately.
Thromboprophylaxis	A measure taken to reduce the risk of thrombosis.
Time horizon	The time span used in the NICE appraisal which reflects the period over which the main differences between interventions in health effects and use of healthcare resources are expected to be experienced, and taking into account the limitations of supportive evidence.
Treatment allocation	Assigning a participant to a particular arm of the trial.
Treatment options	The choices of intervention available.
Utility	A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.
Venous thromboembolism (VTE)	The blocking of a blood vessel by a blood clot dislodged from its site of origin. It includes both DVT and PE.
Venous thrombosis (VT)	A condition in which a blood clot (thrombus) forms in a vein.

1 Introduction

1.1 The need for this guideline

Venous thromboembolism (VTE) is a term used to include the formation of a blood clot (a thrombus) in a vein which may dislodge from its site of origin origin to travel in the blood, a phenomenon called embolism. A thrombus most commonly occurs in the deep veins of the legs; this is called deep vein thrombosis. A dislodged thrombus that travels to the lungs is known as a pulmonary embolism.

VTE includes/encompasses a range of clinical presentations. Venous thrombosis may be completely asymptomatic or it may cause pain and swelling in the leg. Part or all of the thrombus/clot can come free and travel to the lung as a potentially fatal pulmonary embolism. Symptomatic venous thrombosis carries a considerable burden of morbidity, sometimes long-term due to chronic venous insufficiency. This in turn can cause venous ulceration and development of a post-thrombotic limb (characterised by chronic pain, swelling and skin changes).

VTE is an important cause of death in hospitalised patients, and treatment of non-fatal symptomatic VTE and related long-term morbidities is associated with a considerable cost to the health service.

In 2004–05, there were around 64,000 finished consultant episodes (that is, periods of care under a consultant within an NHS trust) with a diagnosis of VTE. In 2005, VTE was registered as the underlying cause of death in more than 6500 patients, although this figure is likely to be an underestimate of the true incidence.

The incidence of VTE in different groups of hospital patients varies greatly in the literature. The risk of PE in the absence of prophylaxis has been estimated at 5% following surgery in the highest risk groups, and around 1% in acutely ill medical patients (Chapter 5)

The risk of developing VTE depends on the condition and/or procedure for which the patient is admitted and on any predisposing risk factors (such as age, obesity and concomitant conditions). Both of these types of risk will be assessed within the guideline.

This guideline examines the risk of venous thromboembolism and assesses the evidence for the effectiveness of primary preventative measures. It provides recommendations on the most clinically and cost effective measures to reduce the risk of venous thromboembolism, whilst considering the potential risks of the various VTE prophylaxis options and patient preferences.

There is no current worldwide consensus on which patients should receive thromboprophylaxis. The inconsistent use of prophylactic measures for VTE has been widely reported. A UK survey[545] suggested that 71% of patients assessed to be at medium or high risk of developing DVT did not receive any form of pharmacological or mechanical thromboprophylaxis.

This guideline incorporates the published NICE guideline 'Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery' (NICE clinical guideline 46). This single piece of guidance covers all patients admitted to hospital.

We start by examining the risk factors for developing VTE (both hospital related and patient related), followed by a review of the evidence of clinical and cost effectiveness for each of the prophylactic methods that we are considering. We continue by examining the data relating to specific patient groups, taking into account the overall effectiveness of the various methods and make recommendations for these specific groups.

1.2 Assumptions made in this guideline

This guideline recommends primary VTE prophylaxis on the basis of their effectiveness in reducing the risk of DVT (both symptomatic and asymptomatic), acknowledging that this is a 'surrogate' endpoint which is frequently employed in randomised controlled trials (RCTs).

There are several difficulties with considering only pulmonary embolism (PE) as an outcome:

1. PE is a rare event, and therefore large trials (or numbers of trials) are needed to demonstrate an effect.

2. Few trials that report PE have made the diagnosis using objective methods (clinical diagnosis being unreliable).

3. Many trials that report PE as an outcome measure have also assessed all included patients for DVT. Trial protocols usually dictate that patients in whom a DVT is detected are removed from the trial and anticoagulation is given, and hence a PE may be prevented that would have occurred in the usual clinical setting.

DVT is a usual precursor of both fatal PE and post-thrombotic syndrome (PTS), although the aetiology and development of the diseases have not yet been fully elucidated. Although asymptomatic DVT is, by definition, covert these thrombi can become pulmonary embolisms and are a clinically useful endpoint for a trial. We therefore consider it appropriate to evaluate both asymptomatic and symptomatic DVT when looking at the effectiveness of prophylactic strategies. Clinical detection of DVT is unreliable and also fails to detect asymptomatic events, hence we have only included trials that assess all patients for DVT using objective methods.

DVT, therefore, is accepted as a suitable endpoint by this guideline which will evaluate trials where patients are assessed for DVT.

1.3 What are clinical practice guidelines?

Our clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care though primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of health care. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific clinical questions.

Clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from the Department of Health
- Stakeholders register an interest in the guideline and are consulted throughout the development process
- The scope is prepared by the National Clinical Guideline Centre- Acute and Chronic Conditions (NCGC), formerly the National Collaborating Centre for Acute Care (NCC-AC)
- The NCGC establish a guideline development group
- A draft guideline is produced after the group assesses the available evidence and makes recommendations
- There is a consultation on the draft guideline
- The final guideline is produced

The NCGC and NICE produce a number of versions of this guideline:

- the **full guideline** contains all the recommendations, plus details of the methods used and the underpinning evidence

- the **NICE guideline** presents the recommendations from the full version in a format suited to implementation by health professionals and NHS bodies

- the **quick reference guide** presents recommendations in a suitable format for health professionals

- information for the public (**'understanding NICE guidance'**) is written using suitable language for people without specialist medical knowledge.

This version is the full version. This and the other versions can be downloaded from the NICE website www.NICE.org.uk.

1.4 The National Clinical Guideline Centre - Acute and Chronic Conditions (formerly the National Collaborating Centre for Acute Care)

This guideline was commissioned by NICE and developed by the National Collaborating Centre for Acute Care (now called the National Clinical Guidelines Centre - Acute and Chronic Conditions). The centre is funded by NICE and comprises a partnership between a variety of academic, professional and patient-based organisations. As a multidisciplinary centre we draw upon the expertise of the healthcare professions and academics and ensure the involvement of patients in our work. Further information on the centre and our partner organisations can be found at our website (http://www.rcplondon.ac.uk/clinical-standards/ncgc/).

1.5 Remit of the guideline

The following remit was received from the Department of Health and the Welsh Assembly Government in March 2007 as part of NICE's 14th wave programme of work.

1.6 What the guideline covers

This guideline covers adults (18 years and older) admitted to hospital as inpatients or formally admitted to a hospital bed for day-case procedures, including:

- surgical inpatients

- inpatients with acute medical illness (for example, myocardial infarction, stroke, spinal injury, severe infection or exacerbation of chronic obstructive pulmonary disease)

- trauma inpatients

- patients admitted to intensive care units

- cancer inpatients

- people undergoing long-term rehabilitation in hospital

- patients admitted to a hospital bed for day-case medical or surgical procedures.

The scope for this guideline can be found in Appendix A.

1.7 What the guideline does not cover

This guideline does not cover:

- People under the age of 18.
- People attending hospital as outpatients.
- People presenting to emergency departments without admission.
- Elderly or immobile people cared for at home, or in external residential accommodation, unless admitted to hospital.
- Patients admitted to hospital with a diagnosis of, or suspected diagnosis of, DVT or PE.

1.8 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline (see section on Guideline Development Group Membership and acknowledgements).

The National Institute for Health and Clinical Excellence funds the National Clinical Guideline Centre- Acute and Chronic Conditions, NCGC (formerly the National Collaborating Centre for Acute Care, NCC-AC) and thus supported the development of this guideline. The Guideline Development Group was convened by the NCC-AC and chaired by Professor Tom Treasure in accordance with guidance from the National Institute for Health and Clinical Excellence (NICE).

The group met every 6-8 weeks during the development of the guideline. At the start of the guideline development process all Guideline Development Group members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent Guideline Development Group meetings, members declared arising conflicts of interest, which were also reported (Appendix B). Members are either required to withdraw completely or for part of the discussion if their declared interest makes it appropriate, however this was not deemed necessary for any group members on this guideline.

A separate orthopaedic subgroup was set up in March 2008 to provide specific expert guidance on VTE prophylaxis for patients having orthopaedic surgery. This group, was chaired by Professor Tom Treasure and comprised seven consultant orthopaedic surgeons representing a range of orthopaedic specialties along with a patient representatives and a nursing representative. The group met 5 times and all members declared conflicts of interests at all meetings (recorded in Appendix B). This orthopaedic subgroup group reviewed the evidence for orthopaedic surgery and provided expert opinion and draft recommendations to the main GDG. The full GDG had the responsibility for final approval of all recommendations in the guideline.

Staff from the NCGC provided methodological support and guidance for the development process. They undertook systematic searches, retrieval and appraisal of the

evidence and drafted the guideline. The glossary to the guideline contains definitions of terms used by staff and the Guideline Development Group.

2 Summary of recommendations

Below are the recommendations that the Guideline Development Group (GDG) selected as the key priorities for implementation followed by the full list of recommendations.

2.1 Key priorities for implementation

The GDG identified ten key priorities for implementation. The decision was made after voting by the GDG. They selected recommendations that would:

- Have a high impact on outcomes that are important to patients **(A)**
- Have a high impact on reducing variation in care and outcomes **(B)**
- Lead to a more efficient use of NHS resources **(C)**
- Promote patient choice **(D)**
- Promote equalities. **(E)**

In doing this the GDG also considered which recommendations were particularly likely to benefit from implementation support. They considered whether a recommendation:

- Requires changes in service delivery (**W**)
- Requires retraining of professionals or the development of new skills and competencies (**X**)
- Affects and needs to be implemented across various agencies or settings (complex interactions) (**Y**)
- May be viewed as potentially contentious, or difficult to implement for other reasons (**Z**)

For each key recommendation listed below, the selection criteria and implementation support points are indicated by the use of the letters shown in brackets above.

- Assess all patients on admission to identify those who are at increased risk of venous thromboembolism (VTE).

(Selection Criteria: A, B, C; Implementation support: W, X Y)

- Regard medical patients as being at increased risk of VTE if they:
    - have had or are expected to have significantly reduced mobility for 3 days or more **or**
    - are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors shown in **Box 1.**

(Selection Criteria: A, B, C; Implementation support: W, X Y)

- Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:

    - surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
    - acute surgical admission with inflammatory or intra-abdominal condition
    - expected significant reduction in mobility
    - have one or more risk factors shown in **Box 1.**

(Selection Criteria: A, B, C; Implementation support: W, X Y

- Assess all patients for risk of bleeding before offering pharmacological VTE prophylaxis*. Do not offer pharmacological VTE prophylaxis to patients with any of the risk factors for bleeding shown in **Box 2,** unless the risk of VTE outweighs the risk of bleeding.

**Consult the summary of product characteristics for the pharmacological prophylaxis being used or planned for further details.*

(Selection Criteria: A, B, C, E; Implementation support: X, Y)

- Reassess patients' risk of bleeding and VTE within 24 hours of admission and whenever the clinical situation changes, to:
    - ensure that the methods of VTE prophylaxis used are suitable
    - ensure that VTE prophylaxis is being used correctly
    - identify adverse events resulting from VTE prophylaxis.

(Selection Criteria: A, B, C, E; Implentation support: W, X, Y)

- Encourage patients to mobilise as soon as possible.

(Selection Criteria: A, B, C; Implentation support: Y)

- Offer pharmacological VTE prophylaxis to general medical patients assessed to be at increased risk of VTE (see section 2.2.1). Choose any one of:
  - fondaparinux sodium
  - LMWH*
  - UFH (for patients with renal failure).

  Start pharmacological prophylaxis as soon as possible after risk assessment has been completed. Continue until the patient is no longer at increased risk of VTE.

**At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off-label use should be obtained and documented.*

(Selection Criteria: A, B, C, E; Implentation support: X)

- Before starting VTE prophylaxis, offer patients and/or their families or carers verbal and written information on:
  - the risks and possible consequences of VTE
  - the importance of VTE prophylaxis and its possible side effects
  - the correct use of VTE prophylaxis (for example, anti-embolism stockings, foot impulse or intermittent pneumatic compression devices)
  - how patients can reduce their risk of VTE (such as keeping well hydrated and, if possible exercising and becoming more mobile)

(Selection Criteria: A, B, C, D, E; Implementation Support: W, X, Y, Z)

- As part of the discharge plan, offer patients and/or their families or carers verbal and written information on:
  - the signs and symptoms of deep vein thrombosis and pulmonary embolism
  - the correct and recommended duration of use of VTE prophylaxis at home (if discharged with prophylaxis)
  - the importance of using VTE prophylaxis correctly and continuing treatment for the recommended duration (if discharged with prophylaxis)
  - the signs and symptoms of adverse events related to VTE prophylaxis (if discharged with prophylaxis)
  - the importance of seeking help and who to contact if they have any problems using the prophylaxis (if discharged with prophylaxis)
  - the importance of seeking medical help if deep vein thrombosis, pulmonary embolism or another adverse events is suspected.

(Selection Criteria: A,B, C, D, E; Implementation Support: W, X, Y, Z)

2.2 The complete list of clinical practice recommendations

2.2.1 Assessing the risks of VTE and bleeding

- Assess all patients on admission to identify those who are at increased risk of venous thromboembolism (VTE).
- Regard **medical patients** as being at increased risk of VTE if they:
  - have had or are expected to have significantly reduced mobility for 3 days or more **or**
  - are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors shown in **Box 1.**
- Regard **surgical patients and patients with trauma** as being at increased risk of VTE if they meet one of the following criteria:
  - surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
  - acute surgical admission with inflammatory or intra-abdominal condition
  - expected significant reduction in mobility
  - one or more of the risk factors shown in **Box 1.**

Box 1 Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (body mass index [BMI] over 30 kg/m^2)
- One or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
- Personal history or first-degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).

- Assess all patients for risk of bleeding before offering pharmacological VTE prophylaxis*. Do not offer pharmacological VTE prophylaxis to patients with any of the risk factors for bleeding shown in **Box 2**, unless the risk of VTE outweighs the risk of bleeding.

**At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH.*

Box 2 Risk factors for bleeding

- Active bleeding
- Acquired bleeding disorders (such as acute liver failure)
- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with international normalized ratio [INR] higher than 2)
- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours
- Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours
- Acute stroke
- Thrombocytopenia (platelets less than 75 x 10^9/l)
- Uncontrolled systolic hypertension (230/120 mmHg or higher)
- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease)

- Reassess patients' risk of bleeding and VTE within 24 hours of admission, and whenever the clinical situation changes, to:
  - ensure that the methods of VTE prophylaxis being used are suitable
  - ensure that VTE prophylaxis is being used correctly
  - identify adverse events resulting from VTE prophylaxis.

2.2.2 Reducing the risk of VTE – general recommendations

- Do not allow patients to become dehydrated unless clinically indicated.
- Encourage patients to mobilise as soon as possible.
- Do not regard aspirin or other antiplatelet agents as adequate prophylaxis for VTE.
- Consider offering temporary inferior vena caval filters to patients who are at very high risk of VTE (such as patients with a previous VTE event or an active

malignancy) and for whom mechanical and pharmacological VTE prophylaxis are contraindicated.

2.2.3 Using VTE prophylaxis

2.2.3.1 Mechanical VTE prophylaxis

- Base the choice of mechanical VTE prophylaxis on individual patient factors including clinical condition, surgical procedure and patient preference. Choose any one of:
  - anti-embolism stockings (thigh or knee length)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length).

Anti-embolism stockings

- Do not offer anti-embolism stockings to patients who have:
  - suspected or proven peripheral arterial disease
  - peripheral arterial bypass grafting
  - peripheral neuropathy or other causes of sensory impairment
  - any local conditions in which stockings may cause damage e.g. fragile 'tissue paper' skin, dermatitis, gangrene or recent skin graft
  - known allergy to material of manufacture
  - cardiac failure
  - severe leg oedema or pulmonary oedema from congestive heart failure
  - unusual leg size or shape
  - major limb deformity preventing correct fit.

  Use caution and clinical judgement when applying anti-embolism stockings over venous ulcers or wounds.

- Ensure that patients who need anti-embolism stockings have their legs measured and that the correct size of stocking is provided. Anti-embolism stockings should be fitted and patients shown how to use them by staff trained in their use.

- Ensure that patients who develop oedema or postoperative swelling have their legs re-measured and anti-embolism stockings refitted.

- If arterial disease is suspected, seek expert opinion before fitting anti-embolism stockings.

- Use anti-embolism stockings that provide graduated compression and produce a calf pressure of 14-15mmHg.

- Encourage patients to wear their anti-embolism stockings day and night until they no longer have significantly reduced mobility.

- Remove anti-embolism stockings daily for hygiene purposes and to inspect skin condition. In patients with a significant reduction in mobility, poor skin integrity or any sensory loss, inspect the skin two or three times per day, particularly over the heels and bony prominences.

- Discontinue the use of anti-embolism stockings if there is marking, blistering or discolouration of the skin, particularly over the heels and bony prominences, or if the patient experiences pain or discomfort. If suitable, offer a foot impulse or intermittent pneumatic compression device as an alternative.

- Show patients how to use anti-embolism stockings correctly and ensure they understand that this will reduce their risk of developing VTE.

- Monitor the use of anti-embolism stockings and offer assistance if they are not being worn correctly.

Foot impulse devices and intermittent pneumatic compression devices

- Do not offer foot impulse or intermittent pneumatic compression devices to patients with a known allergy to the material of manufacture.

- Encourage patients on the ward who have foot impulse or intermittent pneumatic compression devices to use them for as much of the time as is possible and practical, both when in bed and when sitting in a chair.

2.2.3.2 Pharmacological VTE prophylaxis

- Base the choice of pharmacological agents on local policies and individual patient factors, including clinical condition (such as renal failure) and patient preferences.

2.2.4 Reducing the risk of VTE in medical patients

- Offer pharmacological VTE prophylaxis to general medical patients assessed to be at increased risk of VTE (see section 2.2.1). Choose any one of:

  - fondaparinux sodium
  - LMWH*
  - UFH (for patients with renal failure).

  Start pharmacological prophylaxis as soon as possible after risk assessment has been completed. Continue until the patient is no longer at increased risk of VTE.

  **At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should*

consult the summary of product characteristics for the individual LMWH. Informed consent for off-label use should be obtained and documented.

Patients with stroke

- Do not offer anti-embolism stockings for VTE prophylaxis to patients who are admitted for stroke.

- Consider offering prophylactic-dose LMWH* (or UFH for patients with renal failure) if:

  - a diagnosis of haemorrhagic stroke has been excluded, **and**

  - the risk of bleeding (haemorrhagic transformation of stroke or bleeding into another site) is assessed to be low, **and**

  - the patient has one or more of:

    - major restriction of mobility

    - previous history of VTE

    - dehydration

    - comorbidities (such as malignant disease).

  Continue until the acute event is over and the patient's condition is stable.

  **At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off-label use should be obtained and documented.*

- Until the patient can have pharmacological VTE prophylaxis, consider offering a foot impulse or intermittent pneumatic compression device.

Patients with cancer

- Offer pharmacological VTE prophylaxis to patients with cancer who are assessed to be at increased risk of VTE (see section 2.2.1). Choose any one of:

  - fondaparinux sodium

  - LMWH*

  - UFH (for patients with renal failure).

  Start pharmacological VTE prophylaxis as soon as possible after risk assessment has been completed. Continue until the patient is no longer at increased risk of VTE.

  **At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should*

consult the summary of product characteristics for the individual LMWH. Informed consent for off-label use should be obtained and documented. LMWH.

- Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients with cancer having oncological treatment who are ambulant.

Patients with central venous catheters

- Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients with central venous catheters who are ambulant.

- Consider offering pharmacological VTE prophylaxis with LMWH* (or UFH for patients with renal failure) to patients with central venous catheters who are at increased risk of VTE (See section 2.2.1).

  **At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off-label use should be obtained and documented.*

Patients in palliative care

- Consider offering pharmacological VTE prophylaxis to patients in palliative care who have potentially reversible acute pathology. Take into account potential risks and benefits and the views of the patient and their family and/or carers. Choose any one of:

  - Fondaparinux sodium
  - LMWH*
  - UFH (for patients with renal failure).

  **At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off-label use should be obtained and documented.*

- Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients admitted for terminal care or those commenced on an end-of-life care pathway.

- Review decisions about VTE prophylaxis for patients in palliative care daily, taking into account the views of the patient, their family and/or carers and the multidisciplinary team.

Medical patients in whom pharmacological prophylaxis is contraindicated

- Consider offering mechanical VTE prophylaxis to **medical patients** in whom pharmacological prophylaxis is contraindicated. Choose any one of:

  - anti-embolism stockings (thigh or knee length)

- foot impulse devices
- intermittent pneumatic compression devices (thigh or knee length)

2.2.5 Reducing the risk of VTE in surgical patients

2.2.5.1 General recommendations for all surgical patients

- Advise patients to consider stopping oestrogen-containing oral contraceptives or hormone replacement therapy 4 weeks before elective surgery. If stopped, provide advice on alternative contraceptive methods.
- Assess the risks and benefits of stopping pre-existing established antiplatelet therapy 1 week before surgery. Consider involving the multidisciplinary team in the assessment.
- Consider regional anaesthesia for individual patients, in addition to other methods of VTE prophylaxis, as it carries a lower risk of VTE than general anaesthesia. Take into account the patients' preferences, their suitability for regional anaesthesia and any other planned method of VTE prophylaxis.
- If regional anaesthesia is used, plan the timing of pharmacological VTE prophylaxis to minimise the risk of epidural haematoma. If antiplatelet or anticoagulant agents are being used, or their use is planned, refer to the summary of product characteristics for guidance about the safety and timing of these in relation to the use of regional anaesthesia.
- Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients undergoing a surgical procedure with local anaesthesia by local infiltration with no limitation of mobility.

2.2.5.2 Recommendation for specific surgical patient groups

Cardiac surgery

- Offer VTE prophylaxis to patients undergoing **cardiac surgery** who are not having other anticoagulation therapy and are assessed to be at increased risk of VTE (see section 2.2.1)
  - Start mechanical VTE prophylaxis at admission. Choose any one of:
    - anti-embolism stockings (thigh or knee length)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length)

    Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:

    - LMWH

    - UFH (for patients with renal failure).

    Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

Gastrointestinal, gynaecological, urological and thoracic surgery

- Offer VTE prophylaxis to patients undergoing **bariatric surgery**

    - Start mechanical VTE prophylaxis at admission. Choose any one of:

        - anti-embolism stockings (thigh or knee length)

        - foot impulse devices

        - intermittent pneumatic compression devices (thigh or knee length).

        Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

    - Add pharmacological VTE prophylaxis for patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose any one of:

        - fondaparinux sodium

        - LMWH

        - UFH (for patients with renal failure).

        Continue pharmacological VTE prophylaxsis until the patient no longer has significantly reduced mobility (generally 5-7 days).

- Offer VTE prophylaxis to patients undergoing **gastrointestinal surgery** who are assessed to be at increased risk of VTE (see section 2.2.1)

    - Start mechanical VTE prophylaxis at admission. Choose any one of:

        - anti-embolism stockings (thigh or knee length)

        - foot impulse devices

        - intermittent pneumatic compression devices (thigh or knee length).

        Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Add pharmacological VTE prophylaxis for patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose any one of:
    - fondaparinux sodium
    - LMWH
    - UFH (for patients with renal failure).

  Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

➢ Offer VTE prophylaxis to patients undergoing **gynaecological, thoracic or urologic surgery** who are assessed to be at increased risk of VTE (see section 2.2.1)

- Start mechanical VTE prophylaxis at admission. Choose any one of:
    - anti-embolism stockings (thigh or knee length)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length).

  Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:
    - LMWH
    - UFH (for patients with renal failure).

  Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

➢ Extend pharmacological prophylaxis to 28 days postoperatively for patients who have had major cancer surgery in the abdomen or pelvis.

Neurological (cranial or spinal)

➢ Offer VTE prophylaxis to patients undergoing **cranial or spinal surgery** who are assessed to be at increased risk of VTE (see section 2.2.1)

- Start mechanical VTE prophylaxis from admission. Choose any one of:
    - anti-embolism stockings (thigh or knee length)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length).

Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:

  - LMWH

  - UFH (for patients with renal failure).

  Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

➢ Do not offer pharmacological VTE prophylaxis to patients with ruptured cranial or spinal vascular malformations (for example, brain aneurysms) or acute traumatic or non-traumatic haemorrhage until the lesion has been secured or the condition is stable.

Orthopaedic- elective hip replacement

➢ Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing **elective hip replacement surgery**:

- Start mechanical VTE prophylaxis at admission. Choose any one of the following, based on individual patient factors:

  - anti-embolism stockings (thigh or knee length), used with caution (see section 2.2.3.1)

  - foot impulse devices

  - intermittent pneumatic compression devices (thigh or knee length)

  Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Provided there are no contraindications, start pharmacological VTE prophylaxis after surgery. Choose any one of:

  - dabigatran etexilate, starting 1-4 hours after surgery*

  - fondaparinux sodium, starting 6 hours after surgical closure provided haemostasis has been established

  - LMWH, starting 6–12 hours after surgery

  - rivaroxaban, starting 6-10 hours after surgery$

  - UFH (for patients with renal failure), starting 6–12 hours after surgery.

Continue pharmacological VTE prophylaxis for 28-35 days, according to the summary of product characteristics for the individual agent being used.

** Dabigatran etexilate, within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 157(2008).*[476]

$ Rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 170 (2009).[479]

Orthopaedic- elective knee replacement

Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing **elective knee replacement surgery**.

- Start mechanical VTE prophylaxis at admission. Choose any one of the following, based on individual patient factors:
  - anti-embolism stockings (thigh or knee length), used with caution (see section 2.2.3.1)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length).

  Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Provided there are no contraindications, start pharmacological VTE prophylaxis after surgery. Choose any one of:
  - dabigatran etexilate, starting 1-4 hours after surgery*
  - fondaparinux sodium, starting 6 hours after surgical closure provided haemostasis has been established
  - LMWH, starting 6–12 hours after surgery
  - rivaroxaban, starting 6-10 hours after surgery$
  - UFH (for patients with renal failure), starting 6–12 hours after surgery.

  Continue pharmacological VTE prophylaxis for 10-14 days, according to the summary of product charateristics for the individual agent being used.

** Dabigatran etexilate, within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have*

undergone elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 157(2008).[476]

$ Rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 170 (2009).[479]

Orthopaedic- hip fracture

- Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing **hip fracture surgery**.

    - Start mechanical VTE prophylaxis at admission. Choose any one of the following, based on individual patient factors:

        - anti-embolism stockings (thigh or knee length), used with caution (see section 2.2.3.1)
        - foot impulse devices
        - intermittent pneumatic compression devices (thigh or knee length).

        Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

    - Provided there are no contraindications, add pharmacological VTE prophylaxis. Choose any one of:

        - fondaparinux sodium, starting 6 hours after surgical closure, provided haemostasis has been established and there is no risk of bleeding (see **Box 2**)
        - LMWH, starting at admission, stopping 12 hours before surgery and restarting 6–12 hours after surgery.
        - UFH (for patients with renal failure), starting at admission, stopping 12 hours before surgery and restarting 6–12 hours after surgery.

        Continue pharmacological VTE prophylaxis for 28-35 days, according to the summary of product characteristics for the individual agent being used.

- Fondaparinux sodium is not recommended for use preoperatively for patients undergoing **hip fracture surgery**. If it has been used preoperatively it should be stopped 24 hours before surgery and started 6 hours after surgical closure, provided haemostasis has been established and there is no risk of bleeding (see **Box 2**).

Other orthopaedic

- Consider offering combined VTE prophylaxis with mechanical and pharmacological methods to patients having **orthopaedic surgery (other than hip fracture, hip replacement or knee replacement)** based on an assessement of risks (see section 2.2.1) and after discussion with the patient. Start mechanical VTE prophylaxis at admission. Choose one of the following, based on individual patient factors:

  - anti-embolism stockings (thigh or knee length), used with caution (see section 2.2.3.1)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length)

  Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

  - Start pharmacological VTE prophylaxis 6–12 hours after surgery. Choose one of:

    - LMWH
    - UFH (for patients with renal failure).

    Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Do not routinely offer VTE prophylaxis to patients undergoing **upper limb surgery**. If a patient is assessed to be at increased risk of VTE (see section 2.2.1) refer to recommendation for other orthopaedic surgery (above).

Vascular

- Offer VTE prophylaxis to patients undergoing **vascular surgery** who are not having other anticoagulant therapy and are assessed to be at increased risk of VTE (see section 2.2.1). If peripheral arterial disease is present, seek expert opinion before fitting anti-embolism stockings.

  - Start mechanical VTE prophylaxis at admission. Choose any one of:

    - anti-embolism stockings (thigh or knee length)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length)

    Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

  - Add pharmacological VTE prophylaxis for patients who have a low risk of bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:

    - LMWH

- UFH (for patients with renal failure).

Continue pharmacological VTE prophylaxis until the patients no longer has significantly reduced mobility (generally *5-7* days).

Day surgery

- Offer VTE prophylaxis to patients undergoing **day surgery** who are assessed to be at increased risk of VTE (see section 2.2.1)

  - Start mechanical VTE prophylaxis at admission. Choose any one of:

    - anti-embolism stockings (thigh or knee length)

    - foot impulse devices

    - intermittent pneumatic compression devices (thigh or knee length).

    Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

  - Add pharmacological VTE prophylaxis for patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose any one of:

    - fondaparinux

    - LMWH

    - UFH (for patients with renal failure)

    If the patient is expected to have significantly reduced mobility after discharge, continue pharmacological VTE prophylaxis, generally for *5-7* days.

- Offer VTE prophylaxis to patients undergoing surgery **other than that covered in section 2.2.5.2** who are assessed to be at increased risk of VTE (see recommendation 2.2.1).

  - Start mechanical VTE prophylaxis at admission. Choose any one of:

    - anti-embolism stockings (thigh or knee length)

    - foot impulse devices

    - intermittent pneumatic compression devices (thigh or knee length).

    Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

  - Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:

- LMWH
- UFH (for patients with renal failure).

Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

2.2.6 Other patient groups

Major trauma

- Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients with **major trauma**. Regularly reassess the patient's risks of VTE and bleeding.
  - Start mechanical VTE prophylaxis at admission or as early as clinically possible. Choose any one of:
    - anti-embolism stockings (thigh or knee length) used with caution (see section 2.2.3.1)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length)

    Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.
  - If the benefits of reducing the risk of VTE outweigh the risks of bleeding (see **Box 2**) and the bleeding risk has been established as low, add pharmacological VTE prophylaxis and continue until the patient no longer has significantly reduced mobility. Choose one of:
    - LMWH
    - UFH (for patients with renal failure).

    Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility.

Spinal injury

- Offer combined VTE prophylaxis with mechanical and pharmacological methods tor patients with spinal injury. Regularly reassess the patient's risks of VTE and bleeding.
  - Start mechanical VTE prophylaxis at admission or as early as clinically possible. Choose any one of:
    - anti-embolism stockings (thigh or knee length) used with caution (see section 2.2.3.1)
    - foot impulse devices

- intermittent pneumatic compression devices (thigh or knee length)

Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility

- If the benefits of reducing the risk of VTE outweigh the risks of bleeding (see **Box 2**) and the bleeding risk has been established as low, add pharmacological VTE prophylaxis. Choose one of:

  - LMWH

  - UFH (for patients with renal failure).

  Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility

Lower limb plaster casts

- Consider offering pharmacological VTE prophylaxis for patients with lower limb plaster casts after evaluating the risks (see section 2.2.1) and benefits based on clinical discussion with the patient. Offer LMWH (or UFH for patients with renal failure) until lower limb plaster cast removal.

Pregnancy and up to 6 weeks post partum

- Consider offering VTE prophylaxis with LMWH (or UFH for patients with renal failure) to women who are **pregnant or have given birth within the previous 6 weeks who are admitted to hospital but are not undergoing surgery** and have one or more of the following risk factors:

  - expected to have significantly reduced mobility for 3 or more days
  - active cancer or cancer treatment
  - age over 35 years
  - critical care admission
  - dehydration
  - excess blood loss or blood transfusion
  - known thrombophilias
  - obesity (pre-pregnancy or early pregnancy BMI over 30 kg/m^2)
  - one or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
  - personal or a first degree relative with a history of VTE

- pregnancy related risk factor (such as ovarian hyperstimulation, hyperemesis gravidarum, multiple pregnancy and pre-eclampsia)

- varicose veins with phlebitis.

- Consider offering combined VTE prophylaxis with mechanical methods and LMWH (or UFH for patients with renal failure) to women who are **pregnant or have given birth within the previous 6 weeks who are undergoing surgery,** including caesarean section.

- Offer mechanical and/or pharmacological VTE prophylaxis to women who are **pregnant or have given birth within the previous 6 weeks** only after assessing the risks and benefits and discussing these with the patient and with healthcare professionals who have knowledge of the proposed method of VTE prophylaxis during pregnancy and post partum. Plan when to start and stop pharmacological VTE prophylaxis to minimise the risk of bleeding.

Critical Care

- Assess all patients on admission to the **critical care** unit for their risks of VTE (see section 2.2.1) and bleeding (see **Box 2**). Reassess patients' risks of VTE and bleeding daily and more frequently if their condition is changing rapidly.

- Offer VTE prophylaxis to patients admitted to the critical care unit based on the reason for admission, taking into account:

  - any planned interventions

  - the use of other therapies that may increase the risk of complications.

- Review decisions about VTE prophylaxis for patients in **critical care** daily and more frequently if their condition is changing rapidly. Take into account the known views of the patient, comments from their family and/or carers and the multidisciplinary team.

Patients already having antiplatelet agents or anticoagulants on admission or needing them for treatment

- Consider offering additional mechanical or pharmacological VTE prophylaxis to patients who are having antiplatelet agents to treat other conditions and who are assessed to be at increased risk of VTE (see section 2.2.1). Take into account the risk of bleeding (see **Box 2**) and of comorbidities such as arterial thrombosis.

  - If the risk of VTE outweighs the risk of bleeding, consider offering pharmacological VTE prophylaxis according to the reason for admission.

  - If the risk of bleeding outweighs the risk of VTE, offer mechanical VTE prophylaxis.

- Do not offer additional pharmacological or mechanical prophylaxis for VTE to patients who are taking vitamin K antagonists and who are within their therapeutic range, providing anticoagulant therapy is continued.

- Do not offer additional pharmacological or mechanical prophylaxis for VTE to patients who are having full anticoagulant therapy (for example, fondaparinux sodium, LMWH or UFH).

2.2.7 Patient information and planning for discharge

Patient information

- Be aware that heparins are of animal origin and this may be of concern to some patients*. For patients who have concerns about using animal products, consider offering synthetic alternatives based on clinical judgement after discussing their suitability, advantages and disadvantages with the patient.

**See "Religion or belief: a practical guide for the NHS", website: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_093133)*

- Before starting VTE prophylaxis, offer patients and/or their families or carers verbal and written information on:
    - the risks and possible consequences of VTE
    - the importance of VTE prophylaxis and its possible side effects
    - the correct use of VTE prophylaxis (for example, anti-embolism stockings, foot impulse or intermittent pneumatic compression devices).
    - how patients can reduce their risk of VTE (such as keeping well hydrated and, if possible exercising and becoming more mobile)

Planning for discharge

- As part of the discharge plan, offer patients and/or their families or carers verbal and written information on:
    - the signs and symptoms of deep vein thrombosis and pulmonary embolism
    - the correct and recommended duration of use of VTE prophylaxis at home (if discharged with prophylaxis)
    - the importance of using VTE prophylaxis correctly and continuing treatment for the recommended duration (if discharged with prophylaxis)
    - the signs and symptoms of adverse events related to VTE prophylaxis (if discharged with prophylaxis)
    - the importance of seeking help and who to contact if they have any problems using the prophylaxis (if discharged with prophylaxis)
    - the importance of seeking medical help if deep vein thrombosis, pulmonary embolism or other adverse events are suspected.

- Ensure that patients who are discharged with anti-embolism stockings:
    - understand the benefits of wearing them
    - understand the need for daily hygiene removal
    - are able to remove and replace them, or have someone available who will be able to do this for them
    - know what to look for such as skin marking, blistering or discolouration, particularly over the heels and bony prominences
    - know who to contact if there is a problem.
- Ensure that patients who are discharged with pharmacological and/or mechanical VTE prophylaxis are able to use it correctly, or have arrangements made for someone to be available who will be able to help them.
- Notify the patient's GP if the patient has been discharged with pharmacological and/or mechanical VTE prophylaxis to be used at home.

2.3 Recommendations for research

2.3.1 Assessment of risk for VTE

The Guideline Development Group (GDG) recommended the following research question:

- What is the absolute risk of VTE among different groups of hospital patients and can the risk be reliably estimated on admission to hospital to ensure that appropriate patients are offered VTE prophylaxis?

Why this is important

One of the most difficult areas the Guideline Development Group faced when developing the guideline was to identify the absolute risk of VTE among specific patient groups in relation to the reason for admission. A new, large pragmatic cohort study and/or record linkage study using Hospital Episode Statistics and the General Practice Research Database is proposed. This would allow all people admitted to hospital to be studied to identify those who develop VTE, including people who are diagnosed with VTE in primary care after discharge from hospital. Information on baseline patient-related factors, procedures and duration of stay, complications, prophylactic therapies and concomitant drug use should be collected and analysed. It should allow the identification of independent risk factors for VTE and the development and subsequent validation of a risk model to estimate the absolute risk of VTE in individual patients. This research would allow clearer identification of those patients at risk of VTE and those in whom the risk is so low that the bleeding risk of pharmacological VTE prophylaxis would add overall hazard.

2.3.2 VTE prophylaxis for general medical patients

The GDG recommended the following research question:

- What is the clinical and cost effectiveness of pharmacological prophylaxis, mechanical prophylaxis and combined pharmacological and mechanical prophylaxis for reducing the risk of VTE in medical patients?

Why this is important

Only a small number of trials with medical patients were identified and generally the inclusion criteria were narrow, for example, patients with an acute medical illness, with a hospital stay of more than 5 days, and often with severely limited mobility. Further research into less severely ill patient groups would be beneficial.
The evidence concerning mechanical prophylaxis in medical patients is sparse. There have been a few small trials of patients with coronary syndrome but the only large, randomised controlled trial was of patients with stroke. This trial showed that routine care plus thigh-length anti-embolism stockings did not confer significantly more protection against VTE than routine care alone and was associated with significantly more harm. All of these trials included large proportions of patients who were taking aspirin, which may have influenced the results.
New trial(s) should investigate the benefits of reducing the risk of VTE balanced against the risk of bleeding. The trial(s) should compare pharmacological prophylaxis alone, mechanical prophylaxis alone, and combined mechanical and pharmacological prophylaxis. The benefit of extended-duration prophylaxis in medical patient groups may also be investigated.

2.3.3 VTE prophylaxis for patients with lower limb plaster casts

The GDG recommended the following research question:

- What is the clinical and cost effectiveness of pharmacological prophylaxis for reducing the risk of VTE in patients with lower limb plaster casts?

Why this is important

A number of randomised controlled trials have been published reporting the use of VTE prophylaxis in patients with lower limb plaster casts. However, within these trials there has been a range of patients including patients with soft tissue injuries and no operation, those with operated and unoperated fractures and patients having elective procedures. The incidence of VTE in the published trials that did not use VTE prophylaxis ranges from 4%–40%. The implications of providing pharmacological prophylaxis for all patients with lower limb plaster casts are potentially considerable with respect to cost. Trials stratifying patients by reason for plaster cast would be useful to determine which patients should be recommended for prophylaxis.

2.3.4 VTE prophylaxis for patients after stroke

The GDG recommended the following research question:

- What is the overall risk/benefit of low molecular weight heparin and/or fondaparinux sodium in respect of both stroke outcome and the development of VTE for patients with acute stroke?

Why this is important

Patients with either ischaemic or haemorrhagic stroke have a risk of both VTE and bleeding into the brain. 'Stroke: diagnosis and management of acute stroke and transient attack [TIA]' (NICE clinical guideline 68, published July 2008) recommends the use of aspirin for treatment of ischaemic stroke but does not recommend anticoagulants. There is recent evidence to suggest that prophylactic-doses of anticoagulants in addition to aspirin reduce the risk of VTE in patients with ischaemic stroke but there are no data showing an effect of these anticoagulants on the stroke itself. Do they increase the risk of haemorrhagic transformation and so increase neurological damage? This research should include patients with haemorrhagic or ischaemic strokes to identify which patients would benefit from additional pharmacological prophylaxis.

2.3.5 Incidence of post-thrombotic syndrome after venous thromboembolism

The GDG recommended the following research question:

- What is the incidence, loss of quality of life and cost associated with post-thrombotic syndrome after potentially preventable deep vein thrombosis?

Why this is important

During development of the guideline it became apparent that the incidence of post-thrombotic syndrome, particularly after asymptomatic deep vein thrombosis, was not well reported. This study should use standard, validated definitions to identify the incidence of post-thrombotic syndrome both when a deep vein thrombosis has occurred as a result of a hospital admission and in the absence of hospital-acquired deep vein thrombosis. The study also should aim to identify the costs to the NHS of treating post-thrombotic syndrome.

3 Methodology

3.1 Incorporation and update of NICE clinical guideline 46

The remit for this guideline was received from the Department of Health:

*To prepare a clinical guideline on the prevention of VTE in **all** patients admitted to hospital.*

The National Collaborating Centre for Acute Care published a guideline in 2007 on reducing the risk of venous thromboembolism (VTE) in surgical inpatients[473]. As part of the development of the current guideline, the surgical guideline was incorporated. The previous guideline[473] is therefore superseded by this guideline and will be withdrawn.

As part of the incorporation of the surgical guideline, questions on the effectiveness of prophylaxis methods, anaesthesia and patient views & information were updated. This included re-running the searches, systematically reviewing new literature and developing and running network meta-analyses and economic models for appropriate sub-populations. The sections which were not updated were section 5.3.2 (absolute risk of VTE after surgical procedures from clinical registry data) and section 5.3.3 (absolute risk of VTE from prospective cohort studies). In addition an update search for individual patient risk factors VTE in surgical patients was not run (section 5.7), although a search was conducted for individual patient risk factors for medical patients.

The key methodology differences between this guideline and the guideline for surgical inpatients are summarised below:

- A different guideline development group was convened to provide clinical guidance into the evidence review. Some members of the guideline development group for the surgical guideline were included on the current GDG, and a list of all members for both parts of the guideline can be seen in the section titled 'Guideline Development Group membership and Acknowledgements'.

- Some outdated or uncommon interventions (e.g. dextrans, heparinoids, electrical stimulation) were exclued. These were included in the previous guideline but have not been reported in this updated version.

- Although the main outcomes (DVT, PE and major bleeding) were the same in the previous surgical and the current guideline, the different guideline development groups included slightly different criteria for identifying the outcomes. In addition some of the outcomes that the current development

group considered as important (e.g. all cause mortality) were not identified as key outcomes by the guideline development group from the previous surgical guideline. Details of the differences in outcomes considered between previous surgical guideline and the current guideline are presented for each outcome in section 3.5.

- The evidence for each patient population separately was considered separately. In the previous surgical guideline the evidence for different surgical populations was combined.
- Updated methods for network meta-analysis (Section 3.10).
- Updated economic model (chapter 4)

3.2 Guideline methodology

The guideline was commissioned by NICE and developed in accordance with the guideline development process outlined in 'The guidelines manual'[480]. The versions of the guideline manual used for each stage of guideline development are detailed in Table 3-1:

Table 3-1: Version of NICE guideline used

Guideline Development Stage	*Version of NICE Guideline Manual*
Scoping for NICE Clinical guideline 46 (Surgery)	2005
Development of NICE Clinical guideline 46 (Surgery)	2006
Scoping and development of current clinical guideline for all hospital patients	2007
Validation of current clinical guideline for all hospital patients	2009[480]

3.3 Developing the clinical questions

Clinical questions were developed to guide the literature searching process and to facilitate the development of recommendations by the guideline development group.

The clinical questions were initially drafted by the review team and were refined and validated by the guideline development group. The questions were based on the scope (Appendix A).

3.3.1 Questions on effectiveness of interventions to reduce the risk of VTE

The clinical questions were:

- What is the effectiveness of X vs Y in reducing the incidence of VTE?

Where X and Y are the prophylaxis methods in the list of interventions below. Every possible combination was compared.

a) Graduated elastic compression stockings / anti-embolism stockings (GCS)

b) Intermittent pneumatic compression (IPCD) devices

c) Foot pumps or foot impulse devices (FID)

d) Vena caval filters

e) Aspirin or antiplatelet therapy

f) Low-dose unfractionated heparin administered subcutaneously (UFH)

g) Low molecular weight heparin (LMWH)

h) The synthetic pentasaccharide, Fondaparinux

i) Vitamin K Antagonists (For example, warfarin, coumarin)

j) Early mobilisation

k) Foot elevation

l) Hydration

m) New oral anticoagulants licensed during the guideline development period.*

n) Placebo or no intervention

* During the development of the guideline two new oral anticoagulants; dabigatran (direct thrombin inhibitor) and rivaroxaban (direct factor Xa inhibitor) were considered by NICE as part of their health technology appraisal (HTA) programme. The NICE HTA report for dabigatran was published in September 2008[476]. The appraisal on rivaroxaban was published in April 2009[479], and was incorporated into our guideline after the stakeholder consultation.

The effectiveness of combinations of methods of prophylaxis (For example, a combination of a mechanical and a pharmacological intervention or two mechanical devices) were also considered versus no prophylaxis, versus single methods or versus other combinations.

3.3.2 Additional considerations on the use of the above interventions

In addition to the questions of effectiveness of prophylaxis (section 3.3.1) we examined more detail regarding prophylaxis in the following areas:

- Extending pharmacological prophylaxis beyond the hospitalised period.
- Potential variations in effectiveness by fixed or adjusted dose vitamin K antagonists (e.g. warfarin)
- The pre or post operative administration of pharmacological prophylaxis (LMWH)
- The length of mechanical devices anti-embolism stocking or intermittent pneumatic compression devices (e.g. knee-length vs. over the knee)

3.3.3 Anaesthesia

The following clinical questions relating to anaesthesia were examined:

- What is the effectiveness of regional anaesthesia vs general anaesthesia in reducing the incidence of postoperative VTE?
- Does adding a regional to a general anaesthetic reduce the risk of postoperative VTE?

3.3.4 Risk factors

We developed questions to address risk factors for VTE associated with surgical procedure, medical conditions and for individual patient risk characteristics:

- Which surgical procedures carry a high risk of deep vein thrombosis (DVT)/Pulmonary Embolism (PE)?
- Which medical conditions carry a high risk of DVT/PE?
- Which individual patient factors (for both surgical and medical patients) are risk factors for developing DVT/PE?

3.3.5 Patient information and communication

We examined the following clinical questions:

- What specific information about the prophylaxis methods or VTE should be provided to patients who require VTE prophylaxis?
- Does providing patients who were admitted to hospital with information about VTE or VTE prophylaxis methods:
  - reduce the number of DVTs and pulmonary embolisms?
  - affect any of the other outcomes listed or patient adherence?

3.3.6 Patient views and preferences

We searched for evidence of patient views (effectiveness and acceptability) and preferences regarding all the interventions listed in section 3.3.1.

3.4 Patients covered by this guideline

We searched for studies of adults (age 18 years and older) admitted to hospital for any reason. A more detailed list of patient groups that are included or excluded from the guideline can be found in the scope (Appendix A).

3.5 Outcomes

3.5.1 Primary outcomes

3.5.1.1 All cause mortality

This was identified as an important outcome. The evidence for all cause mortality was extracted from any new studies that were reviewed. These data had not been extracted for the previous version of the guideline and it was not possible to extract data for all cause mortality from all of the surgical areas already reviewed.

3.5.1.2 Deep-vein thrombosis (DVT)

DVT (symptomatic and asymptomatic) identified by one of the following methods:

- Radioiodine (125I) fibrinogen uptake
- Venography
- Doppler ultrasound
- Magnetic resonance imaging (MRI)

In order to detect all asymptomatic DVTs the inclusion criteria required that all patients included in the study were screened using one or more of the methods above. Studies that only assessed patients with clinical suspicion of DVT were not included for this outcome.

The following methods of diagnosing DVT were excluded as they were considered to be unreliable (unless used in conjunction with one of the methods outlined above):

- D-dimer blood assay test alone
- Impedance plethysmography (for the medical guideline this test was accepted if it was used as a 'rule out' tool for screening all patients providing the DVT events were subsequently confirmed using one of the objective methods.)
- Clinical examination alone

3.5.1.3 Pulmonary embolism (PE)

PE determined by one or more of the following methods

- Pulmonary angiogram
- Ventilation/perfusion scan (pulmonary scintigraphy)
- CT pulmonary angiogram
- Echiocardiography (medical guideline only)
- Autopsy
- Clinical suspicion confirmed by one of the preceding methods

The following methods of diagnosing PE were excluded as they were considered to be unreliable:

- Chest X-ray alone
- Clinical examination alone

For the studies reviewed for the surgical guideline all pulmonary embolisms were included as the outcome measure and in the medical section only symptomatic pulmonary embolisms were included. This was because the Guideline Development Group agreed that symptomatic pulmonary embolism was more commonly reported in studies.

3.5.1.4 Major bleeding events

A bleeding events were considered to be "major" on the basis of the authors' own established criteria, or if the results reported corresponded to one of the definitions below.

A major bleeding event is defined as a bleeding event that results in one or more of the following:

- death,
- a decrease in haemoglobin concentration of 2g/dl or more,
- transfusion of at least 2 units of blood,
- bleeding from a retroperitoneal, intracranial, or intraocular site
- a serious or life-threatening clinical event,
- a surgical or medical intervention.

We included papers that met our quality criteria if they reported at least one of the following outcomes:

- DVT,
- PE.

3.5.2 Secondary outcomes

The following secondary outcomes were also included in our review where reported:

- post-thrombotic syndrome (PTS),
- chronic thromboembolic pulmonary hypertension (CTEPH),
- heparin-induced thrombocytopenia (HIT),
- neurological events,
- quality of life,
- survival,

- length of stay.

3.5.3 Important methodological issues relating to the outcomes

- Pulmonary emboli, major bleeds, spinal haematomas and heparin-induced thrombocytopenia are rare events, consequently, large numbers of patients are required to obtain an estimate of effect.

- Very few trials assess all patients for pulmonary embolism using objective methods.

- Where trials assess both DVT and pulmonary embolism, protocols usually dictate that patients in whom a DVT is detected are withdrawn and started on anticoagulant therapy which may prevent further progression of the disease. This may result in an underestimation of the PE rate as many of these patients (particularly those with asymptomatic DVT) would not have been picked up in standard practice.

- Chronic thromboembolic pulmonary hypertension and post thrombotic syndrome are long term events that may occur many years after the initial thrombotic event. The follow up period in trials is unlikely to be long enough to identify these events.

- Very few trials reported any of the secondary outcomes.

3.6 Clinical literature search

The aim of the literature search was to find evidence within the published literature in order to answer the clinical questions identified. We searched clinical databases using filters (or hedges), using relevant medical subject headings and free-text terms. Non-English studies and abstracts were not reviewed. Searches were conducted to update the previous guideline.

Each database was searched up to 10 December 2008. We performed one initial search and then two update searches nearer the end of guideline development period. No papers after this date were considered. After the first draft of the guideline had been returned after stakeholder consultation a new study presenting results of the effectiveness of stockings in stroke patients was published in June 2009[158]. This study reported new evidence on the use of stockings in stroke patients. The GDG decided the study should be included and felt that recommendations concerning the use of stockings should be reconsidered. To ensure all stockings studies published since the last searches in December 2008 were identified the search for evidence on stockings was updated to 9 June 2009.

The search strategies can be found in Appendix C.

The following databases were searched:

- The Cochrane Library up to Issue 4 2008

- Medline 1950-2008 (OVID)

- Embase 1980-2008 (OVID)
- Cinahl 1982-2008 (NLH Search 2.0)
- Health Economic and Evaluations Database (HEED) up to December 2008

There was no systematic attempt to search for grey literature or unpublished literature although all stakeholder references were followed up. We searched for guidelines and reports via relevant websites including those listed below.

- Members of the Guidelines International Network's web sites (http://www.g-i-n.net/)
- National Institute of Health and Clinical Excellence (NICE) (www.nice.org.uk)
- National Library for Health (NLH) (http://www.library.nhs.uk/)
- National Institutes of Health Consensus Development Program (consensus.nih.gov)
- New Zealand Guidelines Development Group (NZGG) (http://www.nzgg.org.nz/)
- Scottish Intercollegiate Guideline Network (SIGN) (www.sign.ac.uk)
- US National Guideline Clearing House (www.guidelines.gov)

3.7 Hierarchy of clinical evidence

There are many different methods of ranking the evidence and there has been considerable debate about which system is best. We used the system, developed by the Scottish Intercollegiate Guidelines Network (SIGN), and outlined in the NICE guidelines manual[480], shown in Table 3-2.

Table 3-2:Levels of evidence for intervention studies (reproduced with permission of the Scottish Intercollegiate Guidelines Network)

Level of evidence	*Type of evidence*
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies. High-quality case–control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2-	Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies (For example, case reports, case series)

Level of evidence	*Type of evidence*
4	Expert opinion, formal consensus

For each clinical question the highest level of evidence was sought. Where an appropriate systematic review, meta-analysis or randomised controlled trial was identified, we did not search for studies of a weaker design. Studies assessed as being levels 1- and 2- were excluded.

3.8 Literature reviewing process

References identified by the systematic literature search were screened for appropriateness by title and abstract by an information scientist and systematic reviewer. Studies were selected that reported one or more VTE outcome (DVT, PE) determined by objective/reliable methods. We did not select studies that reported only major bleeding outcomes, but where an included systematic review reported such studies, they were not removed. The guideline development group also suggested further references and we assessed these in the same way.

Selected studies were ordered and assessed in full by a systematic reviewer using agreed inclusion/ exclusion criteria specific to the guideline topic, and using NICE methodology quality assessment checklists appropriate to the study design. These are described in the NICE guidelines manual[480].

3.8.1 Literature review for patient view studies.

Information of patient views regarding thromboprophylaxis and adherence are often more appropriately studied using non-RCT designs (i.e qualitative studies, surveys of patients in observational studies). Unlike interventional studies, there is no established hierarchy of evidence to answer questions on patient views; observational or qualitative designs are not necessarily of lower quality than RCTs. Therefore, no study design limitation was included in the search and review of evidence. Relevant studies where the methods were clearly reported, appropriately designed to answer the study questions and met the quality assessment were included.

Qualitative studies were quality assessed using checklists from the NICE guideline manual[480] and only studies rated as '+' or '++' were included.

The questionnaires used in the various patient view studies found in our searches did not report on how they were designed and validated. This is a major methodological limitation for all studies using questionnaires in this guideline.

It is also important to note that both RCTs and observational studies of patient adherence come with potential biases and limitations. For example, the informed consent process and strict inclusion criteria of RCTs may contribute to better informed or motivated patients. In addition, participation in RCTs is usually associated with closer monitoring and better level of support. This may result in higher adherence than may be expected in routine practise. Adherence may also be higher in studies where patients were checked hourly for adherence or where self-reports were used. However, when a range of results are observed in different study designs and settings, these provide a useful

indication of the types of issues that might be expected from the interventions in usual practice.

3.9 Methods for combining direct evidence

Where possible, meta-analyses were conducted to combine the results of studies addressing the same clinical question using Cochrane's Review Manager Software. Random effects method (Der Simonian and Laird model) was used to calculate risk ratios (relative risk) of an event occurring, that is, all cause mortality, DVT, PE or major bleeding. Statistical heterogeneity was assessed by considering the chi-squared and the I-squared test. Significant heterogeneity was noted for any study where the I-squared value was >50%, or the I-squared value was between 25% and 50% and the chi-squared value was $p < 0.1$. We carried out sensitivity analyses to identify studies whose results were heterogeneous to the overall result. Any such studies were further assessed to identify any clinical or methodological causes. We avoided removing these studies from the meta-analyses unless we identified a serious methodological flaw, as removal would introduce bias into the systematic review.

Where combining results of trials in a meta-analysis was not appropriate a narrative synthesis of studies was undertaken.

3.10 Methods for combining direct and indirect evidence

It is difficult to determine the most effective prophylaxis strategy from the results of conventional meta-analyses of direct evidence for three reasons:

1) Some pairs of alternative strategies have not been directly compared in an RCT (for example, aspirin vs. fondaparinux).

2) Sometimes the direct evidence does not provide enough data and we need to support it with indirect evidence.

3) There are frequently multiple overlapping comparisons (For example, heparin vs. no prophylaxis, heparin vs. stockings and stockings vs no prophylaxis), that potentially give inconsistent estimates of effect.

To overcome these problems, we conducted a network meta-analysis (NMA) that simultaneously pools together all the data. This allowed us to rank the different prophylaxis interventions in order of efficacy at reducing DVTs and PEs and in order of risk of major bleeding. For each of these two outcomes, it gives us a single estimate of effect (with confidence intervals) for each intervention compared with no prophylaxis.

The advantages of a network meta-analysis are that

- It enables the ranking of different interventions
- It facilitates cost-effectiveness analysis
- It never breaks randomisation
- It doesn't discard any randomised evidence

- It is useful for diagnosing inconsistency/heterogeneity between evidence comparisons (3.10.3).

NMA does require an additional assumption over conventional meta-analysis. In the case of a fixed-effects NMA, it assumes that intervention A has the same effect on patients in trials of AvsB as it does in trials of AvsC, etc. In the case of random-effects NMA, the assumption is that intervention A has the same effect distribution across trials of AvsB as it does across trials of AvsC, etc.

3.10.1 Study inclusion criteria

The following **interventions were excluded** from the network meta-analysis:

- dextran, danaparoid, antiplatelet drugs other than aspirin, fixed-dose vitamin K antagonists– since these are unlicensed, dated, and not likely to be recommended

- different anaesthetic regimes, since most of the surgical studies patients had a mixture of types of anaesthesia

- hydration, physiotherapy, continuous passive motion, foot elevation, electrical stimulation and vena caval filters, where there was insufficient RCT evidence.

- A combination of two types of mechanical prophylaxis was not included in the base case analysis because the data are from only a few small trials and the GDG did not consider this evidence to be robust.

Randomised controlled trials (RCTs) that evaluated two or more of the following **interventions were included** in the network meta-analysis (NMA):

- aspirin (low-dose & high-dose), dabigatran, rivaroxaban, fondaparinux, heparin (UFH/LMWH), adjustable-dose vitamin K antagonists (VKA-adj)

- graduated compression / anti-embolism stockings (GCS), intermittent pneumatic compression / foot impulse devices (IPCD/FID)

- nil (i.e. no prophylaxis or placebo)

- combinations of one drug and one mechanical device

- combinations of UFH and aspirin

Our analysis was also restricted to those **populations** and outcomes where there was a substantial amount of RCT data. Thus we chose the following population subgroups:

- hip fracture surgery,

- total hip replacement,

- total knee replacement,

- general surgery (including gastrointestinal, gynaecological, laparoscopic, thoracic and urological surgery),
- general medical admissions.

And the following **outcomes**:

- DVT (asymptomatic+symptomatic) – from studies that screened the whole leg,
- symptomatic pulmonary embolism,
- major bleeding.

Analysis of major bleeding was carried out by pooling the data across all 5 population subgroups, since the data were sparse.

We also looked at all-cause mortality but only for two populations: hip fracture surgery and general medical admissions. Data were not collected for other populations (see Section 3.5.1.1). The event rates were expected to be low for these populations that it was deemed unlikely to allow for useful comparison. Pooling across populations is not appropriate given that both bleeding and pulmonary embolism effects contribute to mortality.

In all our network meta-analyses we considered foot impulse devices and intermittent pneumatic compression devices to be the same class of intervention. This is because of the range of different devices, the lack of evidence to consider them separately (especially in combination with different drugs) and because preliminary analysis suggested that they have a very similar effect. Graduated compression / anti-embolism stockings were kept as a distinct category since the biological mechanism is quite different and because there was some evidence of differential effects when compared with the other types of mechanical prophylaxis.

There are no biological reasons to believe that the presence of mechanical prophylaxis would influence the risk of major bleeding. Therefore, for the major bleeding NMA, mechanical only strategies are categorised as "Nil". Likewise combination strategies are categorised according to their drug component only. We assume that the major bleeding rate for mechanical only strategies is the same as for the Nil strategy.

We included studies where the baseline was admission or surgery and where the interventions lasted up to three weeks (termed 'standard duration'). Trials that started post-discharge were not included in the network meta-analysis. Where there was a choice of follow-up periods, we used the one that was furthest from baseline.

3.10.2 The model

We performed a hierarchical Bayesian NMA method[411] using the software WinBUGS. This specific method is usually referred to as mixed-treatment comparisons analysis but we will continue to use the term network meta-analysis to refer generically to this kind of analysis. We do so since the term 'network' better describes the data structure, whereas 'mixed treatments' could easily be misinterpreted as referring to combinations of treatments.

We adapted a program on the University of Bristol website (https://www.bris.ac.uk/cobm/research/mpes/mixed-treatment-comparisons.html. Last accessed 20th January 2009). The model accounts for the correlation between arms in three-arm trials. We had no four-arm trials in our analysis.

In order to be included in the analysis, a fundamental requirement is that each treatment is connected directly or indirectly to every other intervention in the network. For each population subgroup we have produced a diagram of the evidence network to show which interventions have be included. Trials with zero events in each arm were excluded since these do not contain evidence relevant to the analysis. This explains, in part at least, why there are far fewer trials in our NMAs of pulmonary embolism compared with our NMAs of DVT.

The model takes the form of a random effects logistic regression model. The model parameters are estimated by Markov Chain Monte Carlo Simulation[221]. Being a Bayesian analysis, the evidence distribution is weighted by a distribution of our prior beliefs. We have used non-informative prior distributions to maximise the weighting given to the data. These priors are normally distributed with a mean of zero and standard deviation of 10,000.

For each analysis we conducted a burn-in of 60,000 simulations to allow convergence and then a further 60,000 simulations to give us our output. Convergence was assessed by examining the history, kernel density and autocorrelation plots. We also checked the Monte Carlo error statistic. An alternative set of starting values were used to ensure that the results were not sensitive to these parameters.

We tested the goodness of fit of the model by calculating the residual deviance. If the residual deviance is close to the number of unconstrained data points (the number of trial arms in the analysis) then the model is explaining the data well.

Since the model is a logistic regression, the output parameters are odds ratios. For ease of interpretation we have converted these to relative risks (RR) using the following formula[717]:

$$RR = \frac{OR}{(1-P_0)+(P_0 x OR)}$$

where P_0 is the risk of the event in the control arm. We estimated the RR for each of the 60,000 simulations, treating P_0 as a constant. The point estimate of the RR was taken to be the median of the 60,000 simulations and the 95% confidence intervals for the RR were taken to be the 2.5th and 97.5th centiles from the distribution of the RR.

3.10.3 Dealing with inconsistency

Supposing that there are trials of C vs B that give a relative risk (RR) of 0.8 and trials of B vs A that give a RR of 0.5 (Figure 3-1) then this implies that a comparison of C vs A would give a RR of 0.4 (0.8 x 0.5). But if the actual trials of C vs A indicate a RR of 0.5 then there is some kind of inconsistency within our data network. A network meta-analysis would re-estimate the RRs for all three comparisons using the all data pooled together.

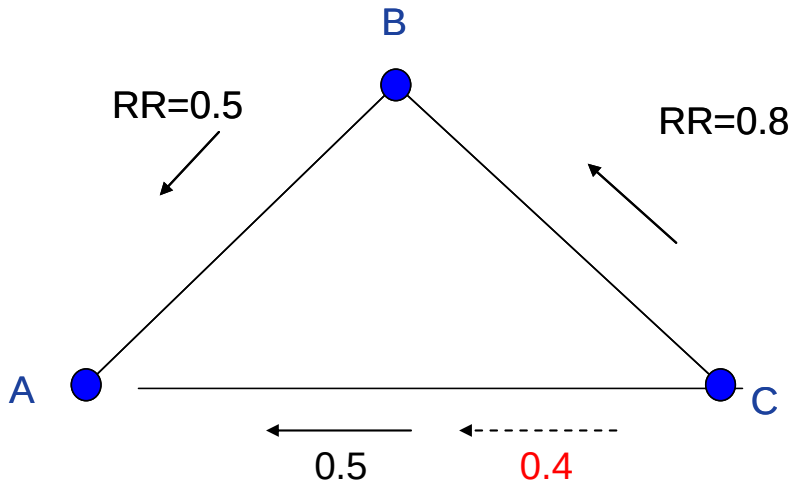


Figure 3-1: Inconsistency between trial comparisons

There are two causes of this inconsistency. The first is *chance*, and if this is the case then the network meta-analysis results are more precise, since they pool more data than conventional estimates. The second is that there are differences in the trials included in the different comparisons. Differences that might potentially lead to inconsistency include:

- Different populations (sex, age, risk factors)
- Different interventions (doses, stocking length)
- Different measures of outcome (fibrinogen uptake, venography)
- Different follow-up periods (7-10 days, 14 days, 3 months)

This heterogeneity is a problem for NMA and needs to be dealt with by subgroup analysis and sometimes by re-defining inclusion criteria.

We identified the presence of heterogeneity by subjectively comparing the NMA odds ratio estimates with odds ratios derived from direct comparison estimates. Then we sought to identify the cause of this heterogeneity by examining the details of the study design, population, interventions and outcomes of the relevant trials.

3.11 Health economic methods

It is important to investigate whether health services are cost-effective (that is, value for money). If a particular prophylaxis or treatment strategy were found to yield little health gain relative to the resources used, then it would be advantageous to re-deploy resources to other activities that yield greater health gain.

In the previous NICE guideline[473] we found great inconsistency in the economic evaluations in the published literature. This was mainly because the evaluations varied in the clinical studies they included and because they used crude methods to deal with indirect evidence. Furthermore most of the published studies did not evaluate cost-effectiveness using NICE's reference case. Therefore in this guideline an original cost-effectiveness analysis was performed which compared a variety of different prophylactic strategies for a number of different hospital population subgroups. In

addition, a systematic review of the economic literature was conducted for populations or interventions not covered by the original cost-effectiveness analysis.

The criteria applied for an intervention to be considered cost-effective were either:

a) The intervention dominated other relevant strategies (that is, it is both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies) **, or**

b) The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy (and compared with no prophylaxis).

The full economic evaluation of any strategy has to be in comparison with another strategy. Hence we refer to:

- incremental cost: the mean cost of one strategy minus the mean cost of a comparator study
- QALYs gained: the mean QALYs associated one strategy minus the mean QALYs of a comparator study
- incremental cost-effectiveness ratio: the incremental cost divided by the respective QALYs gained
- incremental net benefit (INB): the (monetary) value of a strategy compared with an alternative strategy for a given cost-effectiveness threshold (For example: £20,000 per QALY gained).

In our own cost-effectiveness analysis (Chapter 4), we use the following formula to estimate the INB of each strategy:

INB= (QALYs gained compared with no prophylaxis x £20,000) minus the incremental cost compared with no prophylaxis.

This indicates that we will invest up to £20,000 to gain one additional QALY. The strategy that has the highest INB is the optimal (that is, most cost-effective) strategy. Strategies that have a negative INB are not cost-effective even compared with no prophylaxis.

3.11.1 Literature review for health economics

We obtained published economic evidence from a systematic search of the following databases:

- The Cochrane Library up to Issue 4 2008
- Medline 1950-2008 (OVID)
- Embase 1980-2008 (OVID)
- Health Economic and Evaluations Database (HEED) up to December 2008

The information specialists used the same search strategy as for the clinical questions, using an economics filter in the place of a systematic review or randomised controlled trial filter. Each database was searched from its start date up to December 2008. Papers identified after this date were not considered. Search strategies can be found in Appendix C.

Each search strategy was designed to find any applied study estimating the cost or cost-effectiveness of an included prophylaxis intervention. A health economist reviewed the abstracts. Relevant references in the bibliographies of reviewed papers were also identified and reviewed.

Papers were excluded from the review and evidence tables if:

- The population and interventions were covered by an original guideline cost-effectiveness analysis.
- The study did not contain any original data on cost or cost-effectiveness (that is, it was a review or a clinical paper).
- The analysis was not incremental and was not described adequately to allow incremental analysis (so studies reporting only average cost-effectiveness ratios were excluded unless they provided data to allow the calculation of incremental cost-effectiveness ratios).
- Cost analyses were excluded if the results were not presented in a way that would allow the incremental cost per patient to be extracted or derived.

Where a comparison had a large number of evaluations (For example, LMWH vs UFH), we excluded those based on cohort studies and those based on simple models (that is neither a meta-analysis nor a formal decision analytic model).

Included papers were reviewed by a health economist. In the evidence tables costs are reported as given in the paper. However, where costs were in a currency other than pounds sterling, the results were converted to pounds sterling using the relevant purchasing power parity for the study year.

We have included studies from all over the world in our review, however, we use overseas studies with caution since resource use and especially unit costs vary considerably. Particular caution is applied to studies with predominantly private health insurance (For example, USA or Switzerland) where unit costs may be much higher than in the UK and to developing countries where costs may be much lower.

Each study was categorised as one of the following: cost analysis, cost-effectiveness analysis, cost–utility analysis (that is, cost–effectiveness analysis with effectiveness measured in terms of QALYs), or cost consequences analysis. We did not find any 'cost benefit analyses' (studies that put a monetary value on health gain).

Models are analogous to systematic reviews as they are pooling evidence from a number of different studies and therefore if well-conducted they should out-rank studies based on a single RCT. Statistical significance is not usually applicable to models and uncertainty is explored using sensitivity analysis instead. Hence the results reported in our economics evidence tables and write-up may not necessarily imply statistical significance.

In our own cost-effectiveness analysis we rigorously explore the effects of sample variation using Monte Carlo simulation (Chapter 4).

Where QALYs were not estimated, we used thresholds of £20,000 per life-year gained, or £400,000 per life saved.

We state that cost-effectiveness is 'indeterminable' in cases where outcomes are expressed only in terms of VTEs rather than overall health outcomes and where one intervention is both more costly and more effective.

3.11.2 Cost-effectiveness modelling

The following general principles were adhered to:

- The GDG was consulted during the construction and interpretation of the model.
- The model was based on a network meta-analysis derived from the systematic review of clinical evidence.
- Model assumptions were reported fully and transparently (Chapter 4).
- The results were subject to thorough sensitivity analysis and limitations discussed.
- Costs were calculated from a health services perspective.

3.12 Development of recommendations

Over the course of the guideline development process the GDG was presented with the following:

- Evidence tables and narrative summaries of the clinical evidence reviewed. All evidence tables are in Appendix D
- Forest plots of direct meta-analyses (Appendix E).
- Forest plots of network meta-analyses (Chapters 9-12, 23).
- A description of the methods for, and results of, the cost-effectiveness analysis (Chapter 4 and Chapters 9-12, 23).

Although evidence was reviewed for every population, network meta-analysis and cost effectiveness analyses were only conducted for 5 populations, general medical patients, general surgical patients, hip fracture surgery, total hip replacement and total knee replacement. For these populations the recommendations were derived directly from the results of the analyses. If the decision was taken not to recommend the most cost effective strategy the GDG clearly explained their reasoning for this.

For populations which did not have cost effectiveness models conducted, recommendations were based on the direct evidence available for that population and from extrapolating the results from cost-effectiveness models in other populations. The link between evidence and the subsequent recommendations is explained in the relevant sections.

We used a modified version of the nominal group technique of consensus development to agree the final recommendations.

3.13 Research recommendations

When we identified areas for which good evidence was lacking, the guideline development group considered making recommendations for future research. Decisions about inclusion were based on factors such as the importance to patients or the population, national priorities, and the potential impact on the NHS and future NICE guidance. The individual chapters contain a summary of the research recommendations and the justification for the top five priority research recommendations are presented in Appendix F.

3.14 Prioritisation of recommendations for implementation

To assist users of the guideline in deciding the order in which to implement the recommendations, the guideline development group identified ten key priorities for implementation. The decision was made after discussion and voting by the GDG. They selected recommendations that would:

- have a high impact on outcomes that are important to patients,
- have a high impact on reducing variation in care and outcomes,
- lead to a more efficient use of NHS resources,
- promote patient choice,
- promote equalities.

3.15 Validation of guideline

Registered stakeholders were given the opportunity to comment on the draft guideline, which was posted on the NICE website. A Guideline Review Panel also reviewed the guideline and checked that stakeholders' comments had been addressed.

A second consulatation was conducted because the results a large randomised controlled trial was published after the first consultation. As a result of the second consultation, some changes were made for the General Medical Patients (Chapter 23) and Stroke Patients (Chapter 24) recommendations.

3.16 Related NICE guidance

NICE has developed the following guidance (details available from www.nice.org.uk):

- Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults[476] (Publication date September 2008)
- Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults[479] (Publication date April 2009)

3.17 Updating the guideline

NICE clinical guidelines are updated as needed so that recommendations take into account important new information. We check for new evidence 3 years after publication, to decide whether all or part of the guideline should be updated. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations.

4 Development of cost-effectiveness model

4.1 General approach

Our aim in constructing the model was to determine the most cost-effective thromboprophylaxis strategy for different hospital population subgroups. The efficacy of each prophylaxis strategy is based on the results of the trials in our systematic review.

4.1.1 Interventions

The thromboprophylaxis interventions we compared in the model are those which we evaluated in our network meta-analysis (Section 3.10 above), which was based on the RCTs included in our clinical review. Trials that evaluated the following interventions were **excluded** from the network meta-analysis:

- dextran, danaparoid, antiplatelet drugs other than aspirin, fixed-dose vitamin K antagonists– since these are unlicensed, dated, and not likely to be recommended
- different anaesthetic regimes, since most of our studies patients had a mixture of types of anaesthesia
- hydration, physiotherapy, continuous passive motion, foot elevation, electrical stimulation and vena caval filters, where there was insufficient RCT evidence.
- A combination of two types of mechanical prophylaxis was not included in the base case analysis because the data were from only a few small trials and the Guideline Development Group did not consider this evidence to be robust.

Interventions **included** in the network meta-analysis:

- aspirin (low dose & high dose), dabigatran, fondaparinux, unfractionated heparin (UFH), Low molecular weight heparin (LMWH), adjustable-dose vitamin K antagonists (VKA), rivaroxaban
- graduated compression / anti-embolism stockings (GCS), intermittent pneumatic compression / foot impulse devices (IPCD/FID)
- nil (i.e. no prophylaxis or placebo)
- combinations of one drug and one mechanical device

- combinations of UFH and aspirin

4.1.2 Population

We conducted a cost-effectiveness analysis for each of five population subgroups:

- hip fracture surgery
- total hip replacement
- total knee replacement
- general surgery (including other internal surgery)
- general medical admissions

The cost-effectiveness of post-discharge / extended duration prophylaxis was considered separately for hip replacement patients, hip fracture and general surgery patients (Section 4.7).

4.1.3 Outcomes

The primary outcomes are quality-adjusted life-years (QALYs) gained and incremental cost.

The model employed a baseline cost-effectiveness threshold of £20,000 per QALY gained, complying with the reference case advocated by NICE [475], such that costs were estimated from an NHS and personal social services perspective. Future costs and QALYs are discounted at 3.5%.

4.1.4 The model

The model consists of a simple decision tree (Figure 4-2). The tree is repeated for each prophylaxis strategy. Each endpoint of the tree implies a particular cost and a particular health outcome (QALYs). For each prophylaxis strategy, the mean QALYs are calculated by summing across all the tree endpoints, the QALYs multiplied by the probability of reaching that endpoint. For different prophylaxis strategies the probabilities will be different and hence the mean costs and mean QALYs will be different also.

A separate model is constructed for each of the population subgroups stated above. Further models were developed for each of the post-discharge / extended duration population subgroups (Section 4.7).

VTEs and major bleeding events are modelled for the acute period (this is determined by the RCT follow-up, typically only 10-14 days) but QALYs and health service costs arising

from these events are modelled over the patient's lifetime, including treatment of post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH).

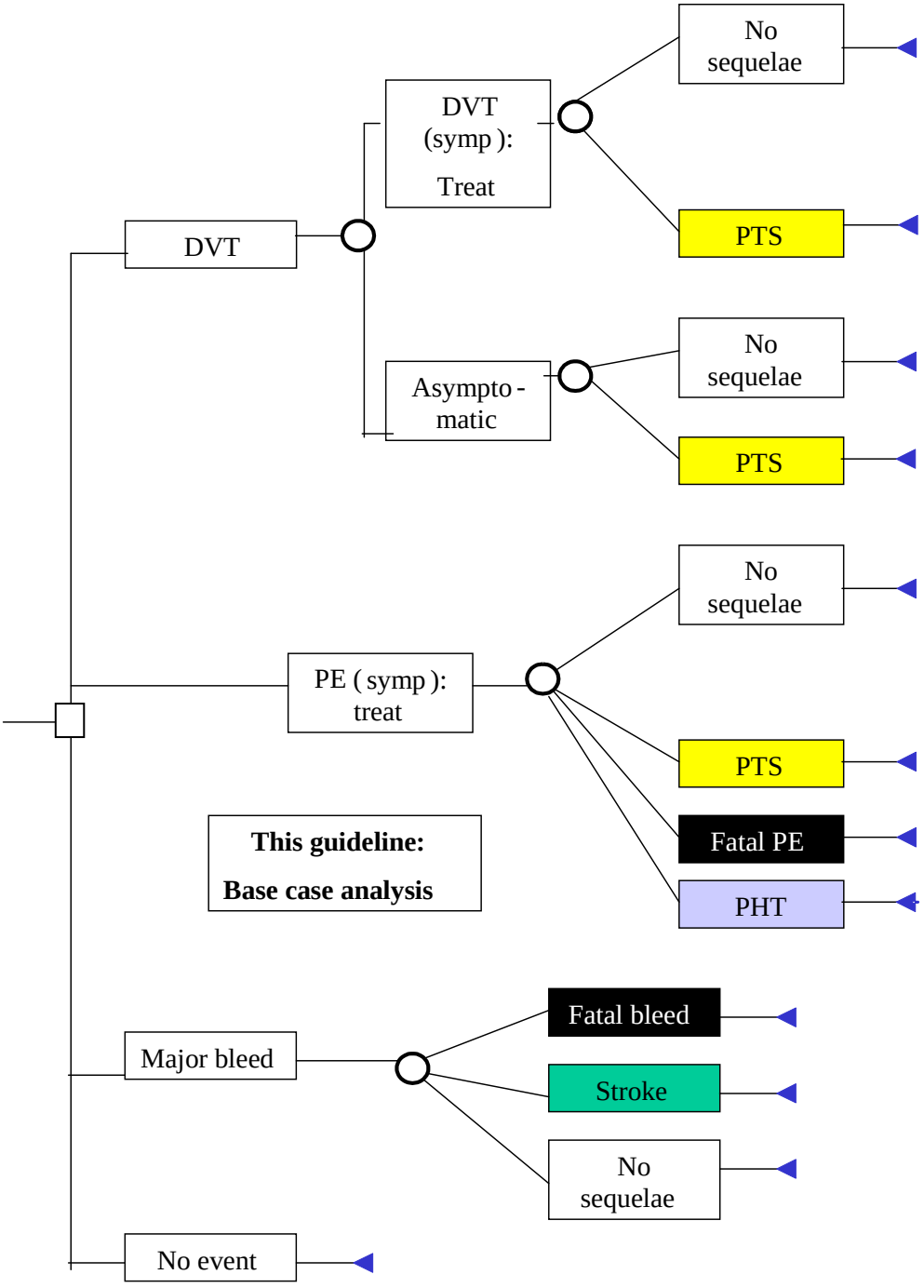


Figure 4-2: Decision tree

PE=pulmonary embolism; PTS=post-thrombotic syndrome, PHT=chronic thrombembolic pulmonary hypertension; symp=symptomatic.

4.2 Relative risks

The between-strategy differences in costs and effects are driven by each strategy's relative risk (RR) reduction for VTE, and its relative risk increase for major bleeding. For example, the number of DVTs occurring under the LMWH strategy is the baseline risk of DVT (in the absence of prophylaxis) multiplied by the DVT RR reduction for LMWH compared with no prophylaxis.

4.2.1 VTE

We use the relative risks from our network meta-analysis of DVT risk (Section 3.10 Methods of combining indirect evidence). These relative risks were estimated in a separate network meta-analysis for each of the five population subgroups. The network meta-analysis uses a simulation approach and therefore for each RR we have a set of (60,000) results. Throughout the guideline, the point estimate for each RR reported is a median of 60,000 simulations. For our probabilistic analysis (see 4.8.1) we sampled 10,000 times from the set of 60,000 relative risks. For our deterministic analysis (i.e. based on point estimates) we used the mean of the 60,000 RRs. We chose the mean (rather than the median, which was used to report the network meta-analysis point estimate - 3.10.2) so that the deterministic results would be as similar as possible to the probabilistic results.

In the model we apply these RR reductions for DVT overall to symptomatic DVT, non-fatal pulmonary embolism, fatal pulmonary embolism, post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension as well as asymptomatic DVT. Thus, if a certain strategy was shown to reduce DVTs by 60% then in the model the incidence of fatal pulmonary embolism etc is also reduced by 60%.

We had conducted separate network meta-analyses for pulmonary embolism. However, these were based on sparse data and therefore the Guideline Development Group decided that the DVT RRs would be more robust estimates of the relative effects of prophylaxis on pulmonary embolism. Hence the pulmonary embolism relative risks were used only in a sensitivity analysis.

4.2.2 Bleeding

We use the mean relative risks (RR) from our network meta-analysis of major bleeding risk (Section 3.10 Methods of combining indirect evidence). These relative risks were pooled across all population subgroups because the data were so sparse that the Guideline Development Group felt that the estimates of major bleeding increase for specific population subgroups would not be sufficiently precise. However, subpopulation-specific estimates were used in a sensitivity analysis.

In the model we apply these RR increases for major bleeding overall to fatal bleeds and strokes as well as non-fatal major bleeding.

We assume that the major bleeding rate for mechanical only strategies is the same as for the nil strategy (i.e. mechanical prophylaxis has no effect on bleeding). This is reasonable on biological grounds.

In the post-discharge analyses the relative risk for major bleeding from the RCTs was less than one for LMWH (implying that LMWH reduces bleeding), although not significantly.

We believe it implausible that LMWH would decrease bleeding and therefore, in these instances for the deterministic analysis we assumed a RR of 1. For the probabilistic analysis we used the RCT point estimate and its standard error.

Similarly the network meta-analysis indicated a substantial reduction in bleeding associated with high-dose aspirin, albeit with wide confidence intervals. Again this seemed highly implausible. We set the major bleeding RR in the model to 1 for both the deterministic and probabilistic analysis. However, we did use the network meta-analysis estimate in a sensitivity analysis. The Guideline Development Group believed that the base case estimate of 1 was still a substantial under-estimate and a higher estimate of 1.3 was also used in a sensitivity analysis from a conventional meta-analysis.

In most cases the network meta-analysis mean RR was very similar to the median RR from the same analysis. In the case of dabigatran in knee replacement surgery it was slightly different. Although the median 0.87 implied a slight reduction in bleeding, the mean 1.001 implied a very slight increase. Since the mean was not less than one, we made no adjustment for dabigatran (unlike aspirin) in the base case. We conducted a sensitivity analysis increasing the risk to the same level as LMWH.

4.2.3 Other complications

The only complications of prophylaxis included in these models are major bleeding (section 4.2.2) and HIT (section 4.3.2), both of which are complications of pharmacological prophylaxis. We believe that these are the most important complications but are aware that there may be others that are also important but difficult to quantify. Mechanical prophylaxis is not without complications. For example a study[158] in stroke patents (section 24.2) found a significant increase in adverse events related to the use of GCS, such as skin breaks, ulcers, blisters or skin necrosis. However, this is a special group of patients and the results are unlikely to be transferrable to other populations. Trials in other populations have not found significant complications and therefore we have not included in our model treatment costs or utility decrements associated with such complications. We do have some survey evidence (section 6.6.1) that reports some patients find stockings uncomfortable (knee-length: 11%; full-length: 21%)[43]. This suggests that there is some disutility (i.e. reduced quality of life) associated with stockings but this disutility is difficult to quantify and might be negligible compared with the patient's underlying condition, especially as the disutility is transient. Perhaps of more concern is that the discomfort might cause patients to wear the stockings incorrectly (especially thigh-length stockings) – this might mean that the effectiveness estimated in trial conditions will not be replicated in practice – but for this reason we have included in our model the cost of nurse time for checking that stockings are fitted correctly(section 4.4.1). The extent to which any of these complications applies to other forms of mechanical prophylaxis is also unclear.

Table 4-3: Baseline risk and other parameters that vary by population subgroup

	Source	Hip Fracture surgery	Total hip replacement (THR)	Total knee replacement (TKR)	General surgery	General medical
Mean age (years)	a) HES 2005-6 [159] b) RCTs from our systematic review (weighted mean)	82(a)	70(a)	70 (a)	60(b)	74(b)

	Source	Hip Fracture surgery	Total hip replacement (THR)	Total knee replacement (TKR)	General surgery	General medical
% Male	a) HES 2005-6[159] b) RCTs from our systematic review	23%(a)	38%(a)	42% (a)	50%(b)	47%(b)
Standardised Mortality Ratio (g)	a) Seagroatt (1994) [595] b) Ramiah (2007) [543] c) Nunley 2003 [494] d) assumed e) Herman Lingen 2001 [277] (f)	461% (a) (1 year)	Men: 85% (b) Women: 98% (b) (10 years)	52% (c) (1 year)	100% (d)	357% (e) (1 year)
Proportion of DVTs that are symptomatic (Ratio of symptomatic DVTs to all DVTs)	a) assumed to be same as THR b) Quinlan (2007) [542] c) RCTs from our systematic review (all patient combined excl TKR & THR)	21.0%(a)	21.0%(b)	5.0%(b)	6.2%(c) (=40/644)	6.2%(c) (=40/644)
Major bleeding fatality rate(h)	a) Muntz (2004)[467] systematic review of thrombo-prophylaxis RCTs b) RCTs from our systematic review	0.8%(a) (=5/632)				14.3%(b) (=8/56)
Pulmonary embolism fatality rate (i)	RCTs in our systematic review	31.0% (=9/29)	6.0% (=11/184)			44.7% (=17/38)
Re-operation rate after major bleed	a) From a review of recent fondaparinux and dabigatran trials [36,175,377,476,651] b) Muntz (2004) [467]	13%(a)			21%(b)	N/A
Baseline risk in the absence of prophylaxis						
DVT risk	No prophylaxis/placebo arms of RCTs from our systematic review (Table 5-17and Table 5-19)	39.8%	45.0%	60.0%	20.9%	13.4%
Symptomatic pulmonary embolism (PE) risk	a) No prophylaxis/placebo arms of RCTs from our systematic review (Table 5-17and Table 5-19) b) An estimate as no studies have presented results for symptomatic PE in the absence of prophylaxis(j).	7.9% (a)	3.4% (a)	1.0% (b)	1.3% (a)	0.9% (a)
Major bleeding risk	No prophylaxis /placebo arms of RCTs from our systematic review (Table 5-20 and Table 5-21)	3.2%	1.6%	1.9%	1.4%	0.4%

(f) Rate calculated from the mortality rate for general medical patients at 1 year (Herman Lingen (2001) [277]) divided by death rate in the general population matched for age and gender. (Office of National statistics (2005)[500].

(g) Standardised Mortality Ratio = Ratio of the death rate in the population subgroup under investigation compared with the death rate in the general population, adjusting for age and sex.

(h) Fatal major bleeds divided by all major bleeds

(i) Fatal PEs divided by all symptomatic PEs

(j) Symptomatic pulmonary embolism in cohort studies with prophylaxis range from 0.2-1.9% [422,674,678,689]

4.3 Baseline risks

Effectiveness and cost-effectiveness are dependent on the change in absolute risk rather than just the relative risk (RR) changes. To estimate absolute risk changes, the model multiplies the RR changes by the baseline risk. We estimated baseline risk of DVT, symptomatic pulmonary embolism and major bleed, from the no prophylaxis arms of the RCTs in our clinical review (Chapter 5 Risk, risk reduction and harm).

Chapter 5 also summarises other differences between population subgroups that are captured by the model. Age, sex and standardised mortality ratio contribute to the estimates of life expectancy and subsequently the magnitude of QALYs gained from averting a fatal pulmonary embolism and the magnitude of QALYs lost from incurring a fatal bleeding event. The baseline risk of events affects the magnitude of total treatment costs (or savings) and the magnitude of total QALYs gained (or lost).

4.3.1 Post-thrombotic syndrome, Chronic thromboembolic pulmonary hypertension and stroke

Some probabilities were assumed, in the absence of evidence, not to vary between population subgroups (Total hip replacement, general medical patient etc.). To estimate the incidence of these symptomatic events we looked for good quality systematic reviews, RCTs or cohort studies for each parameter. We found them primarily by looking at the methods of the economic evaluations retrieved in our systematic reviews but also completed highly specific searches of PubMED to identify other good quality data.

Table 4-4: Symptomatic event rates irrespective of population subgroup

Event	Probability	Source	Method
Proportion of major bleeds that lead to chronic morbidity (i.e. non-fatal strokes)	3%(a)	Muntz (2004)[467] and personal communication from Muntz & Scott (2006)	Systematic review of thromboprophylaxis RCTs
5-year post-thrombotic syndrome rate after symptomatic VTE	25%	Prandoni (1997)[537]	528 consecutive patients with venographically confirmed symptomatic DVT followed for 8 years
5-year post-thrombotic syndrome rate after asymptomatic VTE	15%	Expert opinion – see main text (section 4.3.1). Derived from Wille-Jorgensen (2005)[692]	Meta-analysis of cohort studies (n=364). Follow-up was 2-10 years
2-year chronic thromboembolic pulmonary hypertension rate after symptomatic pulmonary embolism	0.75% (0.5%-1%)	Expert opinion –main text (section 4.3.1). Derived from Miniati (2006)[448]	Cohort study of patients with proven pulmonary embolism (n=320) compared with those without (n=514).

(a) Major bleeds were classified by site of bleeding. The sites were gastrointestinal, surgical site, "other: brain/spine", "other: not brain/spine", and "other: not specified". The stroke rate was estimated as the product of the following two components:
i) The ratio of all 'other site' to all sites=83/378
ii) The ratio of 'other: brain/spine' to ('other: brain/spine' + 'other: not brain/spine' =2/(2+11)
The denominator of ii) is smaller than the numerator of i) because in the majority of cases the exact site was not recorded.

In the case of **post-thrombotic syndrome (PTS)** after a *symptomatic DVT* we used the 5-year incidence from a case series of 528 patients[537]. We assumed the incidence of preventable PTS after symptomatic *pulmonary embolism* to be the same as after a symptomatic DVT. In the case of preventable PTS after an *asymptomatic DVT* we used the incidence from a meta-analysis of 10 cohort studies of over 1200 patients [692]. This study estimated the incidence of preventable PTS to be 8% by comparing the exposure arm rate with the control arm. The Guideline Development Group felt that this was a significant under-estimate and specifically that some of the episodes of PTS observed in the control arm were also attributable to an unidentified DVT occurring during the same episode. The group was split between using the 8% incidence or the 21% rate observed in the exposure arm. So for the base case we used the mid-point of 15%; the other figures were used in sensitivity analyses.

The 2-year incidence of **chronic thromboembolic pulmonary hypertension** (CTEPH) after a symptomatic pulmonary embolism was estimated to be around 1%[448]. However the number of these cases that would be due to a single event and hence would be preventable from a single course of prophylaxis might be half this. Hence we estimate the incidence of preventable CTEPH to be between 0.5% and 1%. In the base case analysis we used the mid-point 0.75%; the other figures were used in sensitivity analyses.

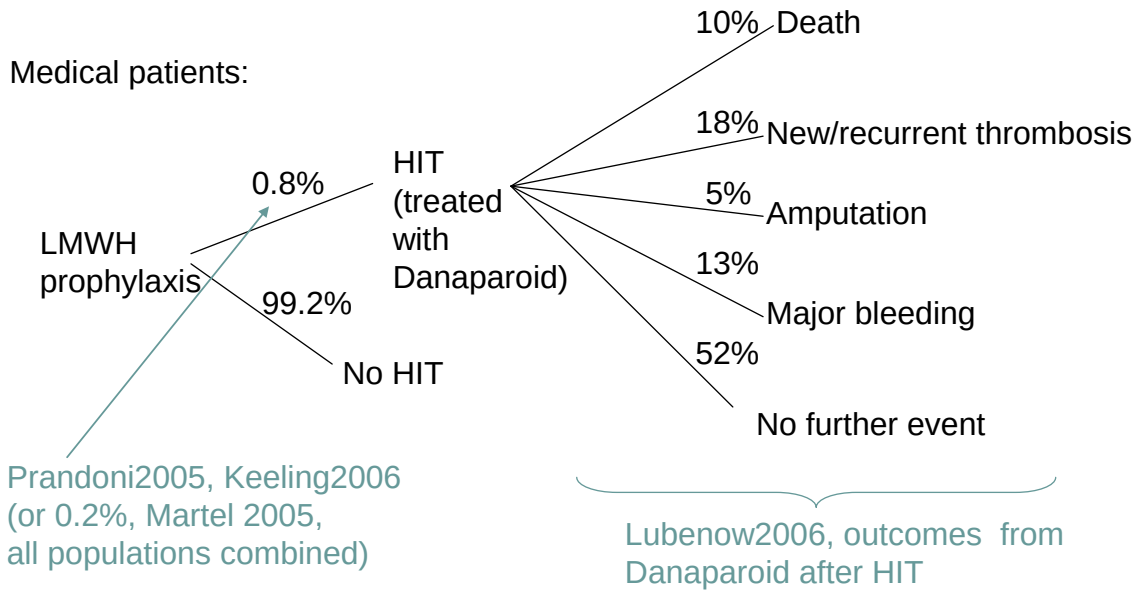
Some major bleeding episodes will have long-term health consequences, notably if the bleed is intracranial or spinal (for simplicity we use the term 'Stroke') (Figure 4-2: Decision tree). We estimated the proportion of bleeds that would fall in to this category to be about 3%, using data from a systematic review of bleeding in VTE prophylaxis RCTs (Chapter 5).

Table 4-5: Incidence of heparin induced thrombocytopenia (HIT) from VTE prophylaxis

	Orthopaedic Surgery	General surgery	General medical
UFH	5% [392]	5% Assumed same as orthopaedic	0.8% [223]
LMWH	0.5% [392]	0.5% Assumed same as orthopaedic	0.8% [536]

4.3.2 Heparin induced thrombocytopenia

The thromboembolic events associated with heparin induced thrombocytopenia (HIT) should be already included within the trial data going in to the model, at least partially, hence it is not explicitly included in the base case analysis. However, we do consider some additional costs and health losses associated with HIT in a sensitivity analysis (see 0). There were little data on heparin-induced thrombocytopaenia in the RCTs and we have not conducted a systematic review of HIT incidence. We have therefore used the figures cited in the British Committee for Safety in Haematology (BCSH) guideline on the management of HIT [332]. We have also looked at a meta-analysis [427], although this doesn't differentiate by category of patient. We use these estimates from this paper (LMWH 0.2%, UFH 2.6%) as an alternative sensitivity analysis.



For surgical patients the sub-tree is the same except that the incidence of HIT is 0.5% instead of 0.8% - see Table 4-5.

Figure 4-3: Heparin induced thrombocytopenia (HIT) sub-tree

The BCSH guidelines recommend danaparoid or lepirudin for the treatment of HIT. We used danaparoid since this was more easily costed, being a fixed dose. A search of PubMed revealed a single paper that evaluated the outcomes after HIT for patients treated with danaparoid [412].

Figure 4-3 shows a sub-tree that indicates the course of HIT used to determine the costs and lost QALYs attributable to HIT. HIT was assumed to affect only UFH or LMWH but not any of the other drug or mechanical strategies.

4.4 Resource use & cost

4.4.1 Prophylaxis

The unit costs of mechanical prophylaxis are given in Table 4-6. Equipment was assumed to have a life expectancy of five years. Drug prices were taken from the current British National Formulary BNF[313] for the recommended thrombo-prophylactic-dose (Table 4-7).

In deciding on the duration of prophylaxis we wanted to reflect the average duration of prophylaxis in the RCTs in our review such that there is consistency between the effect size and intervention cost in the model. However, we also wanted to reflect the licensed dose. We compiled this information in a table and then set a duration that was specific to the population subgroup but constant across the different strategies being compared for that subgroup (Table 4-8). These ranged between 7 and 10 days – longer duration prophylaxis is considered separately 4.7.

We added the cost of nurse time and monitoring tests for each intervention (Table 4-9).

We had difficulty in finding costs for foot impulse device sleeves. In the base case analysis we assumed the same cost as for an IPCD sleeve. After stakeholder consultation, one manufacturer informed us that a typical contract would supply the equipment rent-free and charge £40 for a sleeve to be used for 7 days (£20 for one suitable for use over 2 days). This information arrived too late to be used in our base case analysis but was used in a sensitivity analysis.

Table 4-6: Mechanical prophylaxis unit costs

Component of mechanical prophylaxis	Cost	Source
Anti-embolism stockings – 2 pairs per patient	£6.36 per pair	PASA (2009 Catalogue) average of all brands.
Intermittent pneumatic compression (equipment)	£471.80	PASA (2009 Catalogue)
Intermittent pneumatic compression (sleeves) - 1 pair per patient)	£26.12	PASA (2009 Catalogue)
Foot impulse device (equipment)	£2,228	Submitted by manufacturer
Foot impulse device (pads)	£26.12	Assumed the same as for IPCD sleeves

BNF=British National Formulary, PASA=NHS Purchasing and Supplies Agency

Table 4-7: Pharmacological prophylaxis – information and prices from the British National Formulary

Drug	Dose	Injections per day	Drug cost per day
UFH	5000 units subcutaneous every 8 hours	3	£2.76
LMWH (Medical)	Average of: Dalteparin 5000 units subcutaneous daily Enoxaparin 4000 units subcutaneous daily	1	£3.51
LMWH (General Surgery)	Average of high dose (see dose for major orthopaedic surgery) and moderate dose: Bemiparin 2500 units subcutaneous daily Dalteparin 2500 units subcutaneous daily Enoxaparin 2000 units subcutaneous daily Tinziparin 3500 units subcutaneous daily	1	£3.34
LMWH (Major orthopaedic surgery)	Average of: Bemiparin 3500 units subcutaneous daily Dalteparin 5000 units subcutaneous daily Enoxaparin 4000 units subcutaneous daily Tinziparin 4500 units subcutaneous daily	1	£3.84
Fondaparinux sodium	2.5mg subcutaneous daily	1	£6.66
Vitamin K antagonist (Warfarin)	Dose is adjustable. [Assumed average of 4mg per day]	N/A	£0.04
Aspirin (High dose)	Aspirin is not licensed specifically for thromboprophylaxis [A typical aspirin dose from the RCTs in our review is 1000mg]	N/A	£0.19
Aspirin (Low dose)	Aspirin is not licensed specifically for thromboprophylaxis [A typical aspirin dose from the RCTs in our review is 300mg]	N/A	£0.06
Dabigatran	220mg daily	N/A	£4.20
Rivaroxaban	10mg daily	N/A	£4.50

Table 4-8: Duration of prophylaxis, by population subgroup

	HFS	THR	TKR	GS	GM
Duration of prophylaxis indicated in British National Formulary					
Bemiparin (Zibor)	8 - 11	8 - 11	8 - 11	8 - 11	N/A
Dalteparin (Fragmin)	6 - 8	36	6 - 8	6 - 8	Not time limited
Enoxaparin (Clexane)	8 - 11	8 - 11	8 - 11	8 - 11	6 - 14
Tinziparin (Innohep)	8 - 11	8 - 11	8 - 11	8 - 11	N/A
Fondaparinux (Arixtra)	Longer than 6-10	Longer than 6-10	6 - 10	6 - 10	6 - 14
Dabigatran* (Pradaxa)	N/A	28 - 35	10	N/A	N/A
Rivaroxaban (Xarelto)	N/A	35	14	N/A	N/A
Average duration of prophylaxis in RCTs in our clinical review (excluding extended duration					

prophylaxis)					
Any drug / device	13	10	11	7	10
Duration of prophylaxis costed in the model excluding extended duration prophylaxis (derived from all of the above)					
Any drug / Device	10	10	10	7	10

Table 4-9: Prophylaxis - testing & nurse time

Drug	Tests required (b)	Nurse time(a) associated with administering and monitoring prophylaxis
UFH	Full blood count: baseline (plus the day after start if previous exposure to UFH) then alternate days from day 4-14 (BCSH guidelines, Keeling 2006[332])	2-3 minutes per injection
LMWH	Full blood count: baseline then every 2-4 days until day 14 (BCSH guidelines, Keeling 2006[332])	2-3 minutes per injection
Fondaparinux	-	2-3 minutes per injection
Vitamin K antagonist (Warfarin)	International Normalised Ratio (INR) tests: approximately 3 per week during hospital stay	10-20 minutes per day
Aspirin	-	2-3 minutes per day
Mechanical	-	5-10 minutes per day
Dabigatran	Baseline liver function test	2-3 minutes per day
Rivaroxaban	-	2-3 minutes per day

(a) Staff nurse cost of £22 per hour - Unit Costs of Health and Social Care 2007[139]
(b) The tests were costed at £2.92 per test, the average for a haematology test plus £2.82 phlebotomist cost (NHS Reference Costs 2006/7)[161].

4.4.2 VTE treatment

To devise resource use protocols for diagnosing and treating VTEs, we examined the British Thoracic Society guidelines on the management of pulmonary embolism[86] and British Committee for Standards in Haematology (BCSH) guidance on the prophylaxis and treatment of DVT[332,333]. Members of the VTE (surgical) Guideline Development Group helped develop treatment protocols that could be costed. We have sought to develop protocols that would be considered achievable good practice currently in the NHS. Unit costs were taken from standard NHS sources: NHS reference costs[161], British National Formulary[313], NHS Electronic Drug Tariff [483], NHS Purchasing and Supplies Agency[484], Unit Costs of Health and Social Care 2007[139] (Table 4-10).

In clinical practice there would be no treatment cost associated with asymptomatic DVT. We have assumed that the incremental treatment cost of fatal pulmonary embolism (and fatal bleeding) is £0 - on the one hand treatment of the event would generate additional health service costs but on the other hand the treatment costs for the illness they were admitted will be curtailed.

In the absence of more detailed information, we have assumed that the cost of treating a VTE (or major bleeding episode) does not vary by which population subgroup the patient was from (hip fracture, general surgery, etc).

4.4.3 Post-thrombotic syndrome & chronic thromboembolic pulmonary hypertension

For post-thrombotic syndrome (PTS), chronic thromboembolic pulmonary hypertension (CTEPH) and stroke, the treatment pathways are varied and complex and therefore we took from the literature, costs estimated from relevant cohort studies of patients (Table 4-11). We found these sources primarily by looking at the methods of the economic evaluations retrieved in our systematic reviews but also did quick searches of HEED and PubMED to see if there we could find other good quality data.

Table 4-10: VTE diagnosis and treatment costs

	Symptomatic DVT	Non-fatal Symptomatic pulmonary embolism	Source for resource use	Unit cost	Source for unit cost
Diagnosis					
Doppler ultrasound	1	-	Published guidelines	£64 per test	NHS reference costs 2006/07 [161] (RA24Z)
CT pulmonary angiogram	-	1	Published guidelines	£101 per test	NHS reference costs 2006/07 [161] (RA08Z)
Chest x-ray	-	1	Expert opinion	£29 per test	NHS reference costs 2006/07 (RA28Z)
ECG	-	1	Expert opinion	£27 per test	NHS reference costs 2006/07 [161] (DA01)
D-dimer	1	1	Expert opinion	£12 per test	NHS Health Technology Assessment report on diagnostic strategies for DVT[228]
Emergency admission	1	1	Expert opinion	£38	NHS reference costs 2006/07 [161] (VB112)
Treatment					
LMWH	7 days	7 days	Published guidelines	£8.02 per day	Mean of treatment dose regimens - BNF July 2008 [313]
Full blood count	2	2	Expert opinion	£5.74 per test	NHS reference costs 2006/07 [161] (including £2.82 phlebotomist cost)
Vitamin K antagonist (Warfarin)	3 months x 69% (distal) 6 months x 31% (proximal)(a)	6 months	Published guidelines	£0.04 per day	British National Formulary July 2008[313]
Extended hospital stay	10% x 4 days	90% x 6 days	VERITY database (c) for % / NHS reference costs 2005 for LOS[160]	£192 per day(b)	NHS reference costs 2006/07 [161]
Instruction on self-administration of LMWH (nurse time)	90% x 30 minutes	10% x 30 minutes	Expert opinion	£22 per hour	Unit Costs of Health and Social Care 2007[139]

	Symptomatic DVT	Non-fatal Symptomatic pulmonary embolism	Source for resource use	Unit cost	Source for unit cost
ICU stay	-	10% x 7days	Expert opinion	£1,180 per day	NHS reference costs 2006/07 [161] (XC07ZTHE)
Graduated compression stockings (thigh-length 25-35mmHG at ankle)	6 pairs over 2 years	6 pairs over 2 years	Expert opinion	£13.11 per pair	NHS Electronic Drug Tariff – July 2008 [483]
Anticoagulation clinics (including cost of INR testing)	Distal = 9 visits Proximal = 12 visits	12 visits	Expert opinion	£24 first visit; £18 for each follow-up visit	NHS reference costs 2006/07[161]
Ambulance transport to anticoagulation clinic	5-10% of visits	5-10% of visits	Portsmouth and North Middlesex hospitals 2005/6	£57 for return visit	NHS reference costs 2007/08[162]

INR=International Normalised Ratio
(a) The ratio of proximal DVTs to all DVTs was estimated from the RCTs in our review that reported the incidence of both: (1,991/34,704)/(6,467/35,256)=(6%/18%)=31%
(b) Average cost of an excess bed-day for Healthcare Resource Group codes EB11Z, DZ09A, DZ09B, DZ09C (elective and non-elective).
(c) National Venous Thromboembolism Registry[661]

Table 4-11: Other treatment unit costs

Event	Unit cost	Source	Method
Stroke (first year)	£8397	Grieve et al (2000)[237]	328 NHS patients followed prospectively for 12 months after stroke (inflated to 2006/7 prices)
Stroke (subsequent years)	£4826 per year	NICE Stroke guideline, 2008[477]	Assuming that 38% dependent stroke and 62% independent stroke.
Post-thrombotic syndrome	£653 per year	Average of: 1) Bergqvist et al (1997)[55] 2) Goodacre et al [228]– Health Technology Assessment (HTA) report	1) Retrospective cohort study of 250 Swedish patients followed for 15 years after first symptomatic DVT (converted to UK£ and inflated to 2006/7 prices) 2) Protocol derived for the NHS HTA cost-effectiveness analysis.
Chronic thromboembolic pulmonary hypertension	£1219 per month	NICE technology appraisal on Pulmonary arterial hypertension (adults) - drugs due for publication in 2009 [478]	Overall total cost for New York Heart Association class II functional status per 4 weeks
Major bleeding without re-operation	£722	NHS reference costs 2006/07[161]	Mean cost of a gastro-intestinal bleeding treatment episode (HRG codes: FC08A, FC08B, FC08C (non-elective and elective)
Re-operation (General Surgery)	£1224	NHS reference costs 2006/07[161]	Mean cost of an episode of gastro-intestinal bleeding with major procedure (HRG codes: FA16Z,

			FB06Z (non-elective and elective)
Re-operation (Orthopaedic surgery)	£2154	NHS reference costs 2006/07[161]	Mean cost of a non-trauma minor hip operation (HRG codes: HB15B, HB15C, HB16B, HB16C)
Amputation after heparin induced thrombocytopenia (HIT) – sensitivity analysis only	£32,253 (lifetime)	Patrick et al (2007)[513]	From a cost-utility analysis of strategies for the management of heparin induced thrombocytopenia (HIT)

HRG=Healthcare Resource Group

In the case of post-thrombotic syndrome (PTS) we did not find a suitable cohort based in the UK but we found:

1) A retrospective cohort study of 250 Swedish patients followed for 15 years after first symptomatic DVT[55] (converted to UK£ using purchasing power parities(www.oecd.org/std/ppp November 2008) and inflated to 2006/7 prices using the hospital pay and prices index[139]). Using only post-thrombotic syndrome (PTS) costs (and not recurrent VTE) it was £244 per patient-year. This figure was per patient having a DVT. Assuming an incidence of PTS of 25% in this DVT group (section 4.3.1), this makes £977 per PTS patient per year.

2) An annual protocol derived for an NHS Health Technology Assessment[228] cost-effectiveness analysis consisting of one new vascular surgery outpatient visit, two follow-up vascular surgery outpatient visits and two GP visits. Using current UK costs[139] we re-calculated this to be £329 per year.

Both have advantages and disadvantages: the Swedish study was a well-conducted empirical study but may not be applicable to a UK setting. The Health Technology Assessment is highly relevant but based only on expert opinion. Hence we used a simple average of these two estimates, which came to £653 per year.

For chronic thromboembolic pulmonary hypertension (CTEPH) we derived a monthly cost that is based on an ongoing NICE technology appraisal of pulmonary arterial hypertension in adults[478] We have estimated the cost of CTEPH by adding together the cost of active and supportive therapy as well as the cost associated with primary and secondary care resource use. We took the average cost of bosentan, sitaxentan and sildenafil. We included in the supportive therapy package the cost of oxygen requirement associated with patients in New York Heart Association class II functional status. We also considered this functional status while estimating the cost associated with the use of primary and secondary care resources. We estimated £1,219 as the overall cost of CTEPH per four weeks. This included £1143, the average cost of bosentan, sitaxentan and sildenafil only. In a one-way sensitivity analysis, the cost of active therapies was the average cost of bosentan, sitaxentan, sildenafil, iloprost and epoprostenol. This was £2097, the average cost of the five active therapies. There are different unit costs for the use of epoprostenol in in the first and second year. The four weekly cost of epoprostenol used in the sensitivity analysis was the cost to be incurred in the first year, which was £4283. In a one-way sensitivity analysis, we therefore estimated £2173 as the overall cost of CTEPH per four weeks.

4.4.4 Bleeding & stroke

The cost of treating major bleeding was assumed to vary primarily according to whether there was a decision to re-operate (Table 4-11).

We have been advised that although the cost of a hip revision after infection can be substantial, such cases are rare. Hence we used the cost of a minor hip operation for the cost of a re-operation due to major bleeding (Table 4-11).

For patients with stroke, we used a cost of £8397 first year and £4826 for subsequent years (NICE acute stroke guideline)[477] (Table 4-11).

We hypothesised that the cost of treating major bleeding might vary by prophylaxis strategy due to substantial differences in the cost of antidotes. But in the end we decided that this would be difficult to substantiate, especially given that the prophylaxis is unlikely to be identified as the main cause of the major bleeding. So antidote costs were not explicitly incorporated.

4.4.5 Heparin induced thrombocytopenia (HIT)

The thromboembolic events associated with heparin induced thrombocytopenia (HIT) should be at least partially included within the trial data going in to the model, hence it is not specifically included in the base case analysis.

However, as a sensitivity analysis we assumed the pathway presented in Figure 4-3. The cost of danaparoid was £507 for a prophylactic-dose of 750 units twice daily for on average 8.5 days[313]. The costs associated with death, major bleeding, and no event are the same as for the main model. A new or recurrent VTE was costed the same as a pulmonary embolism in the main model. The cost of amputation was from a US study of the cost-effectiveness of different heparin induced thrombocytopenia (HIT) treatment strategies[513] converted to UK prices using purchasing power parities (www.oecd.org/std/ppp November 2008).

4.5 Life expectancy

4.5.1 Fatal events

Naturally for patients dying during hospitalisation, their expected life-years in the model is zero.

• Fatal pulmonary embolism

• Fatal bleeding event

4.5.2 Patients surviving *without* long-term complications

For patients surviving surgery we estimated life expectancy using a combination of population subgroup-specific data (Table 4-3) and general population data.

• For hip fracture surgery, general surgery and medical patients, from 12 months we had to assume age/sex-specific life expectancy for England & Wales (Source: Government Actuary Department 2007)

• For these patients, for the first 12 months we applied standardised mortality ratios to the relevant England and Wales mortality rate, so that for the first year after surgery we are using disease-specific mortality. Another adjustment was then made to subtract

from this mortality the mortality already captured in the model, so that we don't double count deaths.

• For total hip replacement we were able to apply standardised mortality ratios for 10 years.

4.5.3 Patients surviving *with* long-term complications

In the absence of specific evidence, it was assumed that the life expectancy of patients with preventable **post-thrombotic syndrome** was the same as for other patients in their population subgroup who do not experience post-thrombotic syndrome.

For patients with **chronic thromboembolic pulmonary hypertension,** we assumed a life expectancy of 5 years (treated)[71,133].

For patients with **stroke,** we assumed a life expectancy of 4.5 years (NICE acute stroke guideline).

Table 4-12: Quality of life weights (utilities) for health outcomes

Health state	Utility	Source	Duration of health state after initial event
No long term event (general population average)	0.82	EQ5D instrument completed by 3395 people resident in the UK[347]	Lifetime
Asymptomatic DVT/pulmonary embolism	0.82	Assumed to be the same as the UK average	Lifetime
Warfarin treatment after symptomatic VTE	0.82x0.99 =0.81	Time trade-off, 70 patients with atrial fibrillation[203]	3 months distal 6 months proximal 6 months pulmonary embolism (then return to usual quality of life)
Post-thrombotic syndrome	0.82x0.982 =0.805	O'Meara et al 1994 (severe)[497]	Lifetime
Pulmonary embolism (symptomatic)	0.82*0.94 =0.771	Goodacre et al 2006 [228]	1 month then treatment with vitamin k antagonists(a)
Chronic thromboembolic pulmonary hypertension (CTEPH)	0.765	NICE guideline on pulmonary arterial hypertension [205,348]	Life expectancy: 5 years
Major Bleeding	0.50	Sarasin et al 2000[584] (temporary disability following major gastrointestinal hemorrhage) (based on expert opinion)	1 month then return to usual quality of life*

Stroke	0.52	The FOOD Trial Collaboration, Lancet 2005 EQ5D, 3086 stroke patients in an RCT[634]	Life expectancy: 4¼ years
Amputation after heparin induced thrombocytopenia (HIT) – sensitivity analysis only	0.73	A review in a cost-utility analysis of strategies for the management of heparin induced thrombocytopenia (HIT) [513]	Life time
Fatal Bleeding	N/A		
Fatal Pulmonary Embolism	N/A		

(a)These are assumed since the utility data relate to an acute event.

4.6 Quality of life weightings

We have sought to find quality of life weightings in the published literature, firstly by looking at source data for cost-utility studies included in our review and also by searching the Cost-effectiveness Analysis Registry's Catalog of preference scores[3]. The scores in Table 4-12 were combined with the life expectancy data to estimate QALYs.

For patients with no event, we used the population average quality of life for England and Wales measured using the EQ5D, a widely used and validated measure of overall health-related quality of life.

For other long-term states we took scores from well-conducted studies in the published literature.

4.7 Post-discharge / extended duration prophylaxis

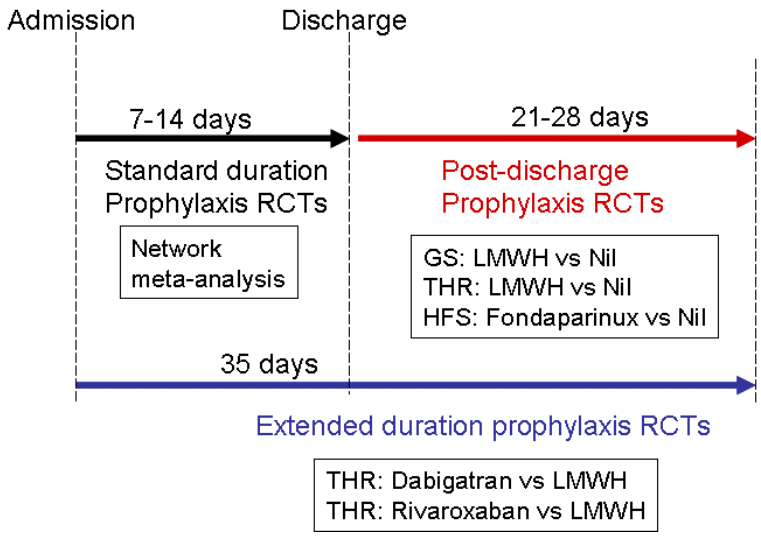


Figure 4-4: Post-discharge and Extended prophylaxis RCTs

We did not include trials that administered prophylaxis for longer than 20 days in our network meta-analyses – typically they were 7-10 days duration. Our main model, which we describe as the standard duration prophylaxis model was based on these trials. Other trials considered longer durations, these were distinguished in to two categories: post-discharge prophylaxis (which start at discharge) and extended duration prophylaxis (which start at admission and continue well beyond discharge) – see Figure 4-4.

There were trial data available on bleeding, pulmonary embolism and major bleeding for the following population subgroups:

- Hip fracture surgery (LMWH vs Nil post-discharge)
- Total hip replacement (LMWH vs Nil post-discharge)
- Total hip replacement (Dabigatran vs LMWH extended duration; Rivaroxaban vs LMWH extended duration)
- General surgery (LMWH vs Nil post-discharge) – most of the patients in these trials were cancer patients.

We modelled the cost-effectiveness of each of these comparisons using the same methods and data as for standard duration prophylaxis. The few differences are outlined as follows.

Table 4-13: Data for post-discharge / extended prophylaxis models

	Hip fracture surgery: post-discharge	Total hip replacement: post-discharge	Total hip replacement: extended duration	General surgery: post-discharge
	Fondaparinux vs Nil	LMWH vs Nil	Dabigatran vs LMWH; Rivaroxaban vs LMWH	LMWH vs Nil
	176	47,132,142,272,378,526	476,479	46,384,547
Relative risks				
DVT	0.04 (0.01, 0.13)	0.41 (0.31, 0.54)	0.80 (0.55, 1.18); 0.22 (0.12, 0.41)	0.46 (0.29, 0.73)
Major bleeding	4.02 (0.86, 18.81)	0.32(a) (0.01, 7.80)	1.29 (0.70, 2.37); 3.02 (0.61, 14.95)	0.83(a) (0.22, 3.12)
Baseline risks				
DVT	33.9%	25.5%	4.4%	10.5%
Pulmonary embolism	0.9%	0.6%	0.2%	0.8%
Major bleeding	0.6%	0.2%	0.4%	0.9%
Other				
Duration of prophylaxis (days)	28	24	35	21

(a)The GDG considered it implausible that these were less than 1 and so they were set to 1 in the deterministic analyses.

4.7.1 Risks

For post-discharge and extended duration prophylaxis we simply used the relative risks compared with no post-discharge from our direct comparison meta-analyses – summarised in Chapter 6. Baseline risks were also from the trials.

4.7.2 Resource use and cost

The duration of prophylaxis was determined by the RCTs – Table 4-8. This was used to calculate the cost of each prophylactic intervention.

We also assumed that 8% of patients would require daily visits from the district nurse to give the injection. This is on the basis of two surveys, which both found that 8% of patients could not comply with administering their own LMWH prophylaxis[128,614]. The patients in these studies were not particularly frail, and therefore in older populations compliance with self-injection might be less. However, we have anecdotal evidence from within our Guideline Development Group and a stakeholder, that self-injection rates (including injection by family members/carers) of greater than 90% are achievable even in hip fracture patients. There maybe some monitoring costs involved but these are difficult to quantify and have not been included in the model.

4.8 Sensitivity analyses

4.8.1 Probabilistic sensitivity analysis

The **deterministic analysis** gives us a point estimate of additional cost, QALYs gained and incremental net benefit (INB) by using only the point estimates of each model parameter. In the **probabilistic analysis** we assign a probability distribution to each parameter (including the relative risk estimates). These probability distributions reflect the standard error of each parameter estimate. For the probabilistic analysis we randomly select from each parameter distribution simultaneously and calculate the cost, QALYs and INB. We then repeat this 5000 times such that we have a set of 5000 estimates of INB reflecting the uncertainty in our parameters. This process is known as Monte Carlo simulation. The analysis can take into account the covariance between different model parameters. However often we are unsure of the magnitude of the covariance and in these circumstances the analysis treats the model parameters as if they were independent of each other.

The best strategy is then the one that has the highest mean INB, averaged across all the 5000 simulations. This strategy may or may not be the one which was cost-effective in more simulations than any other simulation.

The estimates of relative risk in our deterministic analysis were taken from the network meta-analysis – this method is simulation based and therefore the output gives not just a point estimate for each relative risk (RR) but also an entire distribution of 60,000 RR estimates. In each of our 5000 simulations in our probabilistic analysis we randomly sampled from the 60,000 estimates of RR from our network meta-analysis. Each time, for the different strategies (e.g. LMWH vs Nil, LMWH vs fondaparinux and fondaparinux vs nil) we selected from the same network meta-analysis iteration to preserve the covariance between the different relative risk estimates.

For other model parameters we had to define the distribution. The distributions used reflect the nature of the data, so for example probabilities were given a beta distribution, which is bounded by zero and one – see Table 4-14. All of the variables that were probabilistic in the model and their distributional parameters are detailed in

Table 4-15 and Table 4-16.

For simplicity the following variables, were left deterministic (i.e. were not varied in the probabilistic analysis: Age, % male, standardised mortality ratio (since these were deemed to be fixed by the scenario) drug prices (which were subject to a deterministic sensitivity analysis – see below), and the discount rate and cost-effectiveness threshold (which were deemed to be fixed by NICE).

Table 4-14: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
Proportion	Beta	Bounded on 0 – 1 interval. Derived from sample size, number of patients experiencing events
Cost	Gamma	Bounded at 0, positively skewed. Derived from mean and standard error
Length of stay / duration of prophylaxis	Lognormal	Bounded at 0. Derived from log(mean) and standard error
Utility	Beta	Bounded on 0 – 1 interval. Derived from mean and standard error
Relative risk	Lognormal	Bounded at 0. Derived from log (mean) and standard error

Table 4-15: Baseline risk parameters used in the probabilistic sensitivity analysis (a)

Parameter description	Point estimate	Distribution parameters
General surgery		
DVT	20.9%	$\alpha = 860, \beta = 3255$
Symptomatic pulmonary embolism	1.3%	$\alpha = 99, \beta = 7315$
Major bleeding	1.4%	$\alpha = 104, \beta = 7517$
Symptomatic DVT / All DVT	6.2%	$\alpha = 40, \beta = 604$
Pulmonary embolism fatality rate	6.0%	$\alpha = 11, \beta = 173$
Major bleeding fatality rate	0.8%	$\alpha = 5, \beta = 627$
General Medical		
DVT	13.4%	$\alpha = 106, \beta = 685$
Symptomatic pulmonary embolism	0.9%	$\alpha = 24, \beta = 2661$
Major bleeding	0.4%	$\alpha = 11, \beta = 2864$
Symptomatic DVT / All DVT	6.2%	$\alpha = 40, \beta = 604$
Pulmonary embolism fatality rate	44.7%	$\alpha = 17, \beta = 21$
Major bleeding fatality rate	14.3%	$\alpha = 8, \beta = 48$
Hip fracture surgery		
DVT	39.8%	$\alpha = 471, \beta = 712$
Symptomatic pulmonary embolism	7.9%	$\alpha = 63, \beta = 734$
Major bleeding	3.2%	$\alpha = 29, \beta = 877$
Symptomatic DVT / All DVT	21.0%	$\alpha = 223, \beta = 840$
Pulmonary embolism fatality rate	31.0%	$\alpha = 9, \beta = 20$
Major bleeding fatality rate	0.8%	$\alpha = 5, \beta = 627$
Total hip replacement		
DVT	45.0%	$\alpha = 530, \beta = 648$
Symptomatic pulmonary embolism	3.4%	$\alpha = 32, \beta = 909$
Major bleeding	1.6%	$\alpha = 25, \beta = 1538$
Symptomatic DVT / All DVT	21.0%	$\alpha = 223, \beta = 840$
Pulmonary embolism fatality rate	6.0%	$\alpha = 11, \beta = 173$
Major bleeding fatality rate	0.8%	$\alpha = 5, \beta = 627$
Total knee replacement		
DVT	60.0%	$\alpha = 65, \beta = 43$
Symptomatic pulmonary embolism	1.0%	[kept deterministic]
Major bleeding	1.9%	$\alpha = 4, \beta = 270$
Symptomatic DVT / All DVT	5.0%	$\alpha = 17, \beta = 320$
Pulmonary embolism fatality rate	0.8%	$\alpha = 5, \beta = 627$
General surgery (post-discharge)		
DVT	10.5%	$\alpha = 53, \beta = 454$

Parameter description	Point estimate	Distribution parameters
Symptomatic pulmonary embolism	0.8%	α = 4, β = 490
Major bleeding	0.9%	α = 5, β = 570
Symptomatic DVT / All DVT	6.2%	α = 40, β = 604
Pulmonary embolism fatality rate	6.0%	α = 11, β = 173
Major bleeding fatality rate	0.8%	α = 5, β = 627
Total hip replacement (post-discharge)		
DVT	25.5%	α = 136, β = 397
Symptomatic pulmonary embolism	0.6%	α = 5, β = 889
Major bleeding	0.2%	α = 1, β = 531
Symptomatic DVT / All DVT	21.0%	α = 223, β = 840
Pulmonary embolism fatality rate	6.0%	α = 11, β = 173
Major bleeding fatality rate	0.8%	α = 5, β = 627
Hip fracture surgery (post-discharge)		
DVT	33.9%	α = 74, β = 144
Symptomatic pulmonary embolism	0.9%	α = 3, β = 327
Major bleeding	0.6%	α = 2, β = 327
Symptomatic DVT / All DVT	21.0%	α = 223, β = 840
Pulmonary embolism fatality rate	31.0%	α = 9, β = 20
Major bleeding fatality rate	0.8%	α = 5, β = 627
Total hip replacement (extended)		
DVT	4.4%	α = 110, β = 2398
Symptomatic pulmonary embolism	0.2%	α = 5, β =2452
Major bleeding	0.4%	α = 20, β = 3360
Symptomatic DVT / All DVT	21.0%	α = 223, β = 840
Pulmonary embolism fatality rate	6.0%	α = 11, β = 173
Major bleeding fatality rate	0.8%	α = 5, β = 627

(a) The type of distribution used was beta distribution and the sources of the parameters are given in Table 4-3

Table 4-16: Parameters and parameter distributions used in the probabilistic sensitivity analysis that are common to each population subgroup

Parameter description	Point estimate	Probability distribution	Distribution parameters
Baseline Risk			
Post-thrombotic syndrome after symptomatic DVT	25.%	Beta	α = 132, β = 396
Post-thrombotic syndrome after asymptomatic DVT	15.%	Beta	α = 77, β = 436
Cost (£)			
DVT	575.72	Gamma	Mean = 575.72, se = 73.43
Symptomatic (non-fatal) pulmonary embolism	2521.19	Gamma	Mean = 2521.19, se = 321.58
Medical management of major bleeding	721.92	Gamma	Mean = 721.92, se = 92.08
Post-thrombotic syndrome	7551.31	Gamma	Mean = 7551.31, se = 963.12
Chronic thromboembolic pulmonary hypertension	69,122.53	Gamma	Mean = 69,122.53, se = 8816.65
Stroke	22,969.10	Gamma	Mean = 22,969.10, se = 2929.73
Anti-embolism stockings (prophylaxis)	6.36	Gamma	Mean = 6.36, se = 0.81
Anti-embolism stockings (treatment)	13.11	Gamma	Mean = 13.11, se = 1.67
FID (equipment)	2228.00	Gamma	Mean = 2228.00, se = 284.18
IPCD (equipment)	471.80	Gamma	Mean = 471.80, se = 60.18

Parameter description	Point estimate	Probability distribution	Distribution parameters
IPCD (consumable)	26.12	Gamma	Mean = 26.12, se = 3.33
Tests (Full blood count, international normalized ratio)	2.92	Gamma	Mean = 2.92, se = 0.37
Cost of nursing time (staff nurse) (£)	22.00	Gamma	Mean = 22.00, se = 2.81
Cost of nursing time (district nurse) (£)	20.00	Gamma	Mean = 20.00, se = 2.55
Others			
Proportion of major bleeding requiring reoperation (for all orthopaedic surgery subgroups)	13%	Beta	$\alpha = 32, \beta = 214$
Proportion of major bleeding requiring reoperation (general surgery)	21%	Beta	$\alpha = 25, \beta = 93$
Nursing time (injection) (minutes)	2.5	Lognormal	Log (mean) = 0.92, se = 0.10
Nursing time (mechanical prophylaxis) (minutes)	7.5	Lognormal	Log (mean) = 2.01, se = 0.18
Nursing time (wafarin) (minutes)	15	Lognormal	Log (mean) = 2.71, se = 0.18
Nursing time (aspirin) (minutes)	2.5	Lognormal	Log (mean) = 0.92, se = 0.10
Length of stay / Duration of health state			
DVT (years)	0.32	Lognormal	Log (mean) = -1.13, se = 0.13
Pulmonary embolism (years)	0.08	Lognormal	Log (mean) = -2.48, se = 0.13
Major bleeding (years)	0.08	Lognormal	Log (mean) = -2.48, se = 0.13
Stroke after major bleeding (years)	3.02	Lognormal	Log (mean) = 1.11, se = 0.13
Mean duration of prophylaxis (Hip fracture surgery, total hip replacement, total knee replacement and medical only) (days)	10	Lognormal	Log (mean) = 2.30, se = 0.13
Mean duration of prophylaxis (General surgery only) (days)	7	Lognormal	Log (mean) = 1.94, se = 0.13
Prophylaxis relative risks (DVT) – extended duration			
Dabigatran vs LMWH	0.80	Lognormal	Log (mean) = -0.22, se = 0.19
Rivaroxaban vs LMWH	0.22	Lognormal	Log (mean) = -1.51, se = 0.31
Prophylaxis relative risks (DVT) – post-discharge			
LMWH (total hip replacement)	0.41	Lognormal	Log (mean) = -0.89, se = 0.14
Fondaparinux (Hip fracture surgery)	0.04	Lognormal	Log (mean) = -3.22, se = 0.65
LMWH (General surgery)	0.46	Lognormal	Log (mean) = -0.78, se = 0.24
Prophylaxis relative risks (major bleeding) – extended duration			
Dabigatran vs LMWH (total hip replacement)	1.29	Lognormal	Log (mean) = 0.25, se = 0.31
Rivaroxaban vs LMWH (total hip replacement)	3.02	Lognormal	Log (mean) = 1.11, se = 0.82
Prophylaxis relative risks (major bleeding) – post-discharge			
LMWH (total hip replacement)	0.32	Lognormal	Log (mean) = -1.14, se = 1.70

Parameter description	Point estimate	Probability distribution	Distribution parameters
Fondaparinux (Hip fracture surgery)	4.02	Lognormal	Log (mean) = 1.39, se = 0.79
LMWH (General surgery)	0.88	Lognormal	Log (mean) = -0.13, se = 1.21
Utilities			
DVT	0.99	Beta	$\alpha = 36.58, \beta = 0.48$
Pulmonary embolism	0.94	Beta	$\alpha = 19.43, \beta = 1.24$
Post-thrombotic syndrome	0.98	Beta	$\alpha = 232.65, \beta = 5.48$
Chronic thromboembolic pulmonary hypertension	0.77	Beta	$\alpha = 262.06, \beta = 80.50$
Stroke after major bleeding	0.52	Beta	$\alpha = 3.44, \beta = 3.17$

se=standard error
The sources of the model parameter are listed elsewhere in this chapter.

4.8.2 Deterministic sensitivity analysis

In addition to the probabilistic sensitivity analysis, we varied a number of individual key parameters to see if the results were sensitive, as follows.

In particular we looked at the assumptions around the long-term consequences. We investigated the results under the following assumptions

- 0% preventable chronic thromboembolic pulmonary hypertension after pulmonary embolism
- 0% chronic thromboembolic pulmonary hypertension and 0% post-thrombotic syndrome
- Low post-thrombotic syndrome (e.g. 15% after symptomatic DVT and 8% after asymptomatic DVT) – section 4.3.1.
- High post-thrombotic syndrome rate (e.g. 30% after symptomatic DVT and 21% after asymptomatic DVT) – section 4.3.1.
- High and low estimates of chronic thromboembolic pulmonary hypertension rate (section 4.3.1).
- High and low estimates of the cost of post-thrombotic syndrome (section 4.4.3).
- Higher estimate of the cost of treating chronic thromboembolic pulmonary hypertension (section 4.4.3).

Other assumptions that were tested were:

- For those drugs that we understand are substantially discounted to hospitals (LMWH, dabigatran and rivaroxaban), we used a price of £1 per injection/tablet, instead of the British National Formulary list price.
- We assumed a major bleeding fatality rate of 5% (instead of 1% for other types of surgery).

- Explicitly included the costs and health consequences of Heparin Induced Thrombocytopenia in the LMWH and UFH arms (section 4.3.2).

- We used population subgroup-specific major bleeding relative risks instead of relative risks pooled across the whole population.

- We assumed a pulmonary embolism fatality rate of 10% (instead of 6% for elective surgery, 31% for hip fracture surgery and 45% for general medical admissions).

- We varied the high-dose aspirin major bleeding relative risk vs Nil from 1 to

    - Low: Network Meta-analysis estimate of (RR = 0.5)

    - High: From direct meta-analysis (RR = 1.3)

- We increased the dabigatran major bleeding relative risk from 1.001 to be the same as LMWH

- We increased NICE threshold (£30,000/ QALY)

- Zero cost for foot impulse device equipment and £40 for foot impulse device consumable (section 4.4.1).

- We added district nurse visit costs.

As patients are discharged from hospital increasingly early, duration of prophylaxis carried out in-hospital is likely to be considerably shorter than observed in many of the clinical trials. It is possible that these interventions will be conducted post-discharge and if this is the case, additional costs would be incurred for those patients unable to inject themselves. We have conducted a threshold sensitivity analysis on the proportion of patients requiring a district nurse visit – a threshold sensitivity analysis is one where we keep changing the parameter until the optimal strategy switches to a different intervention. This was conducted for the post-discharge prophylaxis models and also for medical patients.

4.8.3 Stratification of results by baseline risk

It was recognised that within any surgical/medical population subgroup the risk of individuals may vary considerably and hence within a population subgroup the most cost-effective strategy will vary. Therefore, for each population subgroup we conducted a two-way sensitivity analysis, to show how the optimal strategy varied by baseline risk of pulmonary embolism and by baseline risk of major bleeding.

4.9 From evidence to recommendations

For each population subgroup, the strategy with the highest mean incremental net benefit (INB) based on the probabilistic analysis, was considered optimal. All INB estimates presented are in comparison with nil (no prophylaxis) with the exception of Total hip replacement extended duration where nil wasn't an option and so INB is measured compared with LMWH.

In some cases one may want to recommend a choice of strategies if the INB is similar for different strategies. Just how similar they have to be was a matter of judgement for the guideline development group. The Guideline Development Group also considered how sensitive the results are to specific key parameters or assumptions – section 4.8.2 and 4.8.3.

5 Risk, risk reduction and harm

5.1 Introduction

In making a judgement on the use of an intervention to reduce the risk of VTE, it is important to consider:

i. the reason for admission to hospital (e.g. a surgical procedure or a medical problem) and factors individual to the patient concerned (e.g. age, gender, pre-existing medical conditions and medication use) that influence the likelihood of VTE

ii. the likely treatment benefit from the specific prophylactic intervention

iii. the possible harmful effect of the intervention (e.g. bleeding from the use of pharmacological VTE prophylaxis).

While clinicians are used to evaluating these factors in a qualitative sense, the Guideline Development Group sought to obtain quantitative information where possible. The risk of VTE, risk reduction with a prophylactic intervention and risk of harm can all be expressed in absolute or relative terms. In some guidelines, patient related risk factors are expressed in relative terms. For example, patients with a prior history of VTE undergoing a surgical procedure were estimated to have an approximately 5-fold higher relative risk of DVT than patients with no such history (section 5.7.3). The current CMO risk assessment tool[163] does not try to quantify the risks.

However, in balancing benefit and harms in an individual patient, it can be more helpful to consider risk in absolute terms. For example, if the absolute risk of VTE during hospitalisation is 10% (i.e. a there is a 1 in 10 chance of VTE), and pharmacological prophylaxis reduces this risk by one half (i.e. a relative risk reduction of 50%), the absolute reduction risk from the intervention would be 5%. In simple terms, this means that there would be 5 fewer VTE events during hospitalisation in every 100 such patients treated, or 1 fewer event for every 20 treated (number needed to treat [NNT]=20). In a lower risk group of patients where the absolute risk of VTE is 1% (i.e. a 1 in 100 chance of VTE during hospitalisation) but the same intervention continues to reduce VTE risk by one half (i.e. the same relative risk reduction), the reduction in absolute risk of VTE would be only 0.5% (NNT=200). If the intervention doubles the risk of major bleeding from 0.5% to 1% in both situations (number needed to harm [NNH]=200), it might be considered to be helpful in the first group of patients but not the second.

5.2 Sources of information on risks, risk reduction and harm

Estimates of effect of treatment are obtained from randomised controlled trials (RCTs). Absolute risk reductions are readily calculated from data in individual RCTs, but meta-analysis of trial data, conducted to encompass the totality of evidence, conventionally generates a pooled estimate of the relative (rather than absolute) risk reduction. This is to overcome the problem that patients studied in different trials of the same intervention can have differing baseline absolute risk of VTE. A clinician may estimate the absolute risk reduction expected from an intervention by simply multiplying the pooled estimate of the relative risk reduction by the absolute risk of VTE in the patient group being considered. This requires reliable information on the absolute risk of VTE in different settings. However, the Guideline Development Group noted that information on the absolute risk of VTE in various clinical situations was limited. Three sources of information were considered:

(i) randomised controlled trials themselves

(ii) registries of routinely collected clinical data (e.g. Hospital Episode Statistics and the General Practice Research Database)

(iii) prospective cohort (incidence) studies

Because both the risk of VTE and the harms from treatment (particularly major bleeding) could differ substantially, information on absolute risks and harms in medical and surgical admission settings were considered separately.

5.3 Absolute risk of VTE during surgical admission

To assess absolute risk of VTE during a surgical admission or soon after, we have extracted data from three sources:

a) randomised controlled trials

b) registries of routinely collected clinical data

c) prospective cohort studies.

5.3.1 Evidence from randomised controlled trials

For these analyses, RCTs were grouped according to types of surgery using categories agreed by consensus within the guideline development group responsible for the development of the surgical guideline. Within each category, the total number of DVT events, the total number of symptomatic PE events and the total number of patients in the control (no prophylaxis arms) of RCTs were recorded. Studies were excluded if they reported any form of background prophylaxis other than early mobilisation. However, some patients may have had off-protocol prophylaxis at the discretion of their physicians. Studies were only included if they scanned all patients to find DVT (including asymptomatic DVT). This will result in the incidence figures reported being higher than the figures generally identified in practise which are usually only symptomatic events.

A pooled estimate of the absolute risk of any (including asymptomatic) DVT, and symptomatic pulmonary embolism (PE) was estimated by a fixed effects meta-analysis,

which used a Freeman-Tukey arcsine transformation to stabilise the variances of the individual study proportions [446] (Table 5-17). The types of surgery with the highest risk of DVT and symptomatic PE were (major) orthopaedic surgery followed by (major) general surgery and then neurosurgery.

The strengths of this source of information is that the patients are being carefully followed, ensuring that disease endpoints are unlikely to have been missed. In addition it is known in the control arms of the RCTs, no intervention was used, providing an estimate of absolute risk in the absence of any treatment. Finally it is known that the diagnosis of VTE was confirmed by appropriate imaging tests. However, the limitation is that patients studied in RCTs may not adequately represent the full spectrum of patients encountered in clinical practice which may limit the ability to generalise the findings. Furthermore, for some categories of surgery the available sample size was small.

Table 5-17: Risk of DVT and pulmonary embolism by type of surgery, from the no prophylaxis arm of RCTs

	Number of patients with an event	*Sample Size*	*Incidence*	*Incidence Lower 95% CL*	*Incidence Upper 95% CL*
DVT					
Cardiac [41,345]	10	65	14%	7%	24%
General[5,13,53,65,88,89,97,112,171,230,238,239,279,289,371,372,385,405,423,498,499,528,550,552,553,560,590,593,594,625,641,643,653,703,711,716]	569	2286	24%	23%	26%
Gynaecology[30,73,113,114,117,414,530,633,644,682]	113	691	16%	13%	19%
Neurological[90,101,441,607,646,647,649,683]	91	446	20%	17%	24%
Orthopaedic (Elective Hip)[12,39,51,151,153,189,207,209,249,261,281,296,301,380,410,433,587,638,650,659,684,705]	530	1172	45%	42%	48%
Orthopaedic (Hip fracture)[74,176,185,209,248,268,312,316,370,381,385,463,464,470,533,613,631,704,710]	471	1139	40%	37%	43%
Orthopaedic (Elective knee)[291,388,436,443,697,699]	65	108	60%	51%	69%
Orthopaedic Mixed[7,27,69,290,521,700]	66	140	47%	39%	55%
Urological[119,266,267,386,668]	18	144	10%	6%	15%
Vascular[615]	2	19			
Mixed[21,54,111,115,166,208,209,284,302,326,416,585,629]	286	1303	22%	19%	24%
Not known[93,337,360,364,718]	102	276	36%	31%	42%
All	2353	8089	29%		
Symptomatic Pulmonary Embolism					
Cardiac	0	0			
General[5,238,280,372,373,405,499,517,552,653]	72	3044	1%	1%	2%
Gynaecology[113,114,117]	2	250	1%	0%	3%
Neurological[607,649]	0	129			
Orthopaedic (Elective Hip)[12,51,261,281,296,410,433,587,612,638,650,684,705]	32	760	3%	2%	5%

	Number of patients with an event	*Sample Size*	*Incidence*	*Incidence Lower 95% CL*	*Incidence Upper 95% CL*
Orthopaedic (Hip fracture)[74,176,178,185,381,463,464,470,533]	63	811	8%	6%	10%
Orthopaedic (Elective Knee)[697]	0	32			
Orthopaedic Mixed[27,695]	23	134	19%	13%	25%
Urological[40,119]	2	41	9%	3%	19%
Vascular[615]	0	19			
Mixed[284,344]	7	711	1%	1%	2%
Not known	0	0			
All	175	5723	3%		

5.3.2 Evidence from clinical registry data

Hospital Episode Statistics

The NHS Hospital Episode Statistics database holds data on every patient admitted to an NHS hospital in England. We extracted data from the year 2003/4. This section has been incorporated from the previous surgical guideline[473] and has not been updated as part of the development of this guideline.

We identified all patients with a secondary diagnosis of symptomatic DVT or pulmonary embolism (ICD10=I26.0, I26.9, I80.2, I80.3, I80.8, I80.9, I82.1, I82.2, I82.8, I82.9) but excluded those that had not been admitted for surgery. We generated categories of surgical treatment by consensus. We then calculated the incidence of VTE for each surgical procedure using the total number of procedures performed over the same period as the denominator.

Table 5-18 shows the different surgical categories in order of the incidence of symptomatic VTE. The types of surgery with the highest risk of VTE are cardiothoracic, major orthopaedic and vascular surgery followed by major abdominal general surgery.

The advantage of this type of data is that they better reflects the spectrum of patients encountered in everyday practice. The disadvantages include the possibility that the diagnosis of VTE may have been inaccurate in some cases, the recording and coding of VTE may have been incomplete, and the absolute risks may not be directly comparable across categories because of the varying lengths of stay involved with different surgical interventions. Moreover, the estimates of absolute risk reflect may not be directly comparable with estimates made using data from the control arm of clinical trials because many patients in the HES registry will have received some form of thromboprophylaxis. Table 5-18 shows this incidence of symptomatic VTE by type of surgery, as recorded in HES.

Table 5-18: Incidence of symptomatic VTE estimated from HES 2003/4

	Number of patients with an event	*Sample Size*	*Incidence*
Femoral head	237	23538	1.01%
Knee replacement	493	52535	0.94%
Vascular	1186	169218	0.70%
Adult cardiac	208	40180	0.52%
Hip replacement	293	57899	0.51%
Transplantation	11	2375	0.46%
Thoracic	117	26002	0.45%
Lower gastrointestinal (GI)	428	95968	0.45%
Renal replacement	140	39733	0.35%
Upper gastrointestinal (GI)	356	110562	0.32%
Fractures	555	181346	0.31%
Intensive Therapy Unit (ITU)	1215	448253	0.27%
Oncology	1311	529069	0.25%
Radiology cardiovascular	404	221317	0.18%
Endoscopic and percutaneous	2383	1376236	0.17%
Joints other	29	17553	0.17%
Spine	76	56559	0.13%
Orthopaedic (other)	254	219116	0.12%
Neurosurgery not spine	229	215533	0.11%
Plastic	259	314817	0.08%
Urology	121	164362	0.07%
Hernia	72	115703	0.06%
Gynaecological	179	443529	0.04%
Arthroscopy	34	112123	0.03%
Anus and piles	26	86671	0.03%
Breast	22	78547	0.03%
Ear, Nose and Throat (ENT)	51	209680	0.02%
Head and neck	16	80258	0.02%
Max facial dental	34	184784	0.02%
Eyes	69	457382	0.02%

US clinical registry data

White et al. (2003)[690] evaluated the incidence of symptomatic VTEs in a database of 1.7 million patients in 76 surgical categories in the USA. They included cases of symptomatic VTE occurring during either the initial hospitalisation or a subsequent hospitalisation within 91 days of the surgery. Procedures in patients without a diagnosis of cancer where the risk of VTE was greater than 2% were:

- Embolectomy or endarterectomy of lower limb artery 2.8%
- Total hip arthroplasty 2.4%
- Neurosurgery involving excision/destruction or biopsy of brain tissue 2.3%
- Partial hip arthroplasty 2.0%

Among patients with cancer, surgical procedures where the absolute risk of symptomatic VTE was greater than 2% were:

- Permanent colostomy 2.6%

- Radical cystectomy 3.7%
- Percutaneous nephrostomy 3.6%
- Exploratory laparotomy 2.4%
- Internal fixation of femur 3.0%

In patients without a malignancy, gynaecological and head and neck, and laparoscopic abdominal surgery conveyed the lowest risk of VTE.

5.3.3 Prospective cohort studies

This section has been incorporated from the previous surgical guideline[473] and has not been updated as part of the development of this guideline.

The sixteen other studies found[19,25,63,187,230,288,309,334,428,432,461,518,566,604,652,677] were difficult to summarise, because of their heterogeneity, but if we compare the incidence rates with those in Table 2, it would seem that there is a relatively high risk of VTE associated with prostatectomy, gynae-oncological surgery and neurosurgery and a low risk associated with surgery for breast cancer or head and neck/ENT surgery (Evidence Table 1, Appendix D).

The data reported in this section are limited because of the heterogeneity of the methods used by the different studies and because it is difficult to control for the use of VTE prophylaxis or anaesthesia.

5.3.4 Discussion of data on surgical risk

We used different sources to estimate the risk of VTE for different categories of surgery compared with other surgery types. The incidence figures for VTE estimated using HES data were much lower than other estimates, implying under-reporting and/or treatment in the community. This was true even when compared to a similar database in the USA[690]. The figures for DVT from the 'no prophylaxis' arms of the RCTs appears higher than other estimates due to the identification of asymptomatic DVT events by screening the legs, as well as symptomatic events.

Hip surgery (elective and hip fracture) had higher rates of VTE by all three approaches. Some categories of cardiothoracic, vascular, urological, neurological and general surgery were also at increased risk compared with other surgery types, although, the rankings were not necessarily the same for the different approaches. Except for cancer-related surgery, gynaecological surgery had some of the lowest rates of VTE by all three approaches – this could in part be due to these patients being younger on average than some of the other patient groups.

Comparisons between different categories of surgery are likely to be confounded by age and differences in prophylaxis and anaesthesia usage. Length of stay is likely to be a contributory factor since immobility is a causal mechanism. However it might also be a confounder since the longer people stay in hospital the more likely that their VTE will be recorded.

The differences in incidence within the broad surgical categories are probably much greater than the differences between categories[690].

The strategy that the Guideline Development Group adopted from this evidence was to consider major orthopaedic surgery as higher risk for VTE than cardiac, thoracic, urological, vascular, gynaecological, neurological and general surgery. Within orthopaedic surgery, hip fracture was considered to be highest risk followed by elective orthopaedic procedures and then other types of major orthopaedic surgery.

The surgical guideline development group decided that the no-prophylaxis arms of the RCTs was the best source for the baseline risk of VTE and major bleeding, and this was used in our cost-effectiveness analysis (Chapter 4). The advantage of these risk estimates is that they control for prophylaxis use. However, the Guideline Development Group acknowledged also the weaknesses in these data. Firstly trial populations might not be representative of surgical patients in general. Second, it has been postulated that the incidence of VTE has fallen over time due to prophylaxis use but also due to other factors. If this is true then the RCT evidence, which goes back to the 1970s may over-estimate the risk of DVT and PE. Conversely, since RCT protocols usually involve surveillance for asymptomatic DVT, they might under-estimate the incidence of PE if DVTs are being diagnosed and actively before the time when they would have become symptomatic in a non-trial setting.

5.4 Absolute risk of VTE during medical admissions

We obtained information on the absolute risk of VTE during a medical admission from:

a) randomised controlled trials

b) incidence studies

5.4.1 Evidence from randomised controlled trials

The incidence of all (including asymptomatic) DVT and symptomatic PE was estimated from the RCTs in our clinical review were extracted and analysed as per the methodology as detailed in Section 5.3. These data are presented in Table 5-19.

Table 5-19: Risk of DVT and symptomatic PE, by medical condition, from the nil arm of RCTs

	Number of patients with an event	*Sample Size*	*Incidence*	*Incidence Lower 95% CL*	*Incidence Upper 95% CL*
DVT					
General Medical Patients[121,141,191,579]	106	827	13%	11%	15%
Stroke [157,167,240,434,435,520,538,540,581]	195	384	50%	45%	55%
Acute Coronary Syndromes[42,209,251,252,338,522,672,709]	76	372	21%	17%	25%
All	377	1583	24%		
Symptomatic Pulmonary Embolism					
General Medical Patients[121,394,579]	24	2400	0.9%	0.6%	1.3%
Stroke [157,520]	2	54	3%	0%	9%
Acute Coronary Syndromes[42,251,445,709]	5	156	4%	2%	8%
All	17	2638	1%		

Alongside the limitations of using RCT data to determine the incidence of DVT as detailed in section 5.3.1 the studies reporting on 'general medical patients' included a range of different medical conditions. Therefore some studies included in this population will have ischaemic stroke or acute coronary syndromes, but it was not possible to identify these separately.

5.4.2 Incidence studies

A search was conducted to identify primary studies reporting the incidence of VTE in medical patients. The Guideline Development Group were concerned that the incidence of VTE may have changed over time due to advances in medical practice and so a time limit was put on the search to only find papers published from 1998 – 2008. After the review and data extraction of some of thse studies (Evidence Table 2, Appendix D) it became apparent that similar problems as those detailed in section 5.3.2 were being encountered and the information provided was not as useful as had been hoped. The studies reviewed differed in the methods used, populations included, outcomes measured and confounding factors considered, particularly the use of VTE prophylaxis. These factors meant that the comparison of the results between studies was not possible. Once this had been identified as a problem, no further papers were reviewed and the results as presented below are used to demonstrate the inconsistency of these data.

Eighteen (18) studies were reviewed, 6 of these studies were database reviews [67,68,241,606,623,624] whereas 12 were cohort studies [77,134,144,149,173,320,349,453,469,501,512,567] (Evidence Table 2, Appendix D).

The larger studies looking across all hospital admissions used database coding in order to identify VTE which may not capture all events, particularly those occurring after discharge. In addition, most database reviews do not provide details on any VTE

prophylaxis, which is likely to be because the prophylaxis strategy was not recorded in the database and may have differed across departments and/or hospitals.

Data from registries

One database review found that the incidence of symptomatic PE in stroke patients[606] (0.51% for ischaemic stroke and 0.68% for haemorrhagic stroke) and in patients admitted with cancer patients[623] (0.6%) were greater that the symptomatic PE rate across all patients admitted to hospital[624] (0.23% [95% CI: 0.21 – 0.25%]) which included medical, surgical and trauma patients.

Cohort studies

Cohort studies specifically for critical care patients (usually including surgical patients) [134,320,512], acute exacerbation of COPD[173], ischaemic stroke[149], congestive heart failure[144] and rehabilitation units[567] were reviewed (Evidence Table 2, Appendix D).

5.5 Absolute risk of major bleeding after surgery

The relative risk increases for major bleeding from pharmacological prophylaxis after surgery are outlined in chapters 9-18. The current section summarises evidence on the absolute risk of bleeding after different surgery.

The absolute risk of bleeding after surgery is even more difficult to find than the absolute risk of VTE. The main source of information that was used to establish the baseline risks of major bleeding in this population were the nil prophylaxis arms of RCTs. These data from individual trials were combined using a meta-analysis technique as described in section 5.3.1.

Use of evidence for major bleeding incidence from RCTs has limitations as although many of the newer studies may use a fairly standard definition of major bleeding. A major bleeding event is defined as a bleeding event that results in one or more of the following: death; a decrease in haemoglobin concentration of 2g/dl or more; transfusion of at least 2 units of blood; bleeding from a retroperitoneal; intracranial; or intraocular site; a serious or life-threatening clinical event; a surgical or medical intervention. Some studies have modified this definition and others use their own trial specific definition. The Guideline Development Group agreed to use the definition of major bleeding as reported in the trials.

Another major limitation of using the absolute bleeding risk from RCTs is that they are likely to have excluded patients at increased risk of bleeding and so the incidence reported may be an underestimate of the total population.

We are not aware of any prospective cohort studies that investigate the absolute risk of bleeding after surgery in the absence of prophylaxis. Many of the definitions may not include the 'minor' bleeding which can cause serious wound complications which can be associated with a considerable loss of quality of life and cost.

Table 5-20: Risk of major bleeding, by type of surgery, from the nil arm of RCTs

	Number of patients with an event	*Sample Size*	*Incidence*	*Incidence Lower 95% CL*	*Incidence Upper 95% CL*
Major Bleeding					
Cardiac[41]	1	25			
General[5,29,53,172,230,238,280,289,319,366,371,385,499,511,517,528,550,553,590,639,653,703,711,716]	83	3980	2%	1%	2%
Gynaecology[113,414,530,633,682]	13	306	4%	2%	7%
Neurological[101,441]	1	113	2%	0%	5%
Orthopaedic (Elective Hip)[12,39,151,153,249,261,380,410,421,587,650,659,684]	25	117	2%	1%	2%
Orthopaedic (Hip fracture)[74,176,178,248,312,316,381,385,463,464,533,704,710]	29	772	3%	2%	5%
Orthopaedic (Elective knee)[388,436,443,699]	4	274	2%	1%	4%
Orthopaedic (Mixed)[7,69,521,700]	0	58			
Urological[14,40,267,386,668]	2	170	2%	0%	4%
Vascular[615]	0	19			
Mixed[54,111,166,326,344,569]	2	1153	0%	0%	0%
Not known[93,337,364,365,718]	2	254	1%	0%	3%
All	167	7241	2%		

The absolute risk of major bleeding rate for most surgery was between 1-2% as reported in the trials, although the Guideline Development Group noted that gynaecological surgery had a higher risk of major bleeding at 4%.

5.6 Absolute risk of major bleeding after medical admissions

The relative risk increases for major bleeding from pharmacological prophylaxis are outlined in chapters 23 to 25. The current section summarises evidence on the absolute risk of bleeding in different settings.

The same method as in section 5.5 was used to identify the absolute risk of bleeding in patients admitted for medical conditions. The incidence of bleeding in the general medical population appeared to be lower than the risk of bleeding after stroke.

Table 5-21: Risk of major bleeding, by medical condition, from the nil arm of RCTs

	Number of patients with an event	*Sample Size*	*Incidence*	*Incidence Lower 95% CL*	*Incidence Upper 95% CL*
Major Bleeding					
General Medical Patients[121,191,394,579]	11	2629	0.4%	0.2%	0.7%
Stroke[167,540,581]	4	107	4%	1%	9%
Acute Coronary Syndromes[70]	0	14	Not Estimable		
All	15	2750	0.6%		

5.7 Individual patient risk factors and relative risks of VTE

Published risk assessment tools

No existing, published risk assessment tools have been recommended because the literature search did not identify any that have been validated in a broad range of patients and been shown to improve patient outcomes. The Department of Health published a risk assessment tool in September 2008[163] and it is intended that this tool will be updated at the time of publication of the NICE guideline to ensure that the wording is consistent.

Search for inidivdual patient risk factors

Because risk factors specific to the patient may modify absolute risk in any setting we searched for systematic reviews on patient related risk factors for DVT or PE. For the previous guideline, the search was confined to patients admitted for surgical procedures. We identified one study that included several systematic reviews encompassing various risk factors in surgical patients[169]. The search was extended to any patient group exposed to a risk factor when insufficient information was found in surgical populations. Several reviews were identified for non-surgical populations[24,156,206,336,444,562,580].

Some reviews only included studies that used an objective test for diagnosing venous thromboembolism such as a fibrinogen uptake or ultrasound, whereas others did not report the method of diagnosis for studies included. The number of cases and controls was not always reported. Details for each systematic review are reported below. We also referred to previous guidelines for their included risk factors[219,591]. The search for individual patient risk factors for VTE in surgical patients was not updated as part of the development of this guideline. Results have been incorporated from the previous surgical guideline [473].

For the current guideline we developed and ran a search to look for any recent systematic reviews of risk factors for hospitalised medical patients (Appendix C). One systematic review of VTE risk factors in hospitalised medical patients was found[556]. Although the paper appears to have completed a systematic search of the literature, limitations include that details of the individual studies included such as the populations and number of patients within the study, is not always presented and the definition of VTE of the method for its detection was often not clear. In addition no pooling of risk was attempted in this paper making an overall summary of the results difficult.

For each risk factor, information is reported in relative rather than absolute terms (using relative risks or odds ratios). One way in which clinicians might use this information is to

scale up absolute risk derived from the sources listed above in a patient with one of the risk factors listed below. For example a patient with a prior history of DVT undergoing a surgical procedure where the absolute risk of DVT is 1% on average might be expected to have personal absolute risk of 5%. However, in patients with more than one risk factor, risks are unlikely to simply be multiplicative because many individual risk factors are unlikely to be independent. For this reason, the Guideline Development Group recommends new prospective cohort studies of hospitalised patients be conducted for the development and validation of a multivariable risk models for the estimation of absolute risk of DVT in individual patients, that could be applied in the clinical setting (section 5.10).

5.7.1 Age

Edmonds et al [169] identified six studies investigating the association between age and postoperative DVT (evidence level 2+). There was a general trend of increased age being associated with an increased risk of DVT in all studies. Two of the studies showed the incidence of DVT to be higher in those over 60 than those under; two studies showed the mean age of patients with DVT to be higher than those without DVT; and two studies showed an incremental increase associated with increasing age, one of them finding the risk to be constant at below 45 years of age. A pooled risk estimate was not possible because of the different ways of investigating across the studies (Evidence Table 3, Appendix D).

Rocha et al[556] identified a further 5 studies, 3 of which were conducted in the general population and the remaining 2 in medical inpatients (evidence level 2+). All studies confirmed a significant increase in VTE risk with increasing age although cut offs were different for each study (cut offs ranged from 50 to 85 years) (Evidence Table 3, Appendix D).

Although the increased risk of DVT with increasing age has been demonstrated by many studies and is relatively uncontroversial, it is difficult to provide useful guidance without providing a cut-off at which a person should be considered at 'increased risk'. There is no universally agreed figure for this cut off. Some guidelines have put an age threshold of 40 although White et al[688] found that the relationship between age, type of surgery and risk is complex, in particular there is no evident step up in risk at 40. Anderson & Spencer[17] noted stratification of risk by the simple dichotomy of age below or above 40 years fails to account for the significantly higher risk among the elderly patients undergoing high risk surgical procedures.

The guideline development group agreed that an age cut off of 60 years should be used. In addition to the evidence detailled above, the decision was also made based on the patients included in the trials. The patients included in the studies for general surgery patients (and therefore included in our cost effectiveness model) had average age of 60 years (chapter 9). It was the decision of the guideline development group that setting an age cut off lower than age 60 may lead to the provision of VTE prophylaxis unnecessarily where no other risk factors were present which could lead to greater harm than benefit.

Although the average age of patients included in VTE prophylaxis trials of medical patients (74 years) was greater than for general surgery trials it was noted that in the recommendation for medical patients both reduced mobility and an age over 60 years was required in order for prophylaxis to be offered.

5.7.2 Obesity

Edmonds et al. [169] identified seven studies investigating the association between obesity and postoperative DVT (evidence level 2+). Five out of the seven studies found a significant association between an increase in obesity and risk of DVT and two found no significant difference. A pooled estimate was not possible because of different definitions for obesity used across the studies (Evidence Table 4, Appendix D).

Rocha et al[556] identified a further nine studies, although the definitions of VTE and of obesity used were unclear within the review (evidence level 2+). Three studies reported that they found no evidence of a correlation between obesity and VTE whereas five studies reported a significant increase in VTE risk (between 2.0 and 3.92). The remaining study found a large VTE relative risk increase (RR rose from 2 to 10) for obese patients using hormonal contraceptives (Evidence Table 4, Appendix D).

We used the definition of obesity as being patients with a body mass index greater than or equal to 30 kg/m^2 which is the definition used in the current NICE guidelines[474].

5.7.3 Personal or family history of VTE

Edmonds et al[169] identified four studies investigating the association between a history of venous thrombosis and postoperative DVT (evidence level 2+). When three of the studies were pooled, they indicated a significant association between past history of venous thrombosis and risk of DVT (OR=5.18, 95% CI: 3.16 to 8.49). The other study suggested no difference but did not provide any data (Evidence Table 5, Appendix D).

Rocha et al.[556] identified six studies in medical patients and the general population (evidence level 2+); four of which were case control reports and the remaining two were cohort studies. All of these studies identified a significant association between a history or previous VTE and a risk of future VTE events. No pooling of events was completed (Evidence Table 5, Appendix D).

In addition to a personal history of VTE, the GDG felt it was important to ask about any family history of previous VTE events in first degree relatives during the risk assessment. In this way it may be possible to identify patients who are at risk of inherited thrombophilias that may remain undiagnosed at the time of admission.

5.7.4 Known thrombophilias

Thrombophilias are the genetic or acquired prothrombotic states that increase the tendency to venous thromboembolism (Evidence Table 6, Appendix D).

Edmonds et al[169] identified two studies investigating the association between activated protein C (APC) resistance or Factor V Leiden (FVL) mutation and postoperative DVT (evidence level 2+). One study reported low sensitivity to APC was shown to be significantly associated with postoperative DVT (RR=4.9, 95% CI: 1.1 to 22.2) with 95% of the cases being attributable to the FVL mutation. The second study reported that a low sensitivity of FVL to APC (OR=2.97, 95% CI: 1.27 to 6.92) and FVL mutation (OR=3.18, 95% CI: 0.99 to 10.2) were associated with postoperative DVT.

Rocha et al.[556] identified nine studies investigating the impact of FVL mutation and VTE (evidence level 2+). The increase in relative risk reported ranged from 2.2 to 6.6 although no pooling was attempted. Five studies reported the impact of protein C

deficiency on VTE and the increase in relative risk ranged from 3.4 to 7.3. (Evidence Table 6, Appendix D). These results support the findings in surgical patients.

Two of the studies included in the review by Edmonds et al.[169] examined antithrombin deficiency (evidence level 2+). One found patients who developed postoperative DVT had a lower level of antithrombin, the other did not find any association. We also identified one systematic review that looked at deficiency in antithrombin, protein C or protein S463. All three were associated with an increased risk of postoperative venous thromboembolism with relative risks of 5, 6.5 and 1.7 respectively. No information was given as to how venous thrombosis was diagnosed. Edmonds et al.[169] found no surgical studies investigating other thrombophilias.

Rocha et al.[556] identified 3 studies investigating anti-thrombin III deficiency (evidence level 2+). These studies all found an increased risk of VTE with the deficiency with the odds ratio varying between 1.7 and 12.6 in the studies (Evidence Table 6, Appendix D).

One additional thrombophilia investigated in the systematic review by Rocha et al. [556] was protein S deficiency. Four papers investigating the risk of VTE with protein S deficiency found that it increased the odds ratio for VTE between 0.7 and 14.4.

We identified one systematic review with 25 studies that looked at the association for lupus anticoagulants and/or anticardiolipin with thrombosis (venous or arterial) in medical populations[206] (evidence level 2+). Results were grouped according to type of event: first event, recurrent event or any event (distinction between first and recurrent events not possible). Lupus anticoagulants were found to be significantly associated with DVT. Five studies investigating lupus anticoagulants and anticardioplatin antibodies gave pooled odds ratios of 5.71 for any event and 9.4 for a first event. None of the studies showed a significant association with anticardioplatin antibodies. Four studies investigating lupus anticoagulants alone gave pooled odds ratios of 16.2 for any event and 4.01 for a recurrent event.

We identified one systematic review with 24 studies that looked at the association between raised homocysteine levels and venous thrombosis[156] (evidence level 2+). No information was given as to how venous thrombosis was diagnosed. The review showed that a 5µmol/L increase in measured plasma total homocysteine is associated with an increased risk of venous thrombosis (OR=1.27, 95% CI: 1.01 to 1.59 from three prospective studies, OR=1.60, 95% CI: 1.10 to 2.34 from 24 retrospective studies). The same review also looked at the association of MTHFR (Methylenetetrahydrofolate reductase) with venous thrombosis. The 677TT genotype was associated with a 20% higher risk of venous thrombosis compared to the 677CC genotype (OR=1.20, 95% CI: 1.08 to 1.32).

We identified one systematic review that looked at the association between prothrombin gene mutation and venous thromboembolism[580] (evidence level 2+). In one study G20210a prothrombin was associated with a three fold increase in risk of venous thromboembolism (OR=2.8, 95% CI: 1.4 to 5.6). Similar results were found in a pooled analysis of eight case-control studies (OR=3.8, 95% CI: 3.0 to 4.9).

Rocha et al.[556] reported eight studies investigating the links between VTE and pro-thrombin gene mutation (evidence level 2+). These concluded that there was an increase in VTE with the mutation with odds ratios reported between 2.0 and 11.5.

Samama et al also looked at the association between elevated plasma levels of coagulation factors and venous thromboembolism[580]. Elevated factor VII, VIII, IX and XI were all found to be significantly associated with venous thromboembolism while elevated factor X or high plasma levels of fibrinogen were not.

Two externally produced guidelines, not specifically in surgical patients, considered risk factors for venous thromboembolism [219,591] and highlighted the following thormbophilic conditions that increased the risk of VTE: myeloprofilerative disease; paraproteinaemia; paroxysmal nocturnal haemoglobinuria and Behcet's Disease. Although these conditions were specifically mentioned within the risk factor list within the NICE guideline for reducing the risk of VTE in surgical in-patients[473], for simplicity it is intended that these conditions are included within the 'known thrombophilia' risk factor in the current guideline.

5.7.5 Varicose veins

Edmonds et al.[169] identified seven studies investigating the association between varicose veins and postoperative DVT (evidence level 2+). A pooled estimate of the six studies with data showed an increase risk (OR 2.39, 95% CI: 1.69 to 3.37). One study did not provide any data (Evidence Table 7, Appendix D).

Rocha et al.[556] investigated varicose veins, venous insufficiency and peripheral arterial disease as risk factors for VTE. Eight studies were found (evidence level 2+). Four studies reported significant increases in risk of VTE in medical patients with varicose veins (OR $\geq$ 2.5) although an additional two studies did not find an association. One study reported that the risk of VTE associated with varicose veins decreases with age. There was an increase in VTE risk found associated with venous insufficiency (OR $\geq$ 1.7) and peripheral arterial disease (OR = 1.9) (Evidence Table 7, Appendix D).

5.7.6 Cardiovascular factors

Edmonds et al[169] identified two studies looking at the association between cardiovascular factors and postoperative DVT (evidence level 2+). Three potential risk factors were identified: recent myocardial infarction, hypertension and congestive cardiac failure. None were shown to be significantly associated with postoperative DVT. Congestive cardiac failure was shown to be significantly associated with DVT in univariate analysis but not in multivariate analysis in two studies, suggesting that the association was potentially explicable by confounding. Another non-surgical study reported by Edmonds showed similar results (Evidence Table 8, Appendix D).

The systematic review by Rocha et al. [556] looked at two cardiovascular factors as risk factors for VTE, acute myocardial infarction and congestive heart failure (CHF) (evidence level 2+). The two studies included for the section on acute myocardial infarction were both RCTs and reported on the populations that did not receive prophylaxis, where they found a high incidence of DVT and PE (62.5% and 12.2% respectively). Five studies were found investigating CHF for VTE. They all reported an increase in VTE in medical patients who had CHF, with the risk increasing with decreasing ejection fraction and increasing functional compromise (Evidence Table 8, Appendix D)

5.7.7 Oral contraceptives

Edmonds et al[169] identified five cohort studies and two case control studies in surgical patients (evidence level 2+). A pooled risk estimate was only possible for three of the studies due to deficiencies in reported data. This showed oral contraceptive pills were

significantly associated with an increased risk of postoperative DVT (OR=2.48, 95% CI: 1.53 to 4.02). Edmonds et al. reported some weaknesses with the data available: the studies were somewhat dated and may not apply to the recent third generation of oral contraceptive pills; and only three out of the five cohort studies screened everyone for DVT. Another systematic review compared third generation with second generation users in non-surgical populations[336] (evidence level 2+). Third generation contraceptives were associated with an increased risk of venous thrombosis compared to second generation contraceptives (unadjusted OR=1.6, 95% CI: 1.3 to 1.9; adjusted odds ratio OR=1.7, 95% CI: 1.4 to 2.0) (Evidence Table 9, Appendix D).

The Royal College of Obstetricians and Gynaecologists offers guidance on venous thromboembolism and hormonal contraceptives[564]. In addition, The BNF [313] states that:

> *"oestrogen-containing contraceptives should preferably be discontinued (and alternative contraceptive arrangements made) 4 weeks before major elective surgery and all surgery to the legs or surgery which involves prolonged immobilisation of a lower limb'* [313].

The BNF recommends that progestogen only methods need not be discontinued prior to surgery even when immobilisation is expected{BNF2008].

If the decision to stop oral contraceptives is taken it is important that women are provided with advice on the use on contraceptives in the interim period. Further information is contained within the BNF.

5.7.8 Hormone replacement therapy

Edmonds et al{EDMONDS2004} found no studies investigating hormone replacement therapy in a surgical population. We identified two recent systematic reviews that identified studies from a non-surgical population. The Royal College of Obstetricians and Gynaecologists[562] identified nine studies but did not pool the relative risks, these varied from 2.1 to 6.9 (evidence level 2+). Miller et al[444] calculated a pooled relative risk of 2.14 (credible interval 1.64 to 2.81) from 12 studies (evidence level 2+). Six of these studies also compared the risk of hormone replacement use in the first year compared to subsequent years of use. Use in the first year had a higher risk estimate (relative risk in first year of use: 3.49, credible intervals: 2.33 to 5.59; relative risk in subsequent years of use: 1.91, credible intervals: 1.18 to 3.52) (Evidence Table 10, Appendix D).

Rocha et al.[556] identified two additional studies (evidence level 2+) published since the publication of Miller et al[444]. One was the Women's Health Initiative RCT which supported a higher rate of VTE in the group receiving HRT compared to the placebo group (relative risk = 2.1; 95% CI = 1.6-2.8). The second study was a case control study which reported a higher VTE rate with oral hormone replacement therapy compared with transdermic administration (odds ratio: 4.0; 95% CI 1.9-8.3) (Evidence Table 10, Appendix D).

The Royal College of Obstetricians and Gynaecologists offers guidance on hormonal replacement therapy and venous thromboembolism[562]. In addition, the BNF also provides guidance indicating that HRT should be considered a risk factor for VTE but it may be prudent to consider stopping treatment 4-6 weeks before major surgery under general anaesthesia[313].Both BNF and RCOG documents highlights that stopping this may not necessary to stop prior to surgery provided that appropriate thromboprophylaxis is used.

5.7.9 Cancer

Edmonds et al[169] identified nine studies investigating the association between cancer and postoperative DVT (evidence level 2+). An assumption in the review is that an effect of cancer on thrombosis following general surgery is the same as the effect when surgery is for the treatment of that cancer. All nine studies found an increased risk associated with cancer giving a pooled odds ratio of 2.94 (95% CI: 2.01 to 4.29). Around a third of the total number of patients also received thromboprophylaxis (Evidence Table 11, Appendix D).

Rocha et al[556] identified 5 studies investigating the risk of VTE with various cancers (evidence level 2+). These studies indicated that although some cancers were associated with an increased risk of VTE (e.g. leukaemia, brain and uterus), others cancers had a lower relative risk of VTE compared to patients with no cancer (e.g. head and neck, bladder cancer, breast cancer). However, very little details are provided about these studies and the additional risk factors that the patient may have (e.g. surgery). A full list of the risk associated with 18 cancer types is presented in the evidence table (Evidence Table 11, Appendix D).

5.7.10 Chemotherapy

No surgical studies were found investigating the association between chemotherapy and postoperative DVT. We identified one systematic review of 32 studies that investigated vascular and neoplastic events associated with tamoxifen in non-surgical patient groups [79] (evidence level 1+). Eleven of the included studies reported pulmonary embolisms and demonstrated overall a significantly increased risk of pulmonary embolism (RR=1.88, 95% CI: 1.17 to 3.01) and 15 of the included studies reported DVT also demonstrating an increased risk (RR=1.87, 95% CI: 1.33 to 2.64). Seven of the 11 pulmonary embolism studies and 11 of the 15 DVT studies investigated the use of tamoxifen in patients with malignancy. The other four studies were for the prevention of cancer (Evidence Table 12, Appendix D).

Rocha et al.[556] reported an additional 5 studies (evidence level 2+). These studies reported significant increases in VTE when patients were 'on chemotherapy' compared with 'off chemotherapy' in breast cancer patients. In addition tamoxifen was highlighted as an additional factor increasing VTE risk for breast cancer patients in three studies. The use of thalidomide was observed to increase DVT in patients with multiple myeloma in another study (Evidence Table 12, Appendix D).

5.7.11 Smoking

Edmonds et al[169] identified four studies investigating the association between smoking and postoperative DVT (evidence level 2+). Two studies showed smokers to have significantly less DVTs than non-smokers; one study showed smoking to be protective in a univariate analysis but not in a multivariate analysis and the fourth study showed no difference. Overall, the studies suggest a non-significant association of fewer postoperative DVTs for smokers despite studies indicating it to be a risk factor for DVT in the general population. However, smoking is associated with other postoperative adverse events such as wound related or cardiopulmonary complications.

Rocha et al[556] did not find any evidence for smoking and venous thromboembolism.

5.7.12 Prolonged travel

Immobility associated with prolonged and continuous travel immediately before or after surgery may increase a patient's risk of developing postoperative VTE. We found no studies that specifically addressed this patient group. We identified one systematic review that investigated venous thromboembolism risk in long distance travel[24] (evidence level 2+). Long haul travel was shown to significantly increase risk (OR=1.59, 95% CI: 1.04 to 2.43) in three case control studies, (RR=2.93, 95% CI: 1.58 to 5.58 from two cohort studies). Two of the studies provided a risk estimate for any form of long distance travel, these also showed an increase risk of venous thrombosis (OR=2.6, 95% CI: 1.79 to 3.79). All the studies related to travel were in journeys over three hours. In three, travel related to the previous four weeks and in the fourth, travel related to the previous three weeks. Meaningful comparison between patients travelling for surgery and data from people on long haul flight is difficult. Long haul flight travellers are often healthier than the general population and, therefore, not a true sample[24] (Evidence Table 13, Appendix D).

Rocha et al[556] did not look for evidence on the any association between prolonged travel and venous thromboembolism.

5.7.13 Admission to critical care

Rocha et al[556], [556] identified admission to a critical care unit as an independent risk factor for VTE (Relative risk 1.8 to 2.9) (evidence level 2+). The review reports the incidence of DVT for patients within critical care as between 25-30% in the absence of prophylaxis. (Evidence Table 14, Appendix D)

5.7.14 Severe medical illness

The systematic review by Rocha et al [556] identified an increase in risk due to medical illnesses such as acute rheumatologic diseases and inflammatory bowel disease, infections, nephrotic syndrome, respiratory diseases and stroke (evidence level 2+) (Evidence Table 15-18, Appendix D). These acute medical illnesses were also identified in other guidelines as risk factors for VTE [219,591].

5.7.15 Reduced mobility

Rocha et al, 2007[556] identified three studies which investigated acute hemiplegia as a risk factor for VTE. One cohort study identified the incidence of VTE as 26% (no confidence intervals provided) and two case control studies identified paralysis as a significant risk factor for VTE compared with no paralysis (Evidence Table 19, Appendix D).The systematic review by Rocha et al[556] also reviewed the evidence for reduced mobility (as opposed to paresis or paralysis of lower extremities) as a risk factor. Again, a significant association between VTE risk and mobility was identified, although the authors commented that the definition of mobility used in each of the studies was different which made it difficult to interpret these data (Evidence Table 21, Appendix D).

Within the recommendations in the guideline we have referred to 'significantly reduced mobility' as a risk factor. This was defined by the GDG as bed bound, unable to walk unaided or likely to spend a proportion of the day in bed or in a chair.

5.7.16 Duration of surgery

Both the work to determine the baseline risk of VTE (section 5.3) and the systematic review of risk in surgical patients[169] identified that VTE risk differed by surgery type. The GDG discussed this in conjunction with the evidence that reduced mobility increased the risk of VTE (section 5.7.15). They agreed that procedures involving general anaesthetic which would involve complete, prolonged immobilisation for the duration of the surgery would increase VTE risk. They agreed that patients undergoing surgery where the total anaesthetic time of 90 minutes should be considered for VTE prophylaxis. In addition, they noted that surgery of the pelvis and lower limbs had an increased risk of VTE (Table 5-17: Risk of DVT and pulmonary embolism by type of surgery, from the no prophylaxis arm of RCTsTable 5-17) and so for any operation in these regions an increased risk should be considered if the surgery time was 60 minutes or more.

5.7.17 Pregnancy and ≤6 weeks postpartum

Rocha et al[556] identified one retrospective case-reference study identifying the incidence of VTE in pregnant patients as 103:100,000 (95% CI: 55 – 177), which was higher than all women where the VTE incidence was 36:100,000 (95% CI: 29– 44) . The authors of the study noted that this incidence was higher than for those patients receiving combined oral contraceptives (Evidence Table 20, Appendix D).

The risk of VTE and prophylaxis for this population is discussed in more detail in chapter 30.

5.7.18 Discussion of data on patient risk

The identified systematic reviews of patient related risk factors varied in the quality of their evidence: the diagnosis of venous thromboembolism was not always achieved using an objective test (for example fibrinogen uptake test, ultrasound); only some of the studies provided the number of cases and controls on which the data were based; some studies gave pooled risk ratios for their results while others only provided the risk ratios for individual studies.

The evidence for risk factors is heterogenous in several ways:

- only some of our evidence comes from surgical populations and some from medcial patients,
- the way risk is measured differed between studies, some use odds ratios while others use relative risk,
- the amount and quality of the evidence differed considerably between risk factors.

We acknowledge that risk factor is information is difficult to use and the risk factors may be additive or interacting. Because of the uncertainty of how to use the risk factor evidence, and the different levels of risk within our included patients we have opted for a simplified approach to the recommendations. We have identified one list of risk factors that can be used in conjunction with accompanying recommendations for medical patients and surgical and trauma patients.

Some operations (e.g. elective hip replacement, elective knee replacement, surgery for fracture of the proximal femur) were felt to constitute a sufficiently high risk alone to

warrant prophylaxis (chapters 10 to 12). For other surgery any patients with any of the risk factors in this list were felt to be at increased risk of VTE should be considered for prophylaxis.

5.8 Individual patient risk factors and relative risk of bleeding

Although many different studies have been completed on risk factors for VTE (section 5.7), he risk of bleeding in patients at risk of VTE does not appear to have studied as rigorously. A full search for bleeding risk factors in patients admitted to hospital was not completed.

During the process of developing recommendations for VTE prophylaxis the GDG identified that assessing the bleeding risk was key and that it needed to be considered prior to offering pharmacological prophylaxis in order to reduce the risk of harm.

The risk factors included in the risk factor list were identified from a number of different sources including exclusion criteria from the randomised controlled trials included in our systematic review, from cautions included in the summary of product characteristics for pharmacological VTE prophylactic agents and the clinical expertise of the GDG. As such, no quantitative assessment of the relative risk of bleeding for each of the factors included in the list was possible.

5.9 Recommendations and link to evidence

The Guideline Development Group felt that while the available quantitative information on relating to absolute risk of VTE and major bleeding had important shortcomings, it was important to collate and report these data. The Guideline Development Group opted to utilise the available data in a semi-quantitative manner as outlined in the following recommendations.

Recommendation	**Assess all patients on admission to identify those who are at increased risk of venous thromboembolism (VTE).**
Trade off between clinical benefit and harms	The risks of VTE must be identified to determine whether the patients are at increased risk of the condition in order for a decision about whether prophylactic measures are appropriate. In order for this decision to be made the risk of VTE must be assessed.
Economic considerations	No cost-effectiveness model was completed to answer whether risk assessment was cost effective. There will be some cost associated with the resources required to complete the risk assessment. However, the benefits of identifying patients at an increased risk of VTE were felt to outweigh the costs of administering the risk assessment tool.
Other considerations	The Guideline Development Group agreed that the best way to ensure that all patients were risk assessed for VTE was to complete the assessment at the initial admission to hospital. This should allow the high risk patients to be identified early and should allow appropriate prophylaxis to be administered without delay.

Recommendation	**Regard medical patients as being at increased risk of VTE if they:** • **have had or are expected to have significantly reduced mobility for 3 days or more, or** • **are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors shown in Box 1.**
Box 1 – Risk factors for VTE	• **Active cancer or cancer treatment** • **Age over 60 years** • **Critical care admission** • **Dehydration** • **Known thrombophilias** • **Obesity (BMI over 30 kg/m^2)** • **One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)** • **Personal history or a first degree relative with a history of VTE** • **Use of hormone replacement therapy** • **Use of oestrogen-containing contraceptive therapy** • **Varicose veins with phlebitis.** **For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).**
Relative values of different outcomes	The main venous thromboembolic outcomes when considering risk factors were asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism.
Trade off between clinical benefit and harms	The decision of whether to provide prophylaxis will be a balance between the increased risk of VTE for the individual patient balanced against their risk of bleeding. The only way that this balance can be determined is by identifying which risk factors for VTE that each patient has.
Economic considerations	No cost-effectiveness model was completed to answer whether risk assessment was cost effective. However, the benefits of identifying patients at an increased risk of VTE were felt to outweigh the costs of administering the risk assessment tool. Many of the individual risk factors that were identified as establishing a person as 'increased risk' for VTE (e.g. reduced mobility with severe medical illness, critical care admission) were criteria for inclusion in the randomised trials on which the cost effectiveness of treatments were based (Chapter 23). Other factors were patients were groups who were generally excluded from the trial evidence (e.g. known thrombophilias) but are likely to have a risk of VTE at least as high as those

patients included in the trials and are discussed in section 5.7.

Quality of evidence

All of the risk factors in the list in the recommendation and in box 1 were established from the evidence from systematic reviews on individual patient risk factors as presented in section 5.7 except for dehydration which is presented in section 7.3. The limitations of the evidence were that the risk factors within the systematic reviews were from many small studies which had different populations and for medical patients no attempts were made to statistically pool these data. No information about the interaction or additive effect of risk factors was identified within the literature.

Other considerations

The GDG discussed the term 'ongoing reduced mobility relative to their normal state' and felt that this should include any time at home with reduce mobility. They concluded that it was not possible to include precise time for this reduced mobility and that this factor would need clinical judgement according to the individual affected.

Recommendation	**Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:** • **surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb** • **acute surgical admission with inflammatory or intra-abdominal condition** • **expected significant reduction in mobility** • **have one or more risk factors shown in Box 1.**

Box 1 – Risk factors for VTE	• **Active cancer or cancer treatment** • **Age over 60 years** • **Critical care admission** • **Dehydration** • **Known thrombophilias** • **Obesity (BMI over 30 kg/m^2)** • **One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)** • **Personal history or a first degree relative with a history of VTE** • **Use of hormone replacement therapy** • **Use of oestrogen-containing contraceptive therapy** • **Varicose veins with phlebitis.** **For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).**
Relative values of different outcomes	The main venous thromboembolic outcomes considered were asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism.
Trade off between clinical benefit and harms	The decision of whether to provide prophylaxis will be a balance between the increased VTE risk for the individual patient balanced against their risk of bleeding. The only way that this balance can be determined is by identifying which factors the patient has which increase the risk of VTE.
Economic considerations	No cost-effectiveness model was completed to answer whether risk assessment was cost effective. However, the benefits of identifying patients at an increased risk of VTE were felt to outweigh the costs of administering the risk assessment tool. Many of the individual risk factors that were identified as establishing a person as 'increased risk' for VTE.
Quality of evidence	All of the risk factors in the recommendation and in box 1 were established from the evidence from systematic reviews on individual patient risk factors as presented in chapter 5.7 except for dehydration which is detailed in section 7.3. The limitations of the evidence were that the risk factors within the systematic reviews were from many small studies which had different populations and which were sometimes difficult to draw accurate conclusions from. No information about the interaction or additive effect of risk factors was identified within the literature.
Other considerations	The risk factor list is different to that presented in the previous surgical guideline[473]. The changes were made in order to clarify and simplify the list of risk factors and to allow one list for all patients admitted to hospital which aims to improve the ease of use in hospital. Five of the risk factors in the previous guideline (active heart or respiratory failure, acute medical

illness, nephrotic syndrome, recent myocardial infarction or stroke and severe infection) were included under the heading 'one or more significant medical comorbidity'

Five of the more specific conditions listed as risk factors in the surgical guideline (antiphospholipid syndrome, behcet's disease, myeloproliferative diseases, paraproteinaemia and paroxysmal nocturnal haemoglobinuria) are included within the 'known thrombophilias' risk factor in this guideline. This decision was taken in order to make the list simpler to use in practice. The GDG felt that junior doctors who might be completing the risk assessment should have an understanding on the conditions constituting 'known thrombophilias'.

Continuous travel was removed from the list as it was felt that the evidence for this was not strong and the risk factor was really immobility rather than travel and hence captured elsewhere.

The inclusion criteria for the previous surgical guideline[473] were all patients undergoing surgery with an overnight stay. As the current guideline extends the inclusion criterion to all patients admitted to hospital the timing of surgical procedure was felt to be a helpful guideline to identy people at risk.

Recommendation	**Reassess patients' risk of bleeding and VTE within 24 hours of admission, and whenever the clinical situation changes, to:** • **ensure that the methods of VTE prophylaxis used are suitable** • **ensure that VTE prophylaxis is being used correctly** • **identify adverse events resulting from VTE prophylaxis.**
Trade off between clinical benefit and harms	The complete picture of the VTE risk for the individual patient may not be entirely clear when first assessed upon admission. In order to ensure that patients are treated appropriately, the Guideline Development Group felt it was important that the patient is reassessed.
Economic considerations	No cost-effectiveness model was completed to answer whether reassessment of risk was cost effective. There will be a cost associated with the resources required to complete the reassessment of VTE risk. However, the benefits of identifying patients at an increased risk of VTE (or of identifying those whose risk is lower than had been previously assessed) were felt to outweigh the cost of completing the assessment. It is clear that the cost-effectiveness of prophylaxis is dependent on maintaining adherence and preventing

complications. In our cost-effectiveness analyses comparing different types of prophylaxis (Chapter 4) we included the cost of clinician time for the administration of prophylaxis.

Other considerations

All of the Guideline Development Group agreed that reassessment of VTE was important, however the timing of the second assessment was more controversial that the first assessment on admission to hospital. There is no evidence for reassessing VTE risk 24 hours after the first assessment, but the Guideline Development Group felt that at this time diagnostic tests required for each patient would have been completed and the bleeding risks were likely to be better established. Some Guideline Development Group members were concerned about the resources available for this recommendation but felt that by providing a timeframe it was more likely to occur.

In addition the Guideline Development Group felt that when the clinical situation changed there was need to reassess the VTE risk of patients to ensure the appropriate prophylaxis is established or continued.

Recommendation	**Assess all patients for risk of bleeding before offering pharmacological VTE prophylaxis*. Do not offer pharmacological VTE prophylaxis to patients with any of the risk factors for bleeding shown in Box 2, unless the risk of VTE outweighs the risk of bleeding.** ***The summary of product characteristics for the pharmacological thromboprophylaxis being used or planned should be consulted for further details.***
Box 2. Risk assessment - Bleeding	**Regard hospitalised patients as being at risk of bleeding if they have any of the following risk factors:** • **Active bleeding** • **Acquired bleeding disorders (such as acute liver failure)** • **Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR higher than 2)** • **Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours** • **Lumbar puncture/epidural/spinal analgesia within the previous 4 hours** • **Acute stroke** • **Thrombocytopenia (platelets less than 75 x 10^9/l)** • **Uncontrolled systolic hypertension (230/120 mmHg or higher)** • **Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease).**
Trade off between clinical benefit and harms	For each of the recommendations about providing prophylaxis the potential benefits of reducing the risk of VTE events (symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism) needs to be balanced against the potential harms of bleeding events (major bleeding, fatal bleeding and stroke). In some patients the risk of bleeding is not cost effective.
Economic considerations	Where cost effectiveness models have been developed and run for different sub-populations within the guideline (Chapters 9-12, 23) the bleeding risk used has been the average bleeding risk of patients within the individual trials. It is known that most of the trials will have excluded patients with a high risk of bleeding and so the recommendations as made in the chapters may not be appropriate to the high bleeding risk population.
Other considerations	The Guideline Development Group developed a list of clinical indications where the risks of bleeding should be carefully considered before providing pharmacological prophylaxis. This list of factors in box 2 was based on the exclusion criteria used in the trials of pharmacological VTE agents in our

	systematic review, information from the summary of product characteristics and the experience of the clinicians within the guideline development group. No quantitative assessment of the relative risk of bleeding for each of the factors included in the list was possible. The GDG felt it was important to reference to the summary of product characteristics as the timing of provision of pharmacological VTE may differ according to the half life of the different agents being used, or planned and needs to be within licensed indication. For example, fondaparinux has a half life of 17-21 hours which is longer than low molecular weight heparins.
Recommendation	**Advise patients to consider stopping oestrogen-containing oral contraceptives or hormone replacement therapy 4 weeks before elective surgery. If stopped, provide advice on alternative contraceptive methods.**
Relative values of different outcomes	The main outcomes considered were venous thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).
Trade off between clinical benefit and harms	The increased risk of VTE through use of oestrogen containing oral contraceptives and hormone replacement therapy was considered.
Economic considerations	No cost effectiveness model was completed to identify the cost effectiveness of stopping these treatments before surgery. The guideline development group felt that the benefits in terms of reducing the risk of VTE after surgery may, in some patients, outweigh the benefits of maintaining therapy, and so felt that it should be considered for all relevant patients.
Quality of evidence	The systematic reviews of risk factors for VTE identified oestrogen containing oral contraceptives and hormone replacement therapy as factors which significantly increased the risk of VTE (section 5.7.7 and 5.7.8). These treatments although improve the quality of the patient's life are unlikely to be life threatening if stopped. Therefore consideration should be given to their continued use.
Other considerations	This recommendation is based on the recommendation from the previous surgical guideline. The Guideline Development Group used both the evidence from systematic reviews and advice provided in the BNF[313], which included the advice of when to stop these hormone treatments before elective surgery (4-6 weeks). Additional guidance can be found in the RCOG guidelines on guidance on venous thromboembolism and hormonal contraceptives[564] and hormonal replacement therapy and

venous thromboembolism [562], and the BNF[313] .

Recommendation	**Assess the risks and benefits of stopping pre-existing established antiplatelet therapy 1 week before surgery. Consider involving the multidisciplinary team in the assessment.**
Trade off between clinical benefit and harms	The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding. The group of patients who are receiving antiplatelet or anticoagulation therapy before surgery are at an increased risk of bleeding.
Economic considerations	No cost effectiveness model was completed to identify the cost effectiveness of stopping these treatments before surgery. The guideline development group felt that the benefits in terms of reducing the risk of bleeding after surgery may, in some patients, outweigh the benefits of maintaining therapy, and therefore felt that it should be considered for all relevant patients.
Other considerations	This recommendation is based on the recommendation from the previous surgical guideline. This recommendation needs to be carefully considered in the context of the individual patient and should take into consideration all of their existing or potential comorbidities that may occur from stopping treatment. In order to balance these factors, advice from different disciplines may be needed. The BNF should be consulted for appropriate timing for stopping and restarting antiplatelet therapies around surgery. Current advice suggests that antiplatelets should be stopped 1 week before surgery.

5.10 Recommendations for research

5.10.1 Research question 1

- What is the absolute risk of VTE among different groups of hospital patients and can the risk be reliably estimated on admission to hospital to ensure that appropriate patients are offered VTE prophylaxis?

Why this is important

One of the most difficult areas the Guideline Development Group faced when developing the guideline was to identify the absolute risk of VTE among specific patient groups in relation to the reason for admission. A new, large pragmatic cohort study and/or record linkage study using Hospital Episode Statistics and the General Practice Research Database is proposed. This would allow all people admitted to hospital to be

studied to identify those who develop VTE, including people who are diagnosed with VTE in primary care after discharge from hospital. Information on baseline patient-related factors, procedures and duration of stay, complications, prophylactic therapies and concomitant drug use should be collected and analysed. It should allow the identification of independent risk factors for VTE and the development and subsequent validation of a risk model to estimate the absolute risk of VTE in individual patients. This research would allow clearer identification of those patients at risk of VTE and those in whom the risk is so low that the bleeding risk of pharmacological VTE prophylaxis would add overall hazard.

Recommended study design: Cohort/ record linkage study.

5.10.2 Research question 2

- What is the incidence, loss of quality of life and cost associated with post-thrombotic syndrome after potentially preventable deep vein thrombosis?

Why this is important

During development of the guideline it became apparent that the incidence of post-thrombotic syndrome, particularly after asymptomatic deep vein thrombosis, was not well reported. This study should use standard, validated definitions to identify the incidence of post-thrombotic syndrome both when a deep vein thrombosis has occurred as a result of a hospital admission and in the absence of hospital-acquired deep vein thrombosis. The study also should aim to identify the costs to the NHS of treating post-thrombotic syndrome.

Recommended study design: Cohort

5.11 Summary of recommendations

- Assess all patients on admission to identify those who are at increased risk of venous thromboembolism (VTE).

- Regard medical patients as being at increased risk of VTE if they:
    - have had or are expected to have significantly reduced mobility for 3 days or more **or**

    - are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors shown in Box 1.

- Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:
    - surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
    - acute surgical admission with inflammatory or intra-abdominal condition
    - expected significant reduction in mobility
    - have one or more risk factors shown in Box 1.

Box 1 Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m^2)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).

- Reassess patients' risk of bleeding and VTE within 24 hours of admission, regularly thereafter and whenever the clinical situation changes, to:
    - ensure that the methods of VTE prophylaxis used are suitable
    - ensure that VTE prophylaxis is being used correctly
    - identify adverse events resulting from VTE prophylaxis.
- Assess all patients for risk of bleeding before offering pharmacological VTE prophylaxis*. Do not offer pharmacological VTE prophylaxis to patients with any of the risk factors for bleeding shown in Box 2, unless the risk of VTE outweighs the risk of bleeding.

* The summary of product characteristics for the pharmacological thromboprophylaxis being used or planned should be consulted for further details.

Box 2. Risk factors for bleeding

- Active bleeding
- Acquired bleeding disorders (such as acute liver failure)
- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR higher than 2)
- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours
- Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours
- Acute stroke
- Thrombocytopenia (platelets less than 75 x 10^9/l)
- Uncontrolled systolic hypertension (230/120 mmHg or higher)
- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease)

➢ Advise patients to consider stopping oestrogen-containing oral contraceptives or hormone replacement therapy 4 weeks before elective surgery. If stopped, provide advice on alternative contraceptive methods.

➢ Assess the risks and benefits of stopping pre-existing established antiplatelet therapy 1 week before surgery. Consider involving the multidisciplinary team in the assessment.

6 Summary of the effectiveness of mechanical and pharmacological prophylaxis

6.1 Introduction

The purpose of this chapter is to provide an overview of all the evidence comparing different prophylaxis methods across all populations (medical, surgical and trauma patients). This chapter also presents some general comparisons that are relevant to many of the patient groups in the guideline.

The chapter is structured in the following way:

- a description of the different types of mechanical and pharmacological prophylaxis,
- a matrix showing for which comparisons evidence was found,
- a summary of the pooled results of these studies by comparison,
- specific comparisons that are relevant across patient groups,
- patient views for mechanical and pharmacological prophylaxis,
- recommendations for the general use of prophylaxis methods.

Data comparing different types of mechanical and pharmacological prophylaxis for each specific population are presented in the chapters relevant to those populations (chapters 9 to 30).

As we are comparing prophylaxis methods across all populations we have not recorded the statistical heterogeneity for each prophylaxis comparison within this chapter. Details on the heterogeneity can be found in the forest plots (Appendix E) and in the discussions for each specific population.

6.2 Description of mechanical and pharmacological prophylaxis

6.2.1 Mechanical methods of prophylaxis

Venous stasis in the deep leg veins causes a decrease in the mean flow and pulsatility of the venous flow trace. Mechanical methods of DVT prophylaxis work to combat venous stasis and include:

- Anti-embolism stockings/ Graduated compression stockings (GCS)
- Intermittent pneumatic compression devices (IPCD)
- Foot impulse devices, also known as foot pumps (FID)

In the previous guideline for surgical patients[473] these three methods were combined into one 'mechanical' category as the evidence did not indicate that there was a difference in effectiveness between the devices. For this guideline, anti-embolism stockings have been separated out from the other methods on the basis that they used a passive mechanism for reducing the risk of VTE whereas the other two methods used 'active' methods. Additionally, the distinction between IPCD and FID is not always clear and therefore in this guideline, intermittent pneumatic compression devices and foot impulse devices have been combined and are treated as equally effective.

Unlike pharmacological prophylaxis, none of the mechanical methods are associated with an increased risk of bleeding.

Anti-embolism stockings / graduated compression stockings (GCS)

The term compression hosiery refers to two different products; anti-embolism stockings (AES) and graduated compression stockings (GCS). Although the terms AES and GCS are often used inter-changeably and both offer graduated compression, they have different indications, different British and European Standards and different levels of compression. AES are designed for the prevention of VTE in the immobile patient and GCS are designed for management and treatment of conditions such as venous leg ulcers and lymphoedema in the ambulant patient. This guideline covers VTE prophylaxis only and therefore any recommendations regarding compression hosiery refer to AES only. Within this guideline we have used the abbreviation "GCS" to cover both antiembolism stockings and graduated compression stockings.

Anti-embolism stockings exert graded circumferential pressure from distal to proximal regions of the leg. They have two potential actions in preventing DVT in the immobile patient exerting graduated compression increases blood flow velocity and promotes venous return, and preventing passive venous distension is thought to prevent sub-endothelial tears and the activation of clotting factors. Application of AES is not without risk, it is important that patients are fully assessed and their legs carefully measured before stockings are fitted and that stocking use is closely monitored.

The Sigel profile which equates to a graduated compression pressure profile of 18mmHg at the ankle, 14mmHg at the mid calf, 8mmHg at the Knee (popliteal break), 10mmHg at the lower thigh and 8mmHg at the upper thigh was found to increase deep venous flow velocity by 75%[600]. The current British and European Standards for AES [BS7672 (1); ENV 12719(70)] do not replicate the Sigel profile and the British Standard only requires pressure to be measured at three points rather than the five specified by Sigel.

Healthcare professionals must consider the clinical evidence available for each individual product when purchasing and prescribing AES.

Anti-embolism stockings are contraindicated in patients with peripheral arterial disease, arteriosclerosis, severe peripheral neuropathy, massive leg oedema or pulmonary oedema, oedema secondary to congestive cardiac failure, local skin/soft tissue diseases such as recent skin graft or dermatitis, extreme deformity of the leg, gangrenous limb and doppler pressure index < 0.8, or cellulitis.

The length of stockings is a controversial issue and there is no clear randomised evidence that one length of stocking is more effective than another. Thigh length stockings can be more difficult to fit and often roll down creating a tourniquet effect. Clinical judgement, patient preference, concordance and surgical site are all important issues when deciding on stocking length.

Intermittent pneumatic compression (IPCD) devices

IPCD involves the use of inflatable garments wrapped around the legs, which are inflated by a pneumatic pump. The pump provides intermittent cycles of compressed air which alternately inflate and deflate the chamber garments, enhancing venous return[231]. It combats VTE through its haemodynamic effect on reducing venous stasis and by stimulating fibrinolytic activity[628]. This fibrinolytic mechanism is involved in the dissolution of clot and prevention of thrombus formation[426].

Foot impulse devices (FID)

Foot impulse devices (or foot pumps) increase venous outflow and reduce stasis in immobilized patients. The haemodynamic effect of the pumping mechanism in the sole of the foot is activated by weight bearing[213]. On weight bearing the venous plexus in the sole is rapidly emptied into the deep veins of the legs. The pulsatile flow produced by walking reduces the risk of thrombus formation. It is within this physiological mechanism that the foot impulse device is designed to stimulate the venous pump artificially by compressing the venous plexus and mimicking normal walking and reducing stasis in immobilised patients.

6.2.2 Pharmacological prophylaxis

Fondaparinux

Fondaparinux is a synthetic pentasaccharide, which is based on the antithrombin binding region of heparin in the body. It acts by potentiating the antithrombin (ATIII) innhibition of factor Xa. However, it does not directly inhibit thrombin, because this requires a minimum of 13 additional saccharide units which is present in unfractionated heparin and low molecular weight heparin. It is therefore a specific, indirect inhibitor of activated factor Xa through its potentiation of antithrombin. It is given subcutaneously postoperatively and administered once daily.

Heparins

Natural heparin is a mixture of mucopolysaccharides of differing chain lengths and hence molecular sizes. Such ‘unfractionated’ pharmaceutical heparin (UFH) consists of

chains of molecular weights from 5000 to over 40,000 Da (average 20,000 Da). Heparin acts as an anticoagulant by binding and accelerating the action of antithrombin, a naturally occurring inhibitor of thrombin and other coagulation enzymes (X, IX, XI and XII).

By distinctly different processes of fractionating or depolymerisation of natural heparin, several preparations of low molecular weight heparins (LMWH) are produced. Thus, although they are dissimilar in physical, chemical and biological properties, they consist of short chains of polysaccharides with an average molecular weight 3000 Da. They bind less avidly to other heparin binding proteins in the blood and are therefore more biologically available at lower doses and have more predictable levels. Both unfractionated and low molecular weight heparins can be administered intravenously (boluses and continuous) or by subcutaneous injections (twice to three times for UFH, once to twice daily for LMWH).

In addition to the outcomes for venous thromboembolism and major bleeding, we also considered heparin-induced thrombocytopenia (HIT). Few trials reported this is outcome, we have reported it when available.

Vitamin K antagonists

Warfarin is a coumarin derivative and acts as a vitamin K antagonist.

The synthesis of active clotting factors II, VII, IX and X (as well as the anticoagulant proteins C and S) requires carboxylation of glutamic acid residues which is dependent on the presence of vitamin K. Antagonism of vitamin K therefore reduces the amount of these factors, thereby producing a state of anticoagulation.

Warfarin is usually given at an adjusted, variable doses to achieve a therapeutic level, as estimated by attaining an INR (International Normalised Ratio) of 2.5. This requires frequent monitoring and takes approximately 5 days for a stable antithrombotic effect to be achieved. There is much variability in responses to warfarin, which is determined by several factors including age, genetic status, medications, diet and medical conditions. The most important complication of anticoagulation is bleeding but, if required, the effect of warfarin can be reversed with vitamin K, prothrombin concentrates and replenishment of clotting factors by the use of fresh frozen plasma.

Aspirin

Aspirin inhibits platelet function through its irreversible inhibition of the enzyme cyclooxygenase- 1 (COX-1) and thereby blocking thromboxane A2 production. Thromboxane induces platelet aggregation (and vessel wall vasoconstriction) which are required for the clotting cascade and thrombus formation. This effect lasts for the duration of the platelet lifespan. However, although it may take 10 days for the entire platelet population to be renewed, haemostasis has been shown to be normal if 20% of them have normal COX activity. The Guideline Development Group separated studies of aspirin into two categories; those using 'high dose' aspirin (classified as 300mg per day or more) or 'low dose' aspirin (classified as less than 300mg per day).

Dabigatran

Dabigatran etexilate is a new oral anticoagulant that has been licensed during the development of the guideline. It is direct inhibitor of the enzyme thrombin. Thrombin is a key enzyme in blood clot (thrombus) formation because it enables the conversion of

fibrinogen to fibrin during the coagulation cascade. Dabigatran was reviewed and approved for use for the prevention of venous thromboembolism after hip or knee replacement surgery in adults in a NICE technology appraisal published in September 2008[476].

Rivaroxaban

Rivaroxaban is a new oral anticoagulant that has been licensed during the development of the guideline. It directly inhibits activated factor X (factor Xa). Inhibiting factor Xa interrupts the pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban was reviewed and approved for use for the prevention of venous thromboembolism after total hip or total knee replacement in a NICE technology appraisal published in April 2009[479].

6.3 Summary of evidence for mechanical and pharmacological prophylaxis

6.3.1 Matrix of comparisons

The following matrix provides an overview of the RCT comparisons we identified that reported at least one of the three outcomes under investigation, DVT (both asymptomatic and symptomatic), Pulmonary Embolism (PE) or major bleeding. All cause mortality was not included in this comparison as these data could not be collected for all of the studies included in the original surgical guideline. Where a systematic review of all cause mortality has been completed for the population, this is presented in the relevant individual population chapter (chapters 9 to 30).

The number in each cell relates to the number of studies that we found investigating that comparison for **all** populations.

	No prophylaxis	Post-discharge	GCS	IPCD/FID	Dabigatran	Fondaparinux	LMWH	Rivaroxaban	UFH	VKA	Asp (HD)	Asp (LD)	GCS + IPCD/FID	Mech + pharm	Other comparisons
GCS	9														
IPCD/FID	20		1												
Dabigatran															
Fondaparinux	1	1													
LMWH	32	13	1	5	3 (a)	2									
Rivaroxaban							4 (c)								
UFH	65	1	3	4			70								
VKA	9	1		3			9		4						
High dose aspirin	29			2					5	2					
Low dose aspirin	1								1						
GCS + IPCD/FID				2											
Mech + pharm	1		17	2			2		9				9	15	
Other comparisons		1 (b)		2					3				1	1	1

Figure 6-5: Number of studies which compared various types of prophylaxis methods.

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicates areas where no studies were identified.

GCS – anti-embolism/graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) - low dose aspirin (≤ 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis

(a) 1 study was Dabigatran vs. LMWH used for an extended period (28-35 days)

(b) 1 study of LMWH vs VKA post discharge

(c) One of these studies compared extended duration prophylaxis from surgery to 28-35 days, another other study investigated extended duration rivaroxaban (28-35 days) compared with standard duration LMWH (14 days)

6.3.2 Summary of most effective interventions

Table 6-22 shows a summary of all the effectiveness data for all hospitalised patients for all the main outcomes (DVT, PE and major bleeding (MB)). Results are shown by comparison. Where there were no studies the comparison is not shown. Where one method was significantly more effective than the other, the most effective method is shown in bold for the relevant outcome. Where the result was not significant 'not sig' is shown. Where there were no data '-' is shown.

The full data for these comparisons can be found later in the guideline and in the evidence tables and forest plots.

Table 6-22: Summary of evidence on the effectiveness of prophylaxis for DVT, symptomatic pulmonary embolism and major bleeding (MB) outcomes.

Intervention(s)	*Comparison(s)*	*Intervention favoured*			*Forest plots (FPs) Appendix E*
		DVT	*PE*	*MB*	
Prophylaxis vs no prophylaxis					
GCS	no prophylaxis	**GCS**	not sig	-	FPs. 1 – 2
IPCD/FID	no prophylaxis	**IPCD/FID**	not sig	-	FPs. 4 – 5
IPCD/FID or GCS	no prophylaxis	not sig	-	-	FP. 7
Fondaparinux	no prophylaxis	not sig	not sig	not sig	FPs. 9 – 11
LMWH	no prophylaxis	**LMWH**	**LMWH**	**no prophylaxis**	FPs. 13 – 15
UFH	no prophylaxis	**UFH**	**UFH**	not sig	FPs. 17 – 19
VKA	no prophylaxis	**VKA**	**VKA**	not sig	FPs. 21 – 23
Aspirin (high dose)	no prophylaxis	**Aspirin**	**Aspirin**	not sig	FPs. 28 – 30
Aspirin (low dose)	no prophylaxis	**Aspirin**	not sig	-	FPs. 32 – 33
UFH + IPCD	no prophylaxis	not sig	-	-	FP. 34
VKA + UFH	no prophylaxis	not sig	-	-	FP. 35
Mechanical vs mechanical prophylaxis					
GCS thigh-length	GCS knee-length	not sig	-	-	FP. 36
IPCD thigh-length	IPCD knee-length	not sig	not sig	-	FPs. 37 – 38
IPCD	GCS	not sig	not sig	-	FPs. 39 – 40
Single pharmacological prophylaxis vs single pharmacological prophylaxis					
Dabigatran	LMWH	not sig	not sig	not sig	FPs. 41 – 43
Rivaroxaban	LMWH	**Rivarox-aban**	not sig	not sig	FPs: 261-263
Fondaparinux	LMWH	**Fonda-parinux**	not sig	not sig	FPs. 44 – 46
LMWH	UFH	**LMWH**	not sig	not sig	FPs. 48 – 50
LMWH	Aspirin	-	not sig	-	FP. 52
VKA	UFH	**UFH**	not sig	not sig	FPs. 54 – 56
VKA	LMWH	**LMWH**	not sig	**VKA**	FPs. 57 – 59
VKA	Aspirin	not sig	not sig	not sig	FPs. 60 – 62
Aspirin (high dose)	UFH	not sig	not sig	not sig	FPs. 64 – 66
Aspirin (low dose)	UFH	not sig	-	-	FP. 68
VKA (adjusted dose)	VKA (fixed dose)	**Adjusted dose**	not sig	not sig	FPs. 69 – 71
Fondaparinux (8 hour postop start)	Fondaparinux (day 2 postop start)	-	not sig	not sig	FPs. 72 – 73
LMWH (preop start)	LMWH (postop start)	not sig	not sig	not sig	FPs. 75 – 77
Aspirin (high dose)	Aspirin (low dose)	not sig	not sig	not sig	FPs. 78 – 80
Mechanical vs pharmacological prophylaxis					
GCS	LMWH	**LMWH**	not sig	not sig	FPs. 81 – 83

Intervention(s)	*Comparison(s)*	*Intervention favoured*			*Forest plots (FPs) Appendix E*
		DVT	*PE*	*MB*	
GCS	UFH	not sig	not sig	not sig	FPs. 84 – 86
IPCD/FID	LMWH	not sig	not sig	not sig	FPs. 87 – 89
IPCD/FID	UFH	not sig	not sig	not sig	FPs. 90 – 92
IPCD/FID	UFH then Asp (HD)	not sig	not sig	-	FPs. 93 - 94
IPCD/FID	VKA	not sig	not sig	not sig	FPs. 95 – 97
IPCD/FID	Asp (HD)	**IPCD/FID**	not sig	not sig	FPs. 98 – 100
(IPCD + GCS) or FID	LMWH	not sig	not sig	-	FPs. 101 – 102
IPCD/FID + GCS	LMWH	not sig	-	-	FP. 104
IPCD/FID + GCS	UFH	**IPCD/FID + GCS**	-	-	FP. 105
Adjuvant studies (mechanical)					
GCS + IPCD/FID	IPCD/FID	not sig	-	-	FP. 106
GCS + LMWH	LMWH	not sig	not sig	-	FPs. 107 – 108
GCS + UFH	UFH	**GCS + UFH**	not sig	-	FPs. 109 – 110
GCS + Fondaparinux	Fondaparinux	not sig	not sig	not sig	FPs. 111 – 113
GCS + Asp (LD)	Asp (LD)	not sig	not sig	-	FPs. 114 – 115
IPCD/FID + GCS	GCS	**IPCD/FID + GCS**	not sig	-	FPs. 117 – 118
IPCD/FID + UFH	UFH	not sig	**IPCD/FID + UFH**	-	FPs. 120 – 121
IPCD/FID + Asp (HD)	Asp (HD)	not sig	-	-	FP. 122
IPCD/FID + GCS + LMWH	GCS + LMWH	not sig	not sig	not sig	FPs. 123 – 125
IPCD/FID + GCS + Asp	GCS + Asp	not sig	not sig	-	FPs. 127 – 128
IPCD/FID + (UFH then Asp(HD))	UFH then Asp (HD)	not sig	-	-	FP. 129
Adjuvant studies (pharmacological)					
Fondaparinux + GCS	GCS	-	-	not sig	FP. 130
Fondaparinux + IPCD	IPCD	**Fon + IPCD**	-	**IPCD**	FPs. 131 – 133
LMWH + GCS	GCS	**LMWH + GCS**	not sig	not sig	FPs. 134 – 136
LMWH + IPCD + GCS	IPCD + GCS	not sig	not sig	not sig	FPs. 138 – 140
UFH + GCS	GCS	**UFH + GCS**	not sig	not sig	FPs. 142 – 144
UFH + IPCD	IPCD	not sig	-	-	FPs. 146
UFH + VKA	VKA	not sig	not sig	not sig	FPs. 147 – 149
UFH + aspirin	aspirin	**UFH + aspirin**	not sig	**Aspirin**	FPs. 150 – 152

Intervention(s)	*Comparison(s)*	*Intervention favoured*			*Forest plots (FPs) Appendix E*
		DVT	*PE*	*MB*	
UFH then Asp(HD) + IPCD/FID	IPCD/FID	not sig	not sig	-	FPs. 153-154
VKA + GCS	GCS	not sig	-	not sig	FPs. 155 – 156
VKA + IPCD + GCS	IPCD + GCS	not sig	-	not sig	FP. 157
VKA + UFH	UFH	not sig	not sig	not sig	FPs. 158 – 160
Aspirin + GCS	GCS	-	not sig	-	FP. 161
Aspirin + UFH	UFH	not sig	not sig	not sig	FPs. 162 – 164
Aspirin + variety of background prophylaxis	Variety of background prophylaxis	-	**Aspirin**	not sig	FPs. 165 - 166
IPC/FID + LMWH	GCS + LMWH	**IPC/FID + LMWH**	not sig	-	FPs. 168 – 169
IPC/FID + Aspirin	GCS + Aspirin	-	not sig	-	FP. 170
Fondaparinux + GCS	LMWH + GCS	**Fondaparinux + GCS**	not sig	not sig	FPs. 171 – 173
LMWH + GCS	UFH + GCS	not sig	not sig	not sig	FPs. 174 – 176
LMWH + IPC	UFH + IPC	not sig	not sig	not sig	FPs. 177 – 179
LMWH + IPCD+ GCS	UFH + IPCD+ GCS	not sig	-	not sig	FPs. 181 – 182
LMWH + Aspirin	UFH + Aspirin	**LMWH + Aspirin**	not sig	not sig	FPs. 184 – 186
LMWH + Intraoperative UFH	UFH + Intraoperative UFH	not sig	not sig	-	FPs. 188 – 189
LMWH + IPCD	Aspirin + IPCD	not sig	not sig	not sig	FPs. 190 – 192
VKA + GCS	UFH + GCS	not sig	-	not sig	FPs. 194 – 195
VKA + GCS	Aspirin + GCS	not sig	not sig	**Aspirin + GCS**	FPs. 196 – 198
VKA + IPCD+ GCS	Aspirin + IPCD+ GCS	-	not sig	-	FP. 199
IPCD+ GCS	UFH + GCS	not sig	-	-	FPs. 200
IPCD+ GCS	LMWH + GCS	not sig	not sig	not sig	FPs. 202 – 204
IPCD+ GCS	VKA + GCS	not sig	not sig	not sig	FPs. 206 – 208
IPCD then LMWH	LMWH	not sig	not sig	-	FPs. 209 – 210
FID + LMWH after 5 days	LMWH	not sig	not sig	-	FPs. 211 – 212
LMWH then FID + GCS	LMWH + GCS	not sig	not sig	not sig	FPs. 214 – 216
Aspirin + IPCD	LMWH	**LMWH**	not sig	-	FPs. 217 – 218
UFH + IPCD	LMWH	-	-	not sig	FP. 219
Post discharge					
Fondaparinux Post Discharge	No Fondaparinux	**Fondaparinux**	not sig	not sig	FPs. 221 – 223

Intervention(s)	*Comparison(s)*	*Intervention favoured*			*Forest plots (FPs) Appendix E*
		DVT	*PE*	*MB*	
LMWH Post Discharge	No LMWH	**LMWH**	not sig	not sig	FPs. 225 – 227
UFH Post Discharge	No UFH	not sig	-	not sig	FPs. 229 – 230
VKA Post Discharge	VKA hospital only	-	not sig	not sig	FPs. 231 – 232
VKA Post Discharge	LMWH Post Discharge	-	not sig	**LMWH**	FPs. 233 – 234

FP – forest plot number in appendix E;; MB = Major bleeding,
The VTE prophylaxis strategy which is significantly more effective in reducing DVT or PE, or resulting in significantly less major bleeding is stated in bold. Not sig = not statistically significant difference. No event= outcomes reported in study(ies) but no events were reported. '-'= not reported. MB = Major bleeding

Overall, there is evidence that mechanical prophylaxis and many of the pharmacological are effective at reducing the risk of DVT and there is evidence that some methods effectively reduce the risk of PE. It is more difficult to draw conclusions on the relative effectiveness between the different prophylaxis methods. There are significant differences with some of the comparisons but there are many areas where there is no significant difference. In some cases this may be due to the included studies having small sample sizes meaning that the trial may not be able to identify a significant difference between treatments if there was one. In chapters 9 to 12 and 23 we describe the network meta-analyses that have been performed for specific patient populations. In these analyses, we have used these data to rank the VTE prophylaxis methods in order of effectiveness. The methodology used for the network meta-analysis is detailed in section 3.10.

6.4 Specific mechanical comparisons not presented elsewhere

The following sections report on studies comparing aspects of mechanical prophylaxis that were not compared within the specific population chapters. They are presented here as comparisons across any population.

6.4.1 Thigh vs knee-length GCS

Table 6-23: Summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Forest plots & Evidence Tables*
DVT					
GCS - thigh vs knee-length[532,694] (a)	2	9/100	9/102	1.06 (0.32, 3.55)	ET: 30 FP:36
GCS thigh-length + LMWH vs GCS knee-length + LMWH[287] (b)	1	8/195	11/99	0.37 (0.15, 0.89)	ET: 30 FP: 36

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis
(a) General surgery patients
(b) Mixed surgical patients

Overall, there is little RCT evidence directly comparing the length of anti-embolism / graduated compression stockings in patients. There is no statistically significant difference between thigh and knee-length stockings alone in reducing the risk of DVT. However, the sample size was small and confidence intervals were wide. No studies reported pulmonary embolism. Thigh-length stockings plus LMWH are more effective than knee-length stockings plus LMWH in reducing the risk of DVT in mixed surgical patients. The analyses of studies using anti-embolism stockings in specific populations have combined all data for knee and thigh-length stockings together rather than analysing separately by length. Most the RCTS comparing stockings with other prophylaxis used thigh-length stockings and where the length of stocking is reported in the paper we have included this information in the evidence table.

6.4.2 Thigh vs knee-length IPCD

Table 6-24: Summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Forest plots & Evidence Tables*
DVT					
IPCD – thigh vs knee-length[611] *(a)*	1	0/47	1/43	0.31 (0.01, 7.31)	ET: 30 FP: 37
Pulmonary embolism					
IPCD – thigh vs knee-length[611] *(a)*	1	1/47	0/43	2.75 (0.12, 65.76)	ET: 30 FP: 38

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis
(a) Urological surgery patients

There is no statistically significant difference between thigh and knee-length IPCD in reducing DVT or pulmonary embolism. Overall, there is little RCT evidence directly comparing the length of intermittent pneumatic compression devices in patients. The analyses of studies using IPCD in specific populations have combined all data for knee and thigh-length devices together. Where the length of IPCD was reported within a study it has been reported in the evidence tables.

6.4.3 Intermittent pneumatic compression devices vs foot impulse devices

Table 6-25: Summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Forest plots & Evidence Tables*
DVT					
*IPCD*vs foot impulse devices [20,170] (a)	2	4/111	16/130	0.29 (0.11, 0.79)	ET:30 FP: 255
IPCD+GCS vs FID+GCS[701] (b)	1	0/59	1/75	0.42 (0.02, 10.18)	ET:30 FP: 259
Pulmonary embolism					
IPCD vs foot impulse devices [20] (c)	1	0/49	1/69	0.47 (0.02, 11.22)	ET: 30 FP: 256
IPCD+GCS vs FID+GCS [701] (b)	1	0/59	1/75	0.42 (0.02, 10.18)	ET: 30 FP: 259
Major bleeding					
IPCD vs FID[170] (d)	1	1/74	0/75	3.04 (0.13, 73.44)	ET: 30 FP: 260

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*

Proph - prophylaxis
(a) One study elective hip or knee replacement patients, the other in head injury patients
(b) Neurosurgery patients
(c) Elective hip or knee replacement patients
(d) Head injury patients

There is evidence that intermittent pneumatic compression devices are significantly more effective than foot impulse devices at reducing DVT from a study in head injury patients. There is no statistically significant difference between IPCD and foot impulse devices in reducing pulmonary embolism. The distinction between IPCD and FID is not always clear and therefore in this guideline, intermittent pneumatic compression devices and foot impulse devices have been combined and are treated as equally effective. The GDG therefore decided to analyse the devices together for the rest of the guideline.

6.5 Specific pharmacological comparisons not presented elsewhere

The following section reports on studies comparing aspects of pharmacological prophylaxis that were not compared within the specific population chapters. They are presented here as comparisons across any population.

6.5.1 Pre vs post op initiation of LMWH

Table 6-26: Summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Forest plots & Evidence Tables*
DVT					
Preop LMWH vs postop LMWH[508] (a)	1	27/65	24/66	1.14 (0.74, 1.76)	ET: 53 FP: 75
Pulmonary embolism					
Preop LMWH vs postop LMWH[508] (a)	1	0/90	0/89	not estimable	ET: 53 FP: 76
Major bleeding					
Preop LMWH vs postop LMWH[508] (a)	1	2/90	3/89	0.66 (0.11, 3.85)	ET: 53 FP: 77

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis
(a) Elective hip replacement patients

There is no statistically significant difference in risk of DVT, PE or major bleeding between starting low molecular weight heparin preoperatively and postoperatively in the one RCT identified. Overall, there is little RCT evidence directly comparing the pre- or post-operative administration of pharmacological agents in patients. In the RCTs comparing LMWH with other prophylaxis methods, LMWH was initiated both preoperatively in some and postoperatively in others and these studies were analysed together.

6.5.2 Vitamin K antagonists – fixed vs adjusted dose

Table 6-27: Summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Forest plots & Evidence Tables*
DVT					
Adjusted vs fixed dose VKA[58,184,530] (a)	3	17/176	33/164	0.51 (0.30, 0.86)	ET: 55 FP: 69

Comparison	No. of studies	Interven-tion	Control	Relative risk	Forest plots & Evidence Tables*
Pulmonary embolism					
Adjusted vs fixed dose VKA[58,184] (b)	2	1/141	0/132	2.97 (0.12, 72.01)	ET: 55 FP: 70
Major bleeding					
Adjusted vs fixed dose VKA[184,530] (c)	1	8/135	6/132	0.95 (0.12, 7.17)	ET: 55 FP: 71

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis
(a) Two studies elective hip replacement patients, one study gynaecological surgery patients
(b) Two studies elective hip replacement patients
(c) One study elective hip replacement patients, one study gynaecological surgery patients

Adjusted dose vitamin K antagonists (VKA) are significantly more effective in reducing the risk of DVT than fixed dose VKA. There is no statistically significant difference between adjusted and fixed dose VKA in reducing pulmonary embolism or increasing major bleeding. As it is more usually given at adjusted dose and the adjusted dose is significantly more effective in reducing DVT, this guideline presents the evidence for just adjusted dose VKA in Chapters 9 to 26. In chapter 27: Patients with central venous catheters, the use of fixed dose VKA is still a topic of interest and the comparison between fixed and adjusted methods has been considered here.

6.6 Patient views

6.6.1 Patient views and adherence to mechanical devices

6.6.1.1 Anti-embolic stockings / graduated compression stockings

We identified one study of anti-embolic stockings in orthopaedic patients[43] and two in mixed surgical patients[33,430,510].

The first study was a RCT was conducted to investigate the effect of graduated compression stockings on venous haemodynamics[43]. In total, 160 patients were randomised to thigh-length or knee-length stockings. After 1 hour of wear, significantly more patients in the thigh-length group had wrinkles in their stockings (17.5% vs 7.5%) and reported discomfort (21% vs 11%). About half of the patients in each group were unable to manage the stockings independently (Evidence table 61, Appendix D).

The second study was carried out in a London hospital with a policy of wearing thigh-length graduated compression stockings[33,510]. A survey (observation) was carried out in 16 mixed-specialty surgical wards over one day. Ninety-nine (46%) of the 218 patients observed were wearing stockings. Of these, more patients wore knee-length stockings correctly (77 out of 85, 91%) compared with thigh-length stockings (9 out of 14, 64%). Overall, 39% (86 patients) wore a graduated compression stockings in a correct manner (Evidence table 61, Appendix D).

The third study was a telephone interview of 12 patients who had worn anti-embolic stockings for at least 48 hours to investigate what type of information should go into a patient information leaflet on stockings[430]. The study found that patients did not receive enough information to support proper use of anti-embolic stockings [430](Evidence table

61, Appendix D). More information about the findings of this study and the provision of patient information in general is presented in chapter 32.

6.6.1.2 Intermittent pneumatic compression devices(IPCD)

Four studies on patient adherence to IPCD were found[247,468,506,626]. The adherence results of these studies are summarised in Table 6-29

One study examined patient views on a new IPCD applied to either the calf or foot of 30 patients having elective joint replacemen [654](Evidence table 61, Appendix D). Twenty three of the 27 patients who gave feedback found the device either 'comfortable' or 'very comfortable'. Three patients who had reported discomfort or sleep disturbance had been allocated to the foot garment.

6.6.1.3 Foot impulse devices (FID)

Five studies reported the acceptability or/and adherence to FID with all studies conducted in hip and/or knee arthroscopy patients [16,103,525,555,687](Evidence table 61, Appendix D). The results of the study are summarised in **Table 6-28**.

Generally, the studies found patients were comfortable with the FIDs[16,103,525,555,687]. Reasons for non-adherence were discomfort around the ankles and sleep disturbances (30% and 70% respectively among patients who discontinued use) in Pitto et al[525]. Robertson et al[555] reported that pain, forceful pulsation, a tight fit and blisters were reasons for non-adherence. For more information about adherence, see Table 6-29.

Table 6-28: Summary of tables which reported patient views of foot impulse devices (FIDs)

Study	*Pitto 2008 525*	*Chan 2007 103*	*Anand 2007 16*	*Robertson 2000 555*	*Westrich 2003 687*
Population	Total knee or hip replacement				Total knee replacement
Sample size	800	30	43	120	100
Setting	NZ	Ireland	UK	US	US
Painful	0.4%		14.0%		
Affects sleep	8.8%	56.7%	27.9%		
Noise	-	26.7%	-		
Too hot	-	43.3%	-		
Restrict mobility	-	-	65.1%		
Uncomfortable	2.5%	30.0%			
Comfortable	63.1%(a)	7.1 (b)	51.2% (a)/ (7.3) (b)	55% (a)	Foot wrap 7.4 (b) Pumping action 6.1 (b)
Soothing/Relaxing	26.5%	-	53.5%		

(a)*Percentage of patients who reported the devices as comfortable.*
(b) Mean scores from questions on comfort. Higher values represent higher comfort. Visual analogues scales (VAS) or Likert items were used. The format and definitions of response choices differ between studies. One study[102] used scales ranging from 1 to 10. Another [16] used a scale ranging from 0 to 10, where a score of 0 was "most uncomfortable" and 10 was "most comfortable". The third study had questions with response choices ranging from 1 to 9[687].(Evidence table 61, Appendix D)

6.6.1.4 Combination of mechanical prophylaxis methods

One observational study was found that investigated the adherence to IPCD and GCS[78] (Evidence table 61, Appendix D). Patients were recruited based on GCS and IPCD orders from the pharmacy records. The paper does not indicate how many patients

should receive both methods. The number of patients who used each of these methods correctly was reported but the total number of people who used both correctly was not reported. This paper, found no correlation between gender and adherence rates, but older patients were more likely to wear GCS or IPCD (Pearson r=0.25, p<0.01).

6.6.2 Patient views and adherence to pharmacological prophylaxis

Five studies which reported patient views or adherence were found and included[106,128,317,492,614] One is a qualitative study conducted to understand patient perception of LMWH prophylaxis[492]. The other four studies looked at self-injection of LMWH in orthopaedic patients; including hip or knee replacement[128], knee replacement[614], spinal cord injury[106] (Evidence table 62, Appendix D. Information about adherence to self-injection in patients with lower limb plaster casts were also extracted from an RCT[317] reviewed for effectiveness of intervention and presented in Table 6-29 (Evidence Table 26, Appendix D).

The qualitative study was conducted among 28 cancer patients receiving palliative care in the UK with all patients having received LMWH for at least 5 days[492]. Recruitment continued until theme saturation was achieved. The study found that patients were aware of the purpose of subcutaneous LMWH thromboprophylaxis, and they understood that death could be a consequence of VTE. The potential benefit of reducing the risk of VTE was balanced against potential side effects (bruising was quoted) and patients found it acceptable to receive the LMWH injections[492] (Evidence table 62, Appendix D).

Colwell et al[128] evaluated postoperative self injection of subcutaneous LMWH injection for 21 days in 51 total hip or knee replacement patients. Patients were given routine instructions and a demonstration by the staff nurses. Written and video instructional materials were also given on discharge. Most patients (86%) performed self-injections with 14% being assisted by a family or friend. Follow up telephone interviews were conducted once per week and each patient was given a self-report diary to complete. Forty patients completed the trial, and their diaries showed that 55%, 37.5% and 7.5% had “full”, “partial” and “noncompliance” to the injection regimen respectively (Evidence table 62, Appendix D for definitions). Most patients (98%) understood the importance of self administering heparin and 68% (34/ 50) felt comfortable doing it. Generally, patients were happy with the level of information received regarding self-injection and felt that the syringe was relatively easy to use. Sixteen reported mild burning or stinging at the injection site and one reported mild bruising. The authors thought that adherence might be higher in this study than in a normal practice due to the weekly phone calls to check how patients were coping.

Spahn et al[614] evaluated postoperative self-injection of LMWH for around 10 days in knee replacement patients. Patients were provided with training for self-injection and were free to choose between self-administration or a nursing service. Assessment was carried out by anonymous questionnaire. Fully completed questionnaires were received from 69% of patients (207/300). Sixteen percent (16%, 31/191) of patients who selected self-administration of injections required family or friends to help. Only 77.3% (160/207) performed self-injection independently while 7.7% (16/207) used the nursing service. Fewer patients who self-injected independently found it ‘very unpleasant’ compared to patients who engaged the help of family members or the nursing service. Overall, adherence was incomplete in 28.3% (54/191) of patients who self injected or required family or friends to help. Some injections were left out by 17.8% (34/191) of patients injections and 13.1 % (25/191) discontinued the injections early. All patients

under 20 years old had incomplete adherence (N=24) compared to 18% (30/167) ($p<0.001$, Chi square test) among patients aged 20 years and above. (Evidence table 61, Appendix D).

The study among patients with spinal cord injury was conducted as an RCT comparing two compounds which required once vs twice daily injections per day[106]. There were no significant differences between the two groups in terms of adherence, pain and perception of hassle of injections. The two groups were combined in analysis. On average, the patients in this did not find the injections painful (mean1.5 (s.d. =0.61) and the range of scores chosen by patients were 1-4 (1=not painful at all, 10=extremely painful). When asked to compare the hassle of injections to taking pills three times a day, the mean score was 2.5 (s.d.= 2.16), and the range of scores chosen by patients was 1 to 10 (1=much less of a hassle, 10= very much of a hassle). The adherence data from this study are shown in Table 6-29.

6.6.3 Comparison of patient views and preferences of different types of interventions

6.6.3.1 Comparison of different types of mechanical devices

We identified two studies that compared mechanical interventions[555,701](Evidence table 61, Appendix D). In one study, IPCD plus anti-embolism / graduated compression stockings (GCS) (n=104) were compared with FIDs (n=120) in hip joint replacement patients[555]. Significantly more patients were "comfortable" or had no complaints with the FID (71% vs. 55% in IPCD plus GCS group). Thirty-five participants in the foot impulse device group were having revision surgery and had previously used an IPCD. Of these, 69% preferred the FID, 20% preferred the IPCD and 11% had no preference (Evidence table 61, Appendix D).

The second study[701] was an RCT that compared the use of pneumatic foot wraps (Plexi-Pulse) with IPCD in adults undergoing major spinal procedures. All participants also wore thigh-length GCS. The devices were started postoperatively and worn when in bed until discharge. There was a wide range of responses in both groups ranging from extremely comfortable to extremely uncomfortable. There was no difference in visual analogue scores for comfort between the two groups (Evidence table 61, Appendix D).

6.6.3.2 Comparison of different types of pharmacological prophylaxis

No studies comparing different types of pharmacological prophylaxis were found.

6.6.3.3 Comparison of different mechanical and pharmacological prophylaxis

We found two studies comparing patient views for mechanical interventions with those for pharmacological interventions[16,429] (Evidence Table 63, Appendix D).

One study looked at the views of 207 women undergoing surgery for gynaecological malignancy who were randomised to LMWH or IPCD in an RCT[429]. Fewer patients (4%) receiving LMWH reported discomfort or side effects compared to the IPCD group (26%) who experienced discomfort, inconvenience, problems and/or side effects. The most common side effect associated with the IPCD was excessive perspiration. Eleven percent indicated that they removed the IPCD when the nurse was out of the room. The IPCD was not optimally functional in 9.6% patients at some point of postoperative recovery period whereas the protocol for LMWH was not strictly adhered to in 6.8% patients. Overall, there were no significant differences in preference or adherence between the two groups

using although IPCD appear to lead to more discomfort. (Evidence Table 63, Appendix D).

A UK study compared the acceptability of FID to subcutaneous LMWH injections among patients who had total hip or knee replacements and received both these prophylactic methods[16]. Patient ratings for comfort and pain were slightly better (not significant) for the FID, (mean score of comfort level was 6.3 for LMWH and 7.3 for FID, 10= most comfortable; 14% found LMWH painful vs. 11.6% for FID). However, significantly more patients answered that they "would rather not have these" for FID (37%) compared to LMWH (14.0%) and willingness to continue the prophylaxis method for 4 weeks was higher for LMWH (76.7% vs. 51.2% in FID) (Evidence Table 63, Appendix D).

Discussion on Patient views

Adherence rates obtained from studies using various thromboprophylaxis methods are tabulated in Table 6-29. Across the studies, there were no consistent definitions of adherence and methods of measurements used. The setting of the studies (e.g. RCTs vs observational studies, different types of wards) and methods of reporting adherence could have contributed to differences identified. In general, adherence for subcutaneous LMWH injection during hospitalisation reached more than 99%, both for once and twice daily injections[106]. However, 12 % dropped out from a post-discharge RCT due to discomfort or refusal to self-inject[317]. Adherence to FIDs ranged from 30% to 95%, depending on the timing of observations and definition of adherence used. Similarly, adherence to GCS and IPCD varies depending on definition of adherence.

Table 6-29: Adherence to pharmacological, mechanical and combination prophylaxis.

Study	*Population & setting*	*Methods and definition of measurement*	*Outcomes (Adherence)*

Study	*Population & setting*	*Methods and definition of measurement*	*Outcomes (Adherence)*
Pharmacological			
SC LMWH (in hospital) [106]	Spinal cord injury (United States)	Adherence with injections as recorded in hospital logs	▪ 99.2% for twice daily ▪ 99.5% for once daily regimen
SC LMWH (self administered) [317]	Below knee plaster cast, N=148 RCT (Denmark)	Number of patients who stayed in trial (no discomfort with self injection)	▪ 88% continued with trial ▪ 60% reported no problems administering self-injection
SC LMWH (self-administered)[614]	TKR N=191 self-injection patients from 300 recruited. (Germany)	Self-reported (questionnaire, interview). Incomplete adherence include early termination or missed doses	▪ 71.7% (137/191) overall ▪ 0% in subgroup of patients under 20 years
SC LMWH (self-administered)[128]	THR/TKR N=51, 40 evaluable Observational (United States)	Self-completed diaries reporting adherence for 21 days.	▪ 55% full adherence, 37.5% partial adherence, 7.5% non-adherence
Mechanical – foot impulse devices (FID)			
FID[555]	THR/TKR, N=104 Observational study (United States)	Total number of hours worn, as measured by the internal measurement device of the FID and hourly nursing observation (b)	▪ 72 % (52/72 hours for 3 days post operatively
FID [687]	TKR, N=100 Observational (United States)	As charted by around clock, hourly observations by clinical staff.	▪ 87.1% overall compliance
FID [102]	THR/TKR, N=30 Observational study (Ireland)	Reported as % of adherent observations per day (3 random observations per day conducted).	▪ Day 3 post surgery: 80-90% ▪ Day 5 post surgery: 30%
FID[ANAND2007]	THR/TKR, N=43 Observational study (UK)	Number of patients who discontinued foot pump due to pain	▪ 95.3% (41/43)
FID+/- GCS[525]	THR/TKR, N=846 RCT study (New Zealand)	1) Internal measurement device of the FID 2) Discontinuation Protocol requires patients to use 16 hours per day	1) 66% (15.9/24 hours) 2) 95 % (800/846) discontinuation
Mechanical – IPCD			
IPCD (thigh-length)[247]	THR, N pre/post intervention(a) = 49/30 Observational (Vancouver)	Monitoring device (external) % time used	▪ Pre-intervention: 78±17% ▪ Post-intervention: 80.6±14.0%
IPCD (non portable vs portable devices) [468]	Trauma, N=33 Observational (US)	Monitoring device Overall % of time used	▪ 58.8% for non portable devices; 77.7% for portable devices
IPCD (length not specified)[626]	Surg (including ICU) N unknown Observational (California)	Reported as % of correct usage observations (once in the morning & once in the evening). Pre and post education imitative	▪ Surgical ward: Pre: 62% (131/213) Post: 65% (93/142) ▪ Non-surgical ward: Pre & post: 48% (73/152)

Study	*Population & setting*	*Methods and definition of measurement*	*Outcomes (Adherence)*
IPCD (calf length) [506]	Orthopaedic (trauma/THR/TKR) N=70 Observational (Pennsylvania)	Surveys (Patients at Day 3/ discharge, staff at end of study) % time used	▪ 81-85% patient reported ▪ 66-71% staff reported
Mechanical - GCS			
GCS [33,510]	Mixed surgery wards N=218 Observational (UK)	Number of patients observed to wear stockings and wearing it correctly. Observation carried out in 16 wards in 1 day.	▪ 9/14 thigh-length ▪ 77/85 knee-length ▪ Overall correct use: 86/218 (39%)
Mechanical – GCS + IPCD or FID			
GCS + IPCD [555]	THR/TKR Observational N=120	Hourly nursing observation (b)	▪ Total of 64.1 hours ▪ 75.4% (54.3/72 hours) for 3 days post operatively
GCS + IPCD [78] 60% and 51% had thigh-length IPCD respectively	Med & surg, N=137 Observational (California)	% wearing IPCD or GCS, and % of correct fitting observed at one time point (timing not stated)	▪ IPCD: 29.2% wearing, 19% wearing correctly ▪ GCS: 62.8% wearing, 25.5% wearing correctly

THR = Total hip replacement; TKR = Total knee replacement; N = number of participants, GCS = anti-embolism stockings/ graduated compression stockings; IPCD – Intermittent pneumatic compression devices; SC = subcutaneous
For details about the studies, see Evidence Tables 61-63, Appendix D.

(a) In this study, adherences were measured pre and post an awareness campaign among staff and provision of a small leaflet to patients to remind them about keeping the devices on. For details, see Chapter 32

(b) The methods of adherence measurement in for the FID and IPCD+GCS arms for Robertson et al[555] was different because the FID had an integral measurement meter. The IPCD+GCS combination had to be done only through hourly observations by nursing staff.

6.7 Recommendations and link to evidence – mechanical prophylaxis

The following recommendations cover the general use of mechanical methods of prophylaxis. Recommendations for specific patient groups are discussed in the later chapters.

Recommendation	**Base the choice of mechanical VTE prophylaxis on individual patient factors including clinical condition, surgical procedure and patient preference. Choose any one of:** • **anti-embolism stockings (thigh or knee length)** • **foot impulse devices** • **intermittent pneumatic compression devices (thigh or knee length)**
Trade off between clinical benefit and harms	There is a lack of strong evidence available to suggest one method of mechanical prophylaxis is better than any other other, or to suggest thigh length of stockings or intermittent pneumatic compression devices are better than knee length.
Economic considerations	None

Other considerations	None

Recommendation	**Do not offer anti-embolism stockings to patients who have:** • **suspected or proven peripheral arterial disease** • **peripheral arterial bypass grafting** • **peripheral neuropathy or other causes of sensory impairment** • **any local conditions in which stockings may cause damage for example fragile 'tissue paper' skin, dermatitis, gangrene or recent skin graft** • **known allergy to material of manufacture** • **cardiac failure** • **severe leg oedema or pulmonary oedema from congestive heart failure** • **unusual leg size or shape** • **major limb deformity preventing correct fit.** **Use caution and clinical judgement when applying anti-embolism stockings over venous ulcers or wounds.**
Trade off between clinical benefit and harms	In cases where patients have a known contra-indication to anti-embolism stockings this outweighs the benefit of reducing the risk of VTE and the stockings should not be offered. The patient should be offered alternative methods of prophylaxis.
Economic considerations	None
Other considerations	None

Recommendation	**Ensure that patients who need anti-embolism stockings have their legs measured and that the correct size of stocking is provided. Anti-embolism stockings should be fitted and patients shown how to use them by staff trained in their use.**
Recommendation	**Ensure that patients who develop oedema or postoperative swelling have their legs re-measured and stockings refitted.**
Trade off between clinical benefit and harms	Stockings protect against venous thrombosis but if incorrectly fitted the harms may outweigh the benefits. Poorly fitted stockings or those of an incorrect shape and size have the potential to cause a tourniquet effect on the proximal part of the limb where the stocking is applied. This can result in ischaemia and an increased risk of thrombosis development.

Economic considerations	Although there is a cost involved in the nursing time required to fit stockings clearly it would not be cost effective to provide stockings that were not effective at reducing the risk of VTE.
Other considerations	Properly fitting stockings increase the effectiveness at reducing VTE. Poorly fitting stockings are unlikely to be worn by patients. Patients legs may swell during hospitalisation, particularly after surgery and so it is important that patients legs are re-measured in this situation.

Recommendation	**If aterial disease is suspected, seek expert opinion before fitting anti-embolism stockings.**
Trade off between clinical benefit and harms	Although it takes staff time to measure pedal pulses the GDG considered that this was worthwhile in certain high risk patients as it is important to ensure the safety of patients wearing anti-embolism stockings.
Economic considerations	It is clear that the cost-effectiveness of stockings is dependent on patient selection, information and adherence. In our cost-effectiveness analyses comparing different types of prophylaxis (Chapter 4) we included the cost of clinician time for the administration of anti-embolism stockings.
Other considerations	None

Recommendation	**Use anti-embolism stockings that provide graduated compression and produce a calf pressure of 14-15mmHg.**
Trade off between clinical benefit and harms	The effectiveness of these prophylactic methods in reducing the risk of pulmonary embolism and deep vein thrombosis was considered against the potential of causing bleeding problems. The correct pressure profile needs to be used to give the best balance between benefits and harms.
Economic considerations	None
Other considerations	The above pressure profile has been identified as the profile which is effective at reducing the risk of venous thromboembolism

Recommendation	**Encourage patients to wear their anti-embolism stockings day and night until they no longer have significantly reduced mobility.**
Recommendation	**Remove anti-embolism stockings daily for hygiene purposes and to inspect skin condition. In patients with a significant reduction in mobility, poor skin integrity or any sensory loss, inspect the skin two or three times per day, particularly the heels and bony prominences.**
Relative values of different outcomes	The GDG considered that it was a priority to reduce the risk of death from PE and to prevent long term morbidity from DVT such as PTS. However the safety of the patient and adverse effects of the prophylaxis should be considered.
Economic considerations	The cost-effectiveness of stockings will continue as long as the patient is immobile. However, they may no longer be cost-effective when the patient has returned to the community because of the need to monitor use. There is no cost-effectiveness evidence for the prophylactic use of stockings beyond discharge.
Other considerations	None

Recommendation	**Discontinue the use of anti-embolism stockings if there is marking, blistering or discolouration of the skin, particularly over the heels and bony prominences or the patient experiences pain or discomfort. If suitable offer a foot impulse device or intermittent pneumatic compression device as an alternative.**
Trade off between clinical benefit and harms	The effectiveness of these prophylactic methods in reducing the risk pulmonary embolism and deep vein thrombosis was considered against the potential of causing harm and patient comfort.
Economic considerations	Clearly, it would not be effective or cost-effective to provide stockings, if contra-indicated. Regular checking will reduce the risk of patients experiencing adverse events caused by the use of stockings which may add additional cost to the health service.
Other considerations	None

Recommendation	**Show patients how to use anti-embolism stockings correctly and ensure they understand that this will reduce their risk of developing VTE.**
Recommendation	**Monitor the use of anti-embolism stockings and offer assistance if they are not being worn correctly.**
Trade off between clinical benefit and harms	Not wearing the stockings as instructed may mean the patient is not adequately protected against VTE. Poorly fitted stockings or those of an incorrect shape and size have the potential to cause a tourniquet effect on the proximal part of the limb where the stocking is applied. This can result in ischaemia and an increased risk of thrombosis development.
Economic considerations	Clearly, it would not be effective or cost-effective to provide stockings, if contra-indicated. Regular checking will reduce the risk of patients experiencing adverse events caused by the use of stockings which may add additional cost to the health service.
Other considerations	None

For patients who are discharged with antiembolism stockings, further guidance is provided in section 32.6

Recommendation	**Do not offer foot impulse or intermittent pneumatic compression devices to patients with a known allergy to the material of manufacture.**
Trade off between clinical benefit and harms	In cases where patients have a known contra-indication to intermittent pneumatic compression devices and foot impulse devices this outweighs the benefit of reducing the risk of VTE and these devices should not be offered. The patient should be offered alternative methods of prophylaxis.
Economic considerations	Clearly, it would not be effective or cost-effective to provide intermittent pneumatic compression devices or foot impulse devices, if contraindicated.
Other considerations	None

Recommendation	**Encourage patients on the ward who have foot impulse or intermittent pneumatic compression devices to use them for as much of the time as is possible and practical, both when in bed and when sitting in a chair.**
Trade off between clinical benefit and harms	Not wearing the using the devices as instructed may mean the patient is not adequately protected against VTE.
Economic considerations	The cost-effectiveness of intermittent pneumatic compression or foot impulse devices will continue as long as the patient is immobile.
Other considerations	None

6.8 Recommendations and link to evidence – pharmacological prophylaxis

Recommendation	**Base the choice of pharmacological agents on local policies and individual patient factors, including clinical condition (such as renal failure) and patient preferences**
Trade off between clinical benefit and harms	Different prophylaxis methods have different levels of evidence of efficacy and safety in different populations. Ideally, the choice of agent should be based on the most evidence-based and cost-effective agent for a given population. However, in situations where there are strong patient concerns, these need to be discussed openly.
Economic considerations	Where a choice of agents is provided within a recommendation this is based either on the results of the cost-effectiveness model for that population, or on the extrapolation of cost-effectiveness results in other populations. In these circumstances the guideline development group were unable to conclusively state which of the strategies were the most cost-effective. Another of the reasons for local factors to influence choice of drug is that the contract prices (and therefore cost-effectiveness) of some of the drugs vary considerably between NHS Trusts.
Other considerations	While it is important to offer patients alternatives if there are concerns about using animal based products, it is also important that patients are aware of the clinical benefits or disadvantages (if any) of using these alternative products. More information is available in section 32.5.

6.9 Summary of recommendations

Mechanical VTE prophylaxis

- Base the choice of mechanical prophylaxis on individual patient factors including clinical condition, surgical procedure and patient preference. Choose any one of:
    - anti-embolism stockings (thigh or knee length)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length)
- Do not offer anti-embolism stockings to patients who have:
    - suspected or proven peripheral arterial disease
    - peripheral arterial bypass grafting
    - peripheral neuropathy or other causes or sensory impairment
    - any local conditions in which stockings may cause damage e.g. fragile 'tissue paper' skin, dermatitis, gangrene or recent skin graft
    - known allergy to material of manufacture
    - cardiac failure
    - severe leg oedema or pulmonary oedema from congestive heart failure
    - unusual leg size or shape
    - major limb deformity preventing correct fit.

  Use caution and clinical judgement when applying anti-embolism stockings over venous ulcers.
- Ensure that patients who need anti-embolism stockings have their legs measured and that the correct size of stocking is provided. Stockings should be fitted and patients shown how to use them by staff trained in their use.
- Ensure that patients who develop oedema or postoperative swelling have their legs re-measured and stockings refitted.
- If aterial disease is suspected, detect pedal pulses and seek expert opinion before fitting anti-embolism stockings.
- Use anti-embolism stockings should provide graduated compression and produce a calf pressure of 14-15mmHg.
- Encourage patients to wear their anti-embolism stockings day and night until they no longer have significantly reduced mobility.

- Remove anti-embolism stockings daily for hygiene purposes and to inspect skin condition. In patients with a significant reduction in mobility, poor skin integrity or any sensory loss, skin should be inspected two or three times per day, particularly the heels and bony prominences.

- Discontinue the use of anti-embolism stockings if there is marking, blistering or discolouration of the skin, particularly over the heels and bony prominences or the patient experiences pain or discomfort. If suitable offer a foot impulse device or intermittent pneumatic compression device as an alternative.

- Show patients how to use anti-embolism stockings correctly and ensure they understand that this will reduce their risk of developing VTE.

- Monitor the use of anti-embolism stockings and offer assistance if they are not being worn correctly.

- Do not offer foot impulse or intermittent pneumatic compression devices to patients with a known allergy to the material of manufacture.

- Encourage patients on the ward who have foot impulse or intermittent pneumatic compression devices to use them for as much of the time as is possible and practical, both when in bed and when sitting in a chair.

Pharmacological VTE prophylaxis

- Base the choice of pharmacological agents on local policies and individual patient factors, including clinical condition (such as renal failure) and patient preferences.

7 Nursing care: early mobilisation, physiotherapy and hydration

7.1 Early mobilisation and leg exercises

7.1.1 Introduction

Immobility and lack of exercise are widely accepted as risk factors for developing venous thromboembolism. When normal venous pump function is lost as a result of bed rest, venous stasis manifests itself in two ways. Firstly, there is a decrease in the linear velocity of blood, affecting venous return from the lower extremities. Secondly, this decrease in the mean flow and pulsavity of the venous flow is followed by dilatation of the vein delaying further venous return and leading to venous stasis.

It has long been suggested that early mobilisation prevents stasis and reduces subsequent risk of thrombi formation[339,671]. Although there are no robust clinical data or RCTs, attesting to support the value of early mobilisation in combating venous stasis, experimental physiology has demonstrated that it promotes venous return and thus reduces the risk of VTE[213,600].

Leg exercises are a safe and effective method of increasing venous return to the heart. The contraction during leg exercises, particularly the calf muscle pump, compresses the deep leg veins and with the aid of the venous valves, moves blood flow toward the heart. Mechanical devices that perform continuous passive motion imitate these contractions and increase the volume and velocity of venous flow.

7.1.2 Clinical evidence

We identified no RCTs that looked at the effect of early mobilisation or leg exercises on venous thromboembolism outcomes measured using objective criteria.

7.1.3 Economic evidence

We did not find any relevant economic evidence.

7.1.4 Patient views

We did not identify any patient views evidence for leg exercises or early mobilisation.

7.2 Leg elevation

7.2.1 Introduction

Leg elevation has a dual physiological effect: it reduces limb swelling and promotes venous return by its gravitational effect. It is generally held that promoting venous return can contribute to the prevention of thrombi formation. In addition, postural changes in the supine position can have a haemodynamic effect and are associated with an increase in blood flow in deep veins and reduction in venous pressure.

7.2.2 Clinical evidence

We found one RCT that compared foot elevation with no intervention[560] (Evidence Table 66, Appendix D). Twenty five mixed surgical patients (elective surgery excluding surgeries performed on the leg below groin) were randomised to either bilateral leg elevation at 15 degrees from pre-medication until one week post surgery, or no leg elevation. The study did not report whether patients received any other VTE prophylaxis. Pulmonary embolism and major bleeding events were not reported.

Effect on DVT: No significant difference was found between leg elevation and no leg elevation (RR=1.08, 95% CI 0.35 to 3.40, one study) (Figure 250, Appendix E).

7.2.3 Economic evidence

We did not find any relevant economic evidence.

7.2.4 Patient views

We did not identify any patient views evidence for foot elevation.

7.3 Hydration

7.3.1 Introduction

It is believed that dehydration predisposes to venous thromboembolism. Kelly et al found a strong association between dehydration after acute ischaemic stroke and VTE[335]. Allowing a patient to become dehydrated during surgery may also be associated with VTE.

7.3.2 Clinical evidence

We found one RCT that looked at the effect of intravenous saline administration on post-operative deep vein thrombosis[308] (Evidence Table 67, Appendix D). Sixty patients undergoing routine abdominal surgery were randomised. Thirty patients received 1 litre of Hartmann's solution per hour of surgery, and then 2-3 litres of dextrose-saline per 24 hours for 2 days. Patients in the second group were given no intravenous fluids either during or after the surgery, but small, increasing amounts of water were allowed by mouth from the first day onwards. The study did not report location of thrombosis, pulmonary embolism or major bleeding events.

Effect on DVT: Intravenous saline was associated with a significantly higher number of DVT events (RR=4.50, 95% CI 1.06-19.11, one study) (Figure 251, Appendix E).

7.3.3 Economic evidence

We did not find any relevant economic evidence.

7.3.4 Patient views

We did not identify any patient views evidence for hydration.

7.4 Recommendations and link to evidence

Recommendation	**Encourage patients to mobilise as soon as possible.**
Relative values of different outcomes	The GDG considered that it was a priority to reduce the risk of death from PE and to prevent long term morbidity from DVT such as Post thrombotic syndrome. However the safety of the patient and adverse effects of the prophylaxis should be considered.
Trade off between clinical benefit and harms	Whilst encouraging patients to mobilise as soon as possible requires staff resources, the benefit of reducing the risk of VTE mean that it is good practice.
Economic considerations	There is no cost-effectiveness evidence for encouraging patients to mobilise early. The GDG believe that this represents a good use of resources.
Quality of evidence	There is no RCT evidence to contradict the practices of encouraging patients to mobilise early or exercising their legs while immobile in bed.
Other considerations	None

Recommendation	**Do not allow patients to become dehydrated unless clinically indicated.**
Relative values of different outcomes	The GDG considered that it was a priority to reduce the risk of death from PE and to prevent long term morbidity from DVT such as PTS.
Trade off between clinical benefit and harms	It was considered that unless clinically indicated for other reasons the potential to increase the risk of VTE whilst dehydrated meant that it was good practice to avoid this happening.
Economic considerations	It seems likely that this is cost-effective, since the cost of the intervention is minimal.

Quality of evidence	We found no RCTs that looked at the effect of oral hydration on venous thromboembolism. This recommendation was developed through GDG consensus.
Other considerations	None

7.4.1 Recommendations for research

Although the GDG did not rate research into nursing care for the prevention of VTE as one of their top 5 research recommendations (See section 2.3) they did acknowledge that there was a lack of research in this area and more research would be beneficial.

7.5 Summary of recommendations

- Encourage patients to mobilise as soon as possible.
- Do not allow patients to become dehydrated unless clinically indicated.

8 Vena caval filters

8.1 Introduction

Vena caval filters are placed in the inferior vena cava by radiologically controlled percutaneous techniques. Their purpose is to trap the thrombus which comes free from the veins of the lower limbs or pelvis and to prevent them reaching the pulmonary circulation. In the earlier designs, once placed they could not be removed, but retrievable and temporary filters are now available. They are usually used in patients who have a known DVT and who may have already had an embolism or for patients in whom anticoagulation is contraindicated.

Filter placement necessitates instrumentation of the veins, either via the groin (femoral vein) or the neck (jugular vein) and there are complications associated with placement. These can occur immediately following placement or develop or come to light months to years later[253]. The complications include misplacement, pneumothorax, haematoma, air embolism, inadvertent carotid artery puncture and arteriovenous fistula.

8.2 Clinical evidence

We found no RCTs investigating vena caval filters, either permanent or retrievable, in surgical patients.

We identified one RCT that compared the use of permanent vena caval filters with no filters in 400 hospitalised patients with proximal DVT considered to be at high risk of pulmonary embolism (Evidence Table 69, Appendix D)[154]. All patients received vitamin K antagonists from the 4th day of the study and continued for at least 3 months. Patients were also randomised to receive either unfractionated heparin (UFH) or low molecular weight heparin (LMWH) for 8 to 12 days.

Significantly more patients had a pulmonary embolism in the first 12 days in patients without the filter than in those with the filter. More patients in the group allocated to receive no filters had symptomatic pulmonary embolism than those allocated to receive filters at 2 years and 8 years. The difference was significant at 8 years[636]. There was no difference in the number of major bleeds. However, significantly more patients using filters had recurrent DVT at 2 years.

8.3 Economic evidence

We found no economic studies evaluating vena cava filters specifically in surgical patients. However, we did find six economic studies that evaluated vena cava filters in other contexts (Evidence Table 70, Appendix D).

Two decision models[80,105] compared the surgical placement of vena cava filters with anticoagulation in high-risk trauma patients and in patients with malignant brain tumour. Both studies found that the filter was not cost-effective. A third decision model[583] found that vena cava filter placement is cost-saving compared with either anticoagulation or observation for patients with advanced cancer. However, their assumption of a 90% reduction in symptomatic VTE attributable to filters seems optimistic compared with the RCT results above.

Four studies, three cohort studies[60,168,303] and one decision model[80] found that bedside percutaneous placement of vena cava filters was less costly and safe compared with surgical placement.

8.4 Patient views

No studies of patient views were identified for vena caval filters.

8.5 Recommendations and link to evidence

Recommendation	**Consider offering temporary inferior vena caval filters to patients who are at very high risk of VTE (such as previous VTE event or an active malignancy) and for whom mechanical and pharmacological VTE prophylaxis are contraindicated.**
Relative values of different outcomes	The GDG considered that it was a priority to reduce the risk of death from PE and to prevent long term morbidity from DVT such as PTS. However the safety of the patient and adverse effects of the prophylaxis should be considered.
Trade off between clinical benefit and harms	This is a more invasive method of prophylaxis and therefore the GDG considered this should only be offered to patients at high risk of VTE where all methods of pharmacological and mechanical prophylaxis are contraindicated. The recommendation is made on the basis that the filter is to remain in situ only for the period of increased risk, and should be removed within 3 months. Permanent insertion of vena caval filters may be associated with an increased long-term risk of lower limb VTE.
Economic considerations	The economic data showed that vena cava filters are unlikely to be cost-effective in patients that can be coagulated. Where filters are prescribed bedside placement may be more cost-effective than surgical placement.

Quality of evidence	There is no evidence on the use of vena cava filters in this patient group. There was a significant reduction in PE on treating hospitalised patients with existing proximal DVTs using vena cava filters and anticoagulation. This recommendation was developed through GDG consensus.
Other considerations	The British Committee for Standards in Haematology have produced guidelines on the use of vena cava filters[85]. They reviewed the clinical studies mentioned above and came to a consensus on the recommendations.

8.6 Summary of recommendations

- Consider offering temporary inferior vena caval filters to patients who are at very high risk of VTE (such as patients with a previous VTE event or an active malignancy) and for whom mechanical and pharmacological VTE prophylaxis are contraindicated.

9 Gastrointestinal, gynaecological, laparoscopic, thoracic and urological surgery

9.1 Introduction

This section covers major abdominal and thoracic surgery. It includes both open and laparoscopic surgery. The introduction is presented in the following sections:

- Gastrointestinal surgery
- Bariatric surgery
- Gynaecological surgery
- Laparoscopic surgery
- Thoracic surgery
- Urological surgery

All data were analysed together when investigating the clinical and cost-effectiveness of VTE prophylaxis in these groups.

Gastrointestinal surgery

This section covers inpatients undergoing open gastrointestinal surgery. Gastrointestinal surgery of its nature is heterogeneous in the age of patients, the pathological conditions being dealt with and organs and systems operated upon. There remain a variety of procedures retained within this category that are specialisations in themselves. These include upper gastrointestinal surgery and lower intestinal surgery (or coloproctology).

We have no data specifically reported as gastrointestinal surgery. Most studies were classified as 'general surgery'. We have estimated from the incidence of RCTs that the risk of developing DVT, pulmonary embolism and major bleeding in general surgery patients not receiving thromboprophylaxis is:

- DVT - 24% (95% confidence intervals: 23% to 26%)
- Symptomatic pulmonary embolism – 1% (95% confidence intervals: 1% to 2%)

- Major bleeding - 2% (95% confidence intervals: 1% to 2%)

Factors that may alter the risk of VTE

- Patients having surgery for cancer will have an increased risk of developing a DVT or pulmonary embolism.

- Patients having emergency procedures are often elderly and will consequently be at higher risk of developing a DVT or pulmonary embolism.

- Some patients having emergency procedures may already be using anticoagulation or antiplatelet therapy. This needs to be considered when deciding on the method of VTE prophylaxis.

There are no specific factors that increase the risk of bleeding or the hazard associated with it in open gastrointestinal surgery.

There are no other special factors that would affect the choice of, and use of, specific methods of VTE prophylaxis in open gastrointestinal surgery.

Bariatric surgery

This section covers inpatients undergoing open gastrointestinal surgery. Although part of gastrointestinal surgery, all patients undergoing bariatric surgery would be considered at increased risk of VTE because they have a BMI of greater than 30 and are therefore classified as obese. Consequently, we have mentioned them separately. Most bariatric surgery is performed laparoscopically.

No data were available specifically investigating patients under bariatric surgery so no estimates are available for the risk of DVT, pulmonary embolism or major bleeding.

All patients are at high risk of developing VTE due to obesity. It is not known whether the presence of additional risk factors will add to this risk.

Factors that may increase the risk of bleeding or the hazard associated with it:

- Difficult access may result in poor views because of obesity

- There is a danger of converting from laparoscopic to open surgery if bleeding occurs

Other factors that may affect the choice of prophylaxis:

- There may be a higher number of patients who are contraindicated to anti-embolism stockings in this group because of an unusal leg size and shape.

- There is a higher incidence of diabetes which may mean a higher number of patients will contraindicated to anti-embolism stockings due to diabetic neuropathy.

Gynaecological surgery

This section covers inpatients undergoing open gynaecological surgery excluding caesarean section (see section 30). This includes abdominal and vaginal surgery.

We have estimated from the incidence of RCTs that the risk of developing DVT, pulmonary embolism and major bleeding in gynaecological surgery patients not receiving thromboprophylaxis is:

- DVT - 16% (95% confidence intervals: 13% to 19%)
- Symptomatic pulmonary embolism – 1% (95% confidence intervals: 0% to 3%)
- Major bleeding - 4% (95% confidence intervals: 2% to 7%)

Factors that may alter the risk of VTE:

- Patients may be using hormonal contraception and hormone replacement therapy, which will increase their risk of developing a DVT or pulmonary embolism.
- Patients having surgery for cancer will have increased risk of developing a DVT or pulmonary embolism.

There are no special factors that increase the risk of bleeding or the hazard associated with it in open gynaecological surgery.

There are no other special factors that would affect the choice of, and use of, specific methods of VTE prophylaxis in open gynaecological surgery.

Urological surgery

This section covers inpatients undergoing open urological surgery. The procedures can be divided into two major groups: pelvic cancer surgery and renal surgery. Patients undergoing these procedures are usually between the ages of 65 and 75.

We have estimated, from the incidence in the RCTs (Chapter 5), that the risk of developing DVT, pulmonary embolism and major bleeding in urological surgery patients not receiving VTE thromboprophylaxis is 10% (95%CI: 6% to 15%) ,

- DVT - 10% (95% confidence intervals: 6% to 15%).
  Its ranking in among other surgery in our HES data would suggest that the risk could be higher.
- Symptomatic pulmonary embolism – 1% (95% confidence intervals: 0% to 3%)
- Major bleeding - 4% (95% confidence intervals: 2% to 7%)

Factors that may alter the risk of VTE:

- Many urological surgery patients get spinal and epidural anaesthesia. This may reduce the risk of developing a deep vein thrombosis.

- Renal surgery procedures may involve division of the renal vein where it drains into the inferior vena cava possibly. This could potentially increase the risk of VTE.

There are no other special factors that would affect the choice of, and use of, specific methods of VTE prophylaxis in open urological surgery.

Thoracic surgery

We did not find data from the placebo arms of RCTs (Section 5.3) that would allow us to estimate the risk of developing deep vein thrombosis in thoracic surgery patients not receiving thromboprophylaxis. However, according to our HES data, its ranking among other surgery would suggest that the risk is high.

Factors that may alter the risk of VTE

- After lung resection, pulmonary embolism to the remaining lung carries a commensurately higher risk of death.

- Most patients having video-assisted thorascopic surgery (VATS), particularly for pneumothorax, are young (less than 30 years) and are able to walk around the ward up to the time of surgery and soon after and have short lengths of stay.

There are no special factors that increase the risk of bleeding or the hazard associated with it in thoracic surgery.

There are no other special factors that would affect the choice of, and use of, specific methods of VTE prophylaxis in thoracic surgery.

Laparoscopic surgery

We did not find data from the placebo arms of RCTs (Section 5.3) that would allow us to estimate the risk of developing deep vein thrombosis in laparoscopic surgery patients not receiving thromboprophylaxis.

Laparoscopic surgery is used in gastrointestinal, gynaecological and urological surgery. The same considerations apply to it in all these specialities.

Factors that may alter the risk of VTE

- There is some concern that the increased pressure in the peritoneal cavity during laparoscopic surgery would cause venous stasis[314,610,698].

- Laparoscopic procedures also tend to last longer than open urological procedures.

Factors that may alter the risk of bleeding

- Laparoscopic procedures may be associated with less bleeding than open surgery.

- Bleeding may make laparoscopic surgery difficult or impossible and result in the need for conversion to open surgery.

There are no other special factors that may affect the choice, and use of, specific methods of VTE prophylaxis in laparoscopic surgery.

9.2 Evidence of methods of prophylaxis

9.2.1 Summary of comparisons identified for any outcome

One hundred and forty six (146) randomised controlled trials which reported at least one of the three main outcomes were identified[1,5,9,10,13,14,29,30,32,37,40,46,48,50,52,54,57,65,72,75,76,82,89,92,100,104,111-117,119,138,140,171,172,179,182,199,207,209,210,224,227,230,238,246,254,262,264,266,267,269,279,280,282,283,308,319,321,324,328,329,358,359,361,363,366,368,371-373,384-386,393,403,406,407,414,416,423,424,429,439,440,486,487,496,498,499,503,504,511,516,517,528,530,532,546,547,550,552,560,568-570,575,585,586,588-590,592-594,599,611,629,633,639-641,643-645,653,656,657,667,670,682,685,691,693,694,703,711,713,716]. Some of these investigated more than two methods of prophylaxis, and some studies reported results in more than one paper. Most the RCTs had their data extracted from systematic reviews. Where applicable the study is cited in the evidence table for that review. Six systematic reviews included RCTs with patients having general surgical procedures[15,21,125,355,450,557].

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

	No prophylaxis	Post-discharge	GCS	IPCD/FID	Dabigatran	Fondaparinux	LMWH	UFH	VKA	Asp (HD)	Asp (LD)	GCS + IPCD/FID	Mech + pharm
GCS	**5**												
IPCD/FID	**8**		**1**										
Dabigitran													
Fondaparinux													
LMWH	**8**	**3**				**1**							
UFH	**29**		**3**	**4**			**45**						
VKA (adjusted dose)	**2**			**1**				**2**					
High dose aspirin	**14**							**2**					
Low dose aspirin													
GCS + IPCD/FID			**2**					**1**					
Mech + pharm			**4**			**1**		**3**		**2**		**2**	
Other comparisons								**1**					**2**

Figure 9-6: Number of studies which compared various types of prophylaxis methods.

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicates areas where no studies were identified.

GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) - low dose aspirin (≤ 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis

9.2.2 Results from pairwise comparisons

Table 9-30: DVT – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
GCS vs no prophylaxis[13,593,599,643,644]	5	30/448	90/435	0.35 (0.24, 0.51)	-0.13 (-0.22, -0.04)	ET: 23 FP: 1
IPCD/FID vs no prophylaxis[65,89,112,114,117,119,279,594]	8	37/402	82/389	0.44 (0.24, 0.81) (a)	-0.12 (-0.21, -0.03)	ET: 24 FP: 4
LMWH vs no prophylaxis[386,423,499,653]	4	6/219	28/214	0.22 (0.10, 0.51)	-0.10 (-0.22, 0.03)	ET: 26 FP: 13
UFH vs no prophylaxis[5,30,54,113,115,119,209,230,238,266,371,385,416,424,528,552,585,629,633,639,703]	21	170 /1729	342 /1586	0.45 (0.36, 0.56)	-0.12 (-0.16, -0.09)	ET: 27 FP: 17
VKA (adj dose) vs no prophylaxis[530,633]	2	4/83	22/85	0.21 (0.07, 0.58)	-0.21 (-0.31, -0.11)	ET: 28 FP: 21

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Aspirin (high dose) +/- other antiplatelet vs no prophylaxis[1,111,172,498,511,528,550,682,711,716]	12	196/836	195/647	0.65 (0.46, 0.92) (b)	-0.11 (-0.20, -0.03)	ET: 29 FP: 28
Single proph vs single						
GCS vs UFH[182,254,546]	3	30/151	30/155	1.07 (0.69, 1.67)	0.01 (-0.06, 0.09)	ET: 37 FP: 84
IPCD vs UFH[116,119,254,363]	4	8/222	15/228	0.61 (0.25, 1.49)	-0.02 (-0.08, 0.03)	ET: 37 FP: 90
IPCD vs VKA (adj dose)[104]	1	4/47	0/53	10.13 (0.56, 183.23)	0.09 (0.00, 0.17)	ET: 37 FP: 95
LMWH vs UFH[9,32,37,50,55,57,72,75,82,92,138,140,171,179,199,210,224,227,262,269,328,329,358,359,361,393,439,496,503,575,586,588,667,670,685]	35	338/ 7436	385/ 7152	0.89 (0.77, 1.03)	0.00 (-0.01, 0.00)	ET: 32 FP: 48
Fondaparinux vs LMWH[10]	1	43/1024	59/1018	0.72 (0.49, 1.06)	-0.02 (-0.03, 0.00)	ET: 31 FP: 44
Aspirin (high dose) vs UFH[406,528]	2	22/101	14/99	1.48 (0.81, 2.70)	0.05 (-0.06, 0.16)	ET: 36 FP: 64
VKA vs UFH[633,656]	2	12/98	4/99	2.74 (0.30, 24.92) (c)	0.08 (-0.08, 0.24)	ET: 33 FP: 54
Double proph vs single						
GCS + IPCD vs IPCD[440,592]	2	8/132	13/132	0.49 (0.06, 4.02)	-0.04 (-0.14, 0.06)	ET: 38 FP: 106
GCS + UFH vs UFH[546,640,691,693]	4	30/352	56/354	0.37 (0.14, 0.98)	-0.08 (-0.12, -0.04)	ET: 38 FP: 109
Fondaparinux + IPCD vs IPCD[645]	1	7/424	22/418	0.31 (0.14, 0.73)	-0.04 (-0.06, -0.01)	ET: 40 FP: 131
Aspirin + UFH vs UFH[406,713]	2	17/107	27/106	0.64 (0.37, 1.09)	-0.10 (-0.20, 0.00)	ET: 42 FP: 162
UFH + GCS vs GCS[368,486,657]	3	5/159	46/168	0.18 (0.04, 0.82) (d)	-0.24 (-0.31, -0.16)	ET: 27 FP: 142
UFH + aspirin vs aspirin[406]	1	5/57	19/63	0.29 (0.12, 0.73)	-0.21 (-0.35, -0.08)	ET: 27 FP: 150
GCS + IPCD vs UFH[487]	1	3/50	7/50	0.43 (0.12, 1.56)	-0.08 (-0.20, 0.04)	ET: 37 FP: 105
Double proph vs double						
IPCD + GCS vs LMWH + GCS[429]	1	1/106	2/105	0.50 (0.05, 5.38)	-0.01 (-0.04, 0.02)	ET: 49 FP: 202
IPCD + GCS vs UFH + GCS[440]	1	10/54	2/52	4.81 (1.11, 20.93)	0.15 (0.03, 0.26)	ET: 50 FP: 120
LMWH + GCS vs UFH + GCS[403,589]	2	6/184	3/139	1.29 (0.32, 5.16)	0.01 (-0.02, 0.05)	ET: 45 FP: 174
Post discharge prophylaxis						
LMWH vs no prophylaxis[46,384,547]	3	23/388	52/402	0.46 (0.29, 0.74)	-0.07 (-0.11, -0.03)	ET: 58 FP: 225

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*

(a) There was significant heterogeneity within the results (chi squared on 6 df =13.52, p=0.04, I^2 =55.6%) which was largely attributable to the inclusion of one study of patients undergoing pelvic surgery for malignancy[114].

(b) There was significant unexplained heterogeneity within the results (chi squared on 11 df =34.99.52, p=0.0002, I^2 =68.6%). This does not appear to be due to speciality, year of publication or antiplatelet dose.

(c) *There was significant heterogeneity between the two studies (chi squared on 1 df =3.00, p=0.08, I^2 =66.7%). One study gave different durations of treatment[633] with vitamen K antagonist given for 14 days and the UFH given for 7 days. This study showed no difference in DVT whereas the other significantly favoured UFH.*

(d) *There was significant heterogeneity within the results (chi squared on 2 df =5.12, p=0.08, I^2 =60.9%). One study[486] had a greater reduction in DVT compared to the other two[368,657].*

Table 9-31: Pulmonary embolism – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
IPCD/FID vs no prophylaxis[114,117,119]	3	6/192	3/186	1.79 (0.43, 7.45)	0.02 (-0.01, 0.05)	ET: 24 FP: 5
LMWH vs no prophylaxis[280,499,504,516,653]	5	2/2551	13/2583	0.22 (0.06, 0.78)	0.00 (-0.01, 0.00)	ET: 26 FP: 14
UFH vs no prophylaxis[5,40,113,119,238,371,373,424,504,552]	10	26/645	48/630	0.52 (0.30, 0.90)	-0.03 (-0.08, 0.01)	ET: 27 FP: 18
Aspirin +/- other antiplatelet vs no prophylaxis[1,111,172,407,511,528,550,682,711,716]	13	5/1820	23/1608	0.27 (0.11, 0.65)	-0.01 (-0.01, 0.00)	ET: 29 FP: 29
Single proph vs single						
GCS vs UFH[254]	1	1/25	1/25	1.00 (0.07, 15.12)	0.00 (-0.11, 0.11)	ET: 37 FP: 85
IPCD vs UFH[119,254,363]	3	3/121	3/121	1.00 (0.21, 4.84	0.00 (-0.04, 0.04)	ET: 37 FP: 91
IPCD vs VKA (adj dose)[104]	1	2/47	0/53	5.63 0.28, 114.27)	0.04 (-0.03, 0.11)	ET: 37 FP: 96
LMWH vs UFH[57,72,75,92,100,199,210,269,283,321,328,359,439,496,504,570,575,670]	18	18/4352	22/4343	0.95 (0.49, 1.84)	0.00 (0.00, 0.00)	ET: 32 FP: 49
Fondaparinux vs LMWH[10]	1	5/1465	3/1462	1.66 (0.40, 6.95)	0.00 (0.00, 0.01)	ET: 31 FP: 45
Aspirin (high dose) vs UFH[406]	1	0/63	2/57	0.18 (0.01, 3.70)	-0.04 (-0.09, 0.02)	ET: 36 FP: 65
Double proph vs single						
GCS + UFH vs UFH[691]	1	0/94	1/84	0.30 (0.01, 7.22)	-0.01 (-0.04, 0.02)	ET: 38 FP: 110
Fondaparinux + IPCD vs IPCD[645]	1	1/650	1/659	1.01 (0.06, 16.17)	0.00 (0.00, 0.00)	ET: 40 FP: 132
Aspirin + UFH vs UFH[406,713]	2	0/107	3/106	0.25 (0.03, 2.25)	-0.03 (-0.07, 0.01)	ET: 42 FP: 163
UFH + GCS vs GCS[368,486,657]	3	5/159	46/168	0.18 (0.04, 0.82)	-0.24 (-0.31, -0.16)	ET: 27 FP: 143
UFH + aspirin vs aspirin[406]	1	0/57	0/63	not estimable	0.00 (-0.03, 0.03)	ET: 27 FP: 151
Double proph vs double						
LMWH + GCS vs UFH + GCS[403]	1	0/103	0/100	not estimable	0.00 (-0.02, 0.02)	ET: 45 FP: 175
Post discharge prophylaxis						
LMWH vs no prophylaxis[46,547]	2	0/370	4/389	0.22 (0.03, 1.94)	-0.01 (-0.02, 0.00)	ET: 58 FP: 226

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*

Table 9-32: Major bleeding – summary of results from RCTs

Comparison	No. of studies	Interven -tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
LMWH vs no prophylaxis[29,280,386,499,504,516,653]	7	75 /2696	37 /2730	2.01 (1.31, 3.07)	0.01 (0.01, 0.02)	ET: 26 FP: 15
UFH vs no prophylaxis[5,14,40,54,113,230,238,266,319,366,371,385,416,424,504,552,569,585,633,639,703]	22	97 /1878	58 /1664	1.38 (0.98, 1.96)	0.01 (0.00, 0.02)	ET: 27 FP: 19
VKA (adj dose) vs no prophylaxis[530,633]	2	11/83	5/85	1.97 (0.75, 5.15)	0.07 (0.00, 0.14)	ET: 28 FP: 23
Aspirin +/- other antiplatelet vs no prophylaxis[111,172,511,528,550,682,711,716]	9	3/568	0/400	2.42 (0.13, 45.97)	0.00 (-0.01, 0.02)	ET: 29 FP: 30
Single proph vs single						
GCS vs UFH[182]	1	0/52	0/45	not estimable	0.00 (-0.04, 0.04)	ET: 37 FP: 86
LMWH vs UFH[37,50,55,72,75,76,92,100,199,210,227,262,269,283,321,324,329,358,361,439,496,503,504,570,575,588,667]	28	232 /6716	239 /6716	1.09 (0.85, 1.40)	0.00 (-0.01, 0.01)	ET: 32 FP: 50
Fondaparinux vs LMWH[10]	1	49/1433	34/1425	1.43 (0.93, 2.21)	0.01 (0.00, 0.02)	ET: 31 FP: 46
Aspirin vs UFH[406]	1	0/63	0/57	Not estimable	0.00 (-0.03, 0.03)	ET: 36 FP: 66
VKA vs UFH[633]	1	3/48	5/49	0.61 (0.15, 2.42)	-0.04 (-0.15, 0.07)	ET: 33 FP: 56
Double proph vs single						
Fondaparinux + IPCD vs IPCD[645]	1	10/635	1/650	10.24 (1.31, 79.73)	0.01 (0.00, 0.02)	ET: 40 FP: 133
Aspirin + UFH vs UFH[406,713]	2	4/107	1/106	3.92 (0.45, 33.84)	0.02 (-0.06, 0.10)	ET: 42 FP: 164
UFH + GCS vs GCS[368,486,657]	3	5/165	1/168	3.08 (0.50, 18.95)	0.01 (-0.01, 0.03)	ET: 27 FP: 144
UFH + aspirin vs aspirin[406]	1	0/57	0/63	not estimable	0.00 (-0.03, 0.03)	ET: 27 FP: 152
Double proph vs double						
LMWH + GCS vs UFH + GCS[403,589]	2	2/187	0/142	2.53 (0.12, 51.53)	0.00 (-0.02, 0.03)	ET: 45 FP: 176
Post discharge prophylaxis						
LMWH vs no prophylaxis[46,547]	2	4/458	5/470	0.88 (0.08, 9.09) (a)	0.00 (-0.02, 0.02)	ET: 58 FP: 227

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*

(a) There was significant unexplained heterogeneity within the results (chi squared on 1 df =2.22, p=0.14, I^2 =54.9%).

9.2.3 Additional information

9.2.3.1 All cause mortality

All cause mortality was not identified as a key outcome during the development of the surgical guideline. Much of the data were identified from systematic reviews where all cause mortality was not reported. There was not time during the development of this guideline to review all cause mortality for this population.

9.2.3.2 Other outcomes

Chronic thromboembolic pulmonary hypertension, post thrombotic syndrome or heparin induced thrombocytopenia were not identified as key outcomes during the development of the surgical guideline. Much of the data were identified from systematic reviews where these outcomes were not reported. There was not time during the development of this guideline to check all RCTs for these outcomes.

9.2.3.3 Additional studies

An additional study compared post-discharge LMWH after video laparoscopic surgery[637]. Patients were randomised after on average just under 4 days in hospital to 7 days LMWH or no prophylaxis. Although most of the procedures could be described as general or other internal procedures, this paper appeared to include a different population to the other post-discharge studies: patients were in hospital for a shorter period, the duration was shorter and all procedures were laparoscopic. Also, the study planned to recruit 760 patients but stopped at 200 when it became apparent that the DVT risk in this group was far lower than expected. Consequently, it was not included in the network meta-analysis or economic model for post-discharge prophylaxis. There was only 1 DVT occurring within the 28 day post-discharge follow up that occurred in the group not receiving prophylaxis.

9.3 Network meta-analysis results

9.3.1 Introduction

A network meta-analysis was completed for DVT, symptomatic pulmonary embolism and major bleeding. Details on the network meta-analysis methods can be found in section 3.10.

9.3.2 Results

DVT results

There were 95 studies included in the network meta-analysis for DVT [1,5,9,10,13,14,30,32,37,50,52,54,57,72,82,89,92,104,111-117,119,138,171,172,179,182,209,210,224,230,238,254,262,264,266,267,269,279,328,329,358,359,361,363,368,371,372,385,393,403,406,416,423,439,486,496,498,499,503,511,528,530,546,550,552,553,575,585,586,589,593,594,599,629,633,639-641,643-645,653,656,667,670,682,685,691,693,703,713,716]. Six of these studies were trials comparing three prophylaxis methods within the same trial[119,254,406,528,546,633].

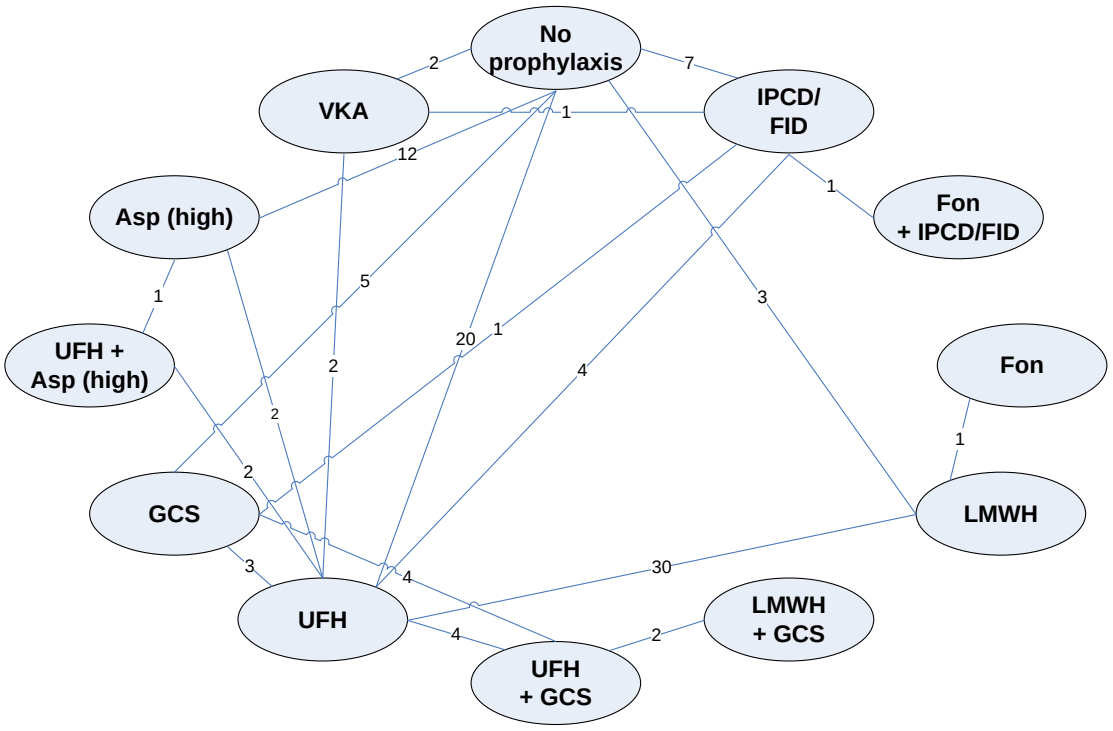


Figure 9-7: Network diagram for DVT. Numbers indicate the number of studies which contributed results for each comparison

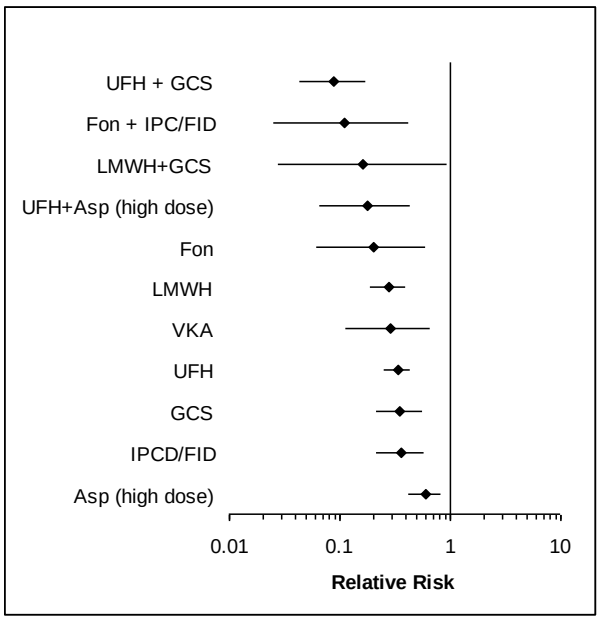


Figure 9-8: DVT – network meta-analysis results of interventions compared to no prophylaxis

Table 9-33: DVT – network meta-analysis results

Intervention (compared with no prophylaxis)	Relative Risk (95% credible intervals)
UFH + GCS	0.09 (0.04, 0.17)
Fondaparinux + IPCD/FID	0.11 (0.03, 0.43)
LMWH + GCS	0.16 (0.03, 0.94)
UFH + Asp (high dose)	0.18 (0.07, 0.44)
Fondaparinux	0.20 (0.06, 0.59)
LMWH	0.28 (0.19, 0.40)
VKA	0.29 (0.11, 0.66)
UFH	0.34 (0.25, 0.44)
GCS	0.35 (0.21, 0.56)
IPCD/FID	0.36 (0.22, 0.58)
Asp (high dose)	0.60 (0.42, 0.83)

Credible intervals are the Bayesian equivalent of confidence intervals. The residual deviance was 209.1, which is quite close to the number of data points of 196, implying that the model fits the data well.

Pulmonary embolism results

There were 37 studies included in the network meta-analysis for PE[5,10,40,57,72,100,104,113,114,117,119,199,238,254,280,283,359,363,371,372,406,407,424,439,496,499,516,517,550,552,553,575,590,645,670,682,691,713,716]. Of these, three studies compared three prophylaxis methods within the same trial[119,254,406].

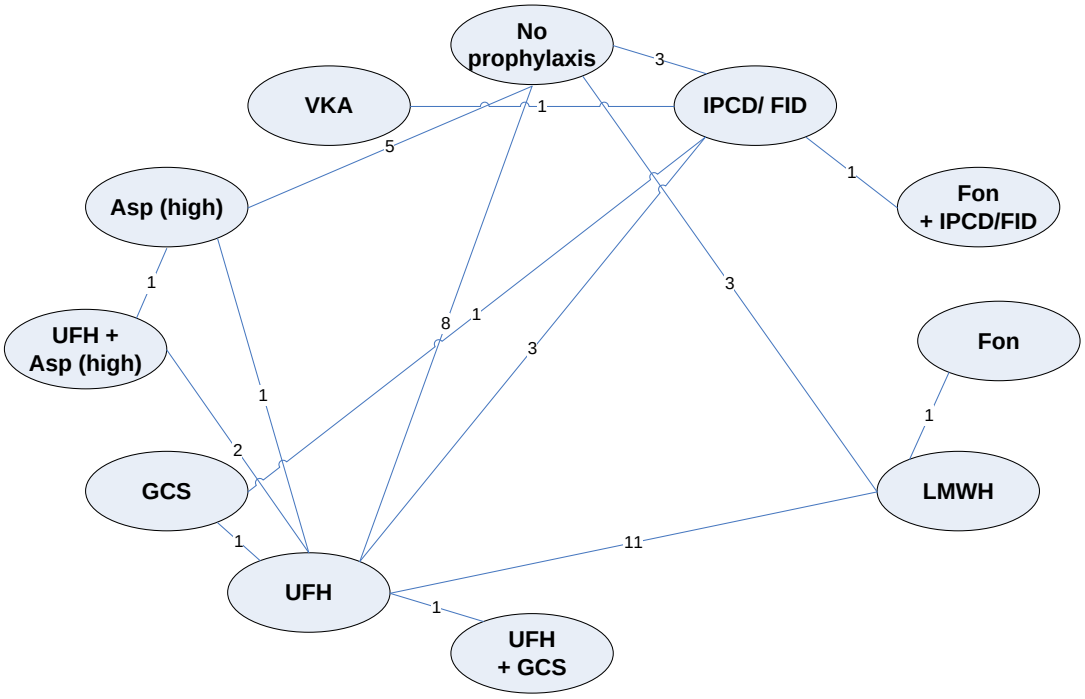


Figure 9-9: Network diagram for PE. Numbers indicate the number of studies which contributed results for each comparison

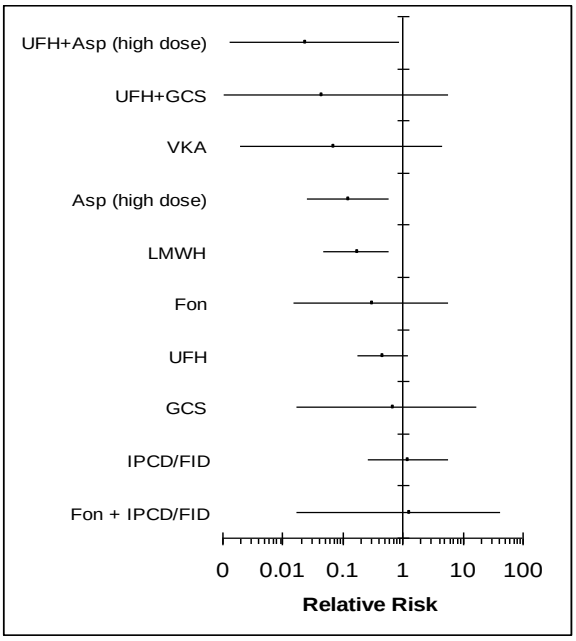


Figure 9-10: PE – network meta-analysis results of interventions compared to no prophylaxis

Table 9-34: Pulmonary embolism – network meta-analysis results

Intervention (compared with no prophylaxis)	Relative Risk (95% credible intervals)
UFH + Aspirin (high dose)	0.02 (0.00, 0.87)
UFH + GCS	0.04 (0.00, 5.63)
VKA (adjusted-dose)	0.07 (0.00, 4.49)
Aspirin (high dose)	0.13 (0.03, 0.58)
LMWH	0.18 (0.05, 0.59)
Fondaparinux	0.32 (0.02, 5.69)
UFH	0.48 (0.18, 1.26)
GCS	0.70 (0.02, 16.83)
IPCD/FID	1.27 (0.27, 5.80)
Fondaparinux + IPCD/FID	1.30 (0.02, 41.56)

Credible intervals are the Bayesian equivalent of confidence intervals.

The residual deviance was 79.3, which is quite close to the number of data points of 77, implying that the model fits the data well.

Major bleeding results

A network meta-analysis for major bleeding was conducted using studies across hip fracture surgery, hip replacement surgery, knee replacement surgery, general medical patients and general surgical patients.

One hundred and twenty eight (128) studies were included in the analysis of which:

- 10 studies were in **medical patients**[45,121,191,256,257,350,387,390,394,579],
- 48 studies were in **general surgery patients**[10,14,29,40,50,52,72,75,76,92,113,199,210,227,230,238,262,266,267,269,280,283,321,324,329,358,366,385,439,496,499,503,504,516,517,530,552,553,570,575,588,589,633,639,641,645,657,667,703,711,713],
- 28 studies were in **elective hip replacement patients**[126,129,151,153,174,188,195,201,202,243,260,293,299,377,380,400,409,421,465,527,573,574,635,650,651,659,684],
- 9 studies were in patients undergoing **hip fracture surgery**[175,178,204,248,463,533,609,704,715]
- 15 studies were in **elective knee replacement patients**[36,66,130,186,201,202,274,388,389,399,436,476,479].
- 7 studies were in **mixed orthopaedic surgery patients**[69,200,242,250,292,459,531]
- 11 studies were in **mixed surgery patients**[54,166,270,271,340-344,396,416,486,568,569,575,585,655].

Seven of these studies included three comparison arms[153,299,380,504,533,633,655].

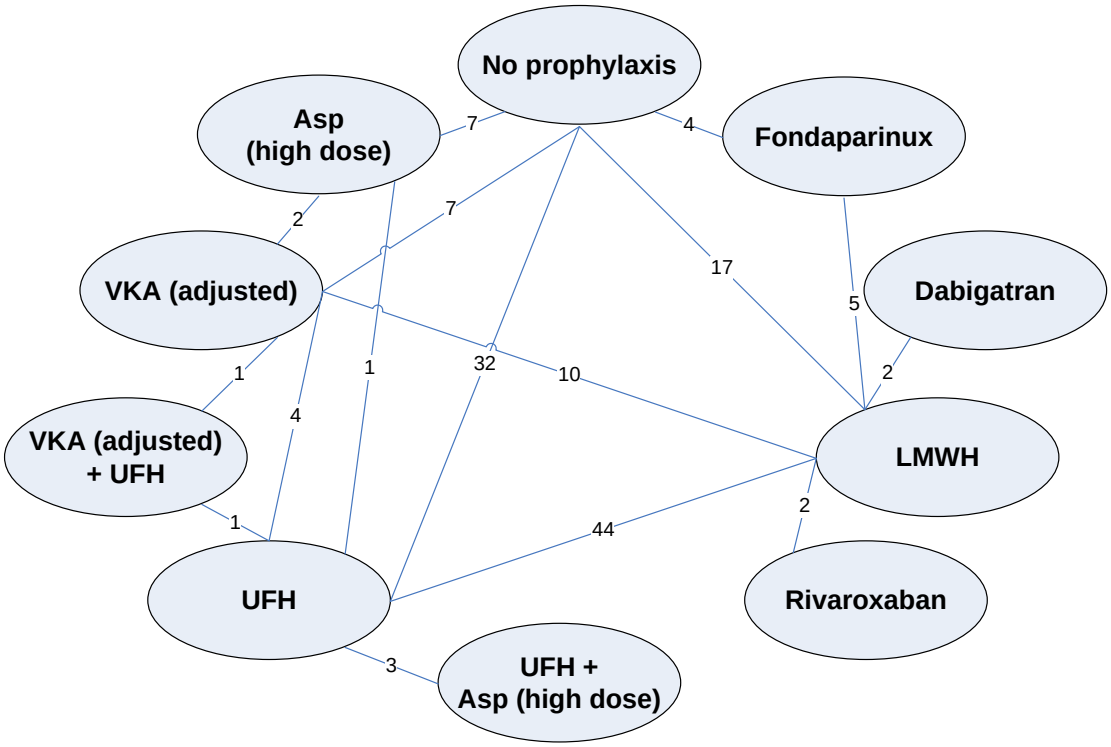


Figure 9-11: Network diagram for major bleeding. Numbers indicate the number of studies which contributed results for each comparison

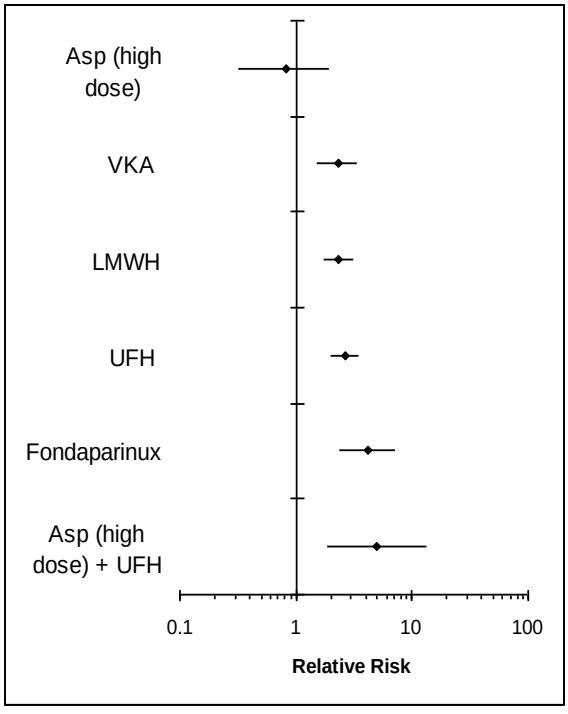


Figure 9-12: Major bleeding – network meta-analysis results of interventions compared to no prophylaxis (pooled across all population subgroups)

Table 9-35: Major bleeding – network meta-analysis results (pooled across all population subgroups)

Intervention (compared with no prophylaxis)	Relative Risk (95% credible intervals)
Aspirin (high dose)	0.83 (0.32, 1.98)
VKA	2.30 (1.54, 3.44)
LMWH	2.33 (1.74, 3.17)
UFH	2.66 (1.99, 3.56)
Fondaparinux	4.14 (2.41, 7.30)
Aspirin (high dose) + UFH	5.03 (1.89, 13.27)

Credible intervals are the Bayesian equivalent of confidence intervals.
The residual deviance was 291.5, which is quite close to the number of data points of 263, implying that the model fits the data well.

9.4 Cost-effectiveness evidence

9.4.1 Introduction

General assumptions and methods for model are described in chapter 4.

The results are driven by the network meta-analysis above. Other data used for the cost-effectiveness analysis which are specific to general surgical patients can be found in Table 9-36 and

Table 9-37.

Table 9-36: Baseline risk and other population specific parameters used in the economic model for general and other internal organ surgery patients

Baseline Characteristics	*Source*	*Value*
Mean age (years)	Systematic review of RCTs(b) (weighted mean)	60
% Male	Systematic review of RCTs(b)	50%
Standardised Mortality Ratio (a) (1 year)	Assumed	100%
Mean duration of prophylaxis (days)	Systematic review of RCTs(b)	7
Proportion of DVTs that are symptomatic (Ratio of symptomatic DVTs to all DVTs)	Systematic review of RCTs(b)	6.2% (40/644)
Major Bleed Fatality Rate (c)	Systematic review of RCTs[467]	0.8% (5/632)
PE Fatality Rate (d)	Systematic review of RCTs[557] (all elective surgery)	6.0% (11/184)
DVT risk	Systematic review of RCTs(b)	20.9%
Symptomatic PE risk	Systematic review of RCTs(b)	1.3%
Major bleeding risk	Systematic review of RCTs(b)	1.4%

(a) Ratio of the death rate in the surgical group compared with the death rate in the general population, adjusting for age and sex
(b) This refers to the systematic review of RCTs for the current guideline
(c) Fatal major bleeds divided by all major bleeds
(d) Fatal PEs divided by all symptomatic PEs

Table 9-37: Weights used for events in the base case analysis

Event	Cost (£)	QALYs lost	Net loss (£) (a)
DVT Asymptomatic	0	0.0000	0
DVT Symptomatic	576	0.0035	645
Post-thrombotic syndrome	9,998	0.2700	15,397
Chronic pulmonary hypertension	69,123	9.2206	253,534
Pulmonary embolism - fatal	0	12.5578	251,156
Pulmonary embolism - symptomatic	2,521	0.0041	2,603
Major bleeding - No long-term sequalae	827	0.0267	1,361
Major bleeding - Stroke	23,797	10.4943	233,683
Major bleeding - fatal	0	12.5578	251,156
Heparin-induced thrombocytopaenia (sensitivity analysis only)	2,714	1.8750	40,213

QALY=Quality-adjusted life-year
(a) Net loss is the sum of the resource cost plus the QALY loss multiplied £20,000

9.4.2 Base case results

Event rates by strategy can be found in Appendix G.

9.4.2.1 Standard duration prophylaxis results

Table 9-38: Base case results – deterministic and probabilistic results

a	*Deterministic INB*	*Probabilistic INB*	
Intervention	*Mean*	*Mean*	*% of simulations where strategy was most cost effective*
GCS	489	488	38.3%
IPCD-FID	463	464	24.5%
UFH_plus_GCS	409	408	4.1%
LMWH_plus_GCS	349	348	10.1%
LMWH	348	347	0.3%
AspirinHD	314	314	0.7%
UFH	241	241	0.0%
Fondaparinux_plus_IPCD-FID	130	127	0.2%
Fondaparinux	106	104	0.5%
VKA	317	75	0.0%
Nil	0	0	0.0%
UFH_plus_AspirinHD	-70	-694	21.3%

INB = Incremental Net Benefit. The strategy with the highest probabilistic mean INB is the most cost effective overall

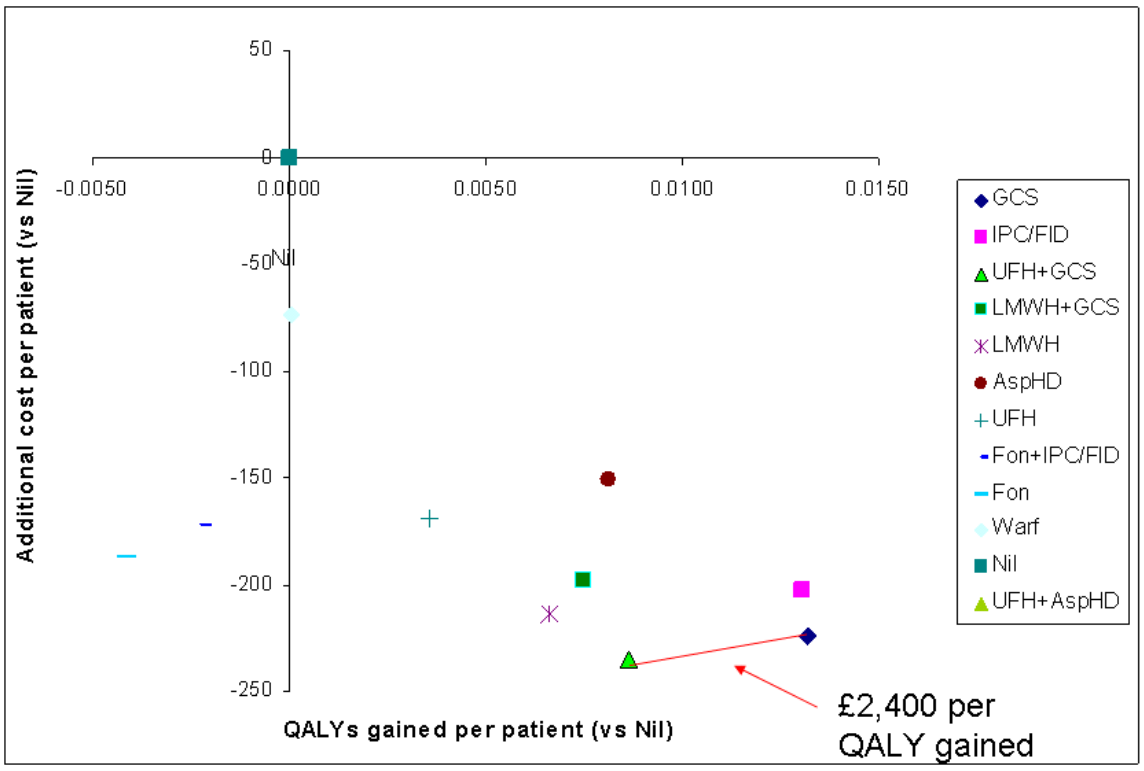


Figure 9-13: Base case results of the cost effectiveness analysis for general surgery and other internal organ patients: standard duration prophylaxis

'+' indicates two interventions used in parallel, UFH=unfractionated heparin, GCS=anti-embolism stockings, LMWH=low molecular weight heparin, IPC/FID=intermittent pneumatic compression device or foot impulse device, warf=vitamin k antagonist, fon=fondaparinux, nil=no prophylaxis, AspHD=high dose aspirin (>300mg)

9.4.3 Base case results – post-discharge prophylaxis

There was one study which investigated extended prophylaxis post-discharge. This study compared LMWH with no prophylaxis and randomised patients 10 -12 days after surgery

Table 9-39: Results for study post discharge comparing LMWH with no prophylaxis

a	*Deterministic INB*	*Probabilistic INB*	
Intervention	*Mean*	*Mean*	*% of simulations where strategy was most cost effective*
LMWH	123	49	77.5%
Nil	0	0	22.5 %

INB = Incremental Net Benefit. The strategy with the highest probabilistic mean INB is the most cost effective overall

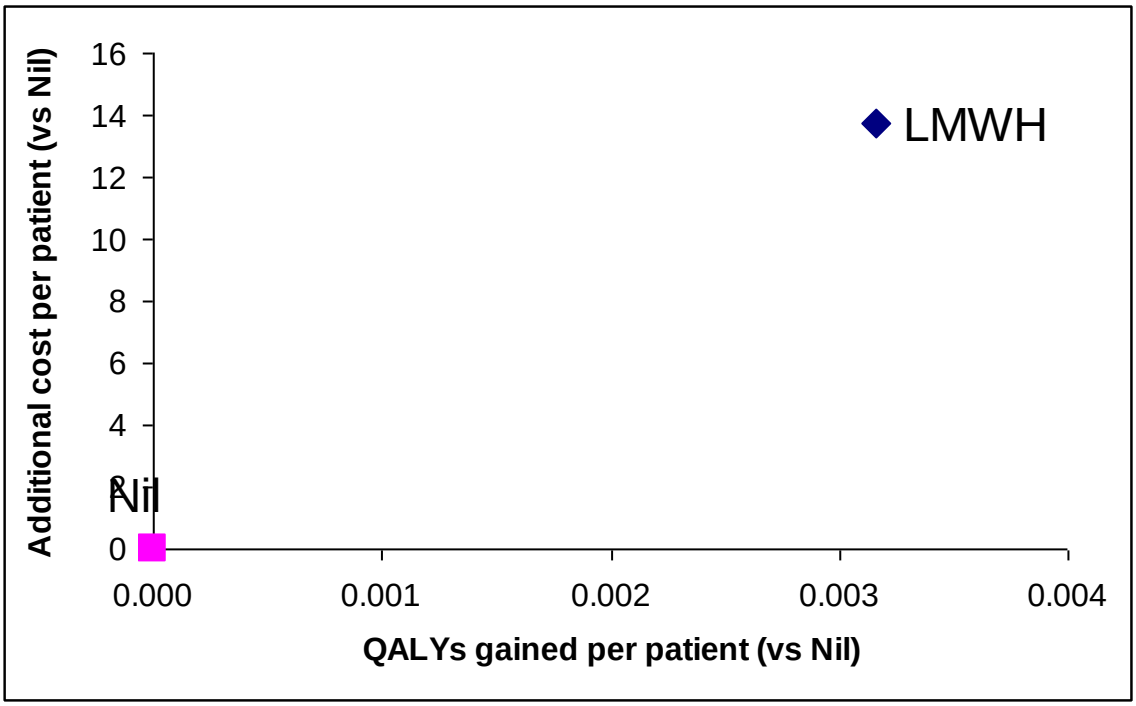


Figure 9-14: Base case results of the cost effectiveness analysis for general surgery and other internal organ patients: post-discharge prophylaxis

9.4.4 Deterministic sensitivity analysis

Table 9-40: Deterministic sensitivity analysis results

Factors changed within the Model	*Most Cost Effective Strategy*	
	Standard duration prophylaxis	*Post Discharge (LMWH vs Nil)*
Base case	GCS	LMWH
Base case (probabilistic)	GCS	LMWH
Chronic Thromboembolic Pulmonary Hypertension and Post Thrombotic Syndrome		
0% Chronic Thromboembolic Pulmonary Hypertension	GCS	LMWH
0.5% Chronic Thromboembolic Pulmonary Hypertension	GCS	LMWH
1% Chronic Thromboembolic Pulmonary Hypertension	GCS	LMWH
0% Chronic Thromboembolic Pulmonary Hypertension and 0% Post Thrombotic Syndrome	GCS	LMWH
High Post Thrombotic Syndrome rate (e.g. 30% after symptomatic DVT and 21% after asymptomatic DVT)	GCS	LMWH
Low Post Thrombotic Syndrome (e.g. 15% after symptomatic DVT and 8% after asymptomatic DVT)	GCS	LMWH
Low cost for Post Thrombotic Syndrome	GCS	LMWH
High cost for Post Thrombotic Syndrome	GCS	LMWH
High cost for Chronic Thromboembolic Pulmonary Hypertension	GCS	LMWH
Other Sensitivity Analyses		
Explicitly include Heparin Induced Thrombocytopenia (LMWH=0.8%, UFH=0.8%)	GCS	N/A
Explicitly include Heparin Induced Thrombocytopenia (LMWH=0.2%, UFH=2.6%)	GCS	N/A
Using population specific pulmonary embolism relative risk	High dose Aspirin	N/A
Using population specific major bleeding relative risks	GCS	N/A
Low aspirin major bleeding relative risk from Network Meta-analysis (RR = 0.5)	GCS	N/A
High aspirin major bleeding relative risk from aspirin vs. nil arms (RR = 1.3)	GCS	N/A
Discounted LMWH cost = £1	GCS	LMWH
Fatality after PE = 10%	GCS	LMWH
Fatality after Major Bleeding = 5%	GCS	LMWH
Foot Impulse Device (consumable: £40, pump: £0)	GCS	N / A
Increased NICE threshold (£30,000/QALY)	GCS	LMWH

QALY=quality-adjusted life-year, N/A=not applicable

Table 9-41: Most cost-effective strategy by baseline risk of pulmonary embolism and major bleeding

PE risk \ Major bleeding risk	0%	0.5%	1%	1.5%	2%	2.5%	3%	3.5 %	4%	4.5 %	5%	5.5 %	6%
0%	UFH +GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS
0.5 %	UFH +GCS	UFH +GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS
1%	UFH +GCS	UFH +GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS
1.5 %	UFH +GCS	UFH +GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS
2%	UFH +GCS	UFH +GCS	UFH +GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS
2.5 %	UFH +GCS	UFH +GCS	UFH +GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS
3%	UFH +GCS	UFH +GCS	UFH +GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS
3.5 %	UFH +GCS	UFH +GCS	UFH +GCS	UFH +GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS
4%	UFH +GCS	UFH +GCS	UFH +GCS	UFH +GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS
4.5 %	UFH +GCS	UFH +GCS	UFH +GCS	UFH +GCS	UFH +GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS
5%	UFH +GCS	UFH +GCS	UFH +GCS	UFH +GCS	UFH +GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS
5.5 %	UFH +GCS	UFH +GCS	UFH +GCS	UFH +GCS	UFH +GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS
6%	UFH +GCS	UFH +GCS	UFH +GCS	UFH +GCS	UFH +GCS	UFH +GCS	GCS	GCS	GCS	GCS	GCS	GCS	GCS

Table 9-42: Most cost-effective strategy by baseline risk of pulmonary embolism and major bleeding: post-discharge

PE risk \ Major bleeding risk	0%	0.5%	1%	1.5%	2%	2.5%	3%	3.5%	4%	4.5%	5%	5.5%	6%
0%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
0.5%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
1%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
1.5%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
2%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
2.5%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
3%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
3.5%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
4%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
4.5%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
5%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
5.5%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
6%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH

In a threshold sensitivity analysis, we found that post-discharge prophylaxis was no longer cost-effective if greater than 37% of patients require district nurse visits to deliver their prophylaxis.

Table 9-43: Most cost-effective strategy by life expectancy of patient and proportion of patients requiring district nurse visits to deliver prophylaxis

		Life Expectancy (Years)			
		5	10	15	20
District Nurse Visits	0%	Nil	LMWH	LMWH	LMWH
	5%	Nil	LMWH	LMWH	LMWH
	10%	Nil	Nil	LMWH	LMWH
	15%	Nil	Nil	LMWH	LMWH
	20%	Nil	Nil	LMWH	LMWH
	25%	Nil	Nil	Nil	LMWH
	30%	Nil	Nil	Nil	LMWH

9.4.5 Conclusion

Anti-embolism / Graduated Compression Stockings (GCS) alone was the most cost effective standard duration strategy for general surgery patients in both the deterministic base case and in the probabilistic sensitivity analysis. GCS was the most effective at increasing QALYs (as well as the most cost-effective strategy) since the QALYs lost due to major bleeding seemed to offset the QALY benefits of adjunctive drug prophylaxis. There was only one situation in the deterministic sensitivity analysis in which the most cost effective strategy changed: high dose aspirin alone was the most cost effective strategy when the population specific pulmonary embolism relative risks were used.

The results were highly sensitive to baseline risk of major bleeding and baseline risk of pulmonary embolism (Table 9-41). For patients at lowest risk of major bleeding, we find that combination prophylaxis is cost-effective, rather than mechanical prophylaxis alone.

Post discharge, LMWH was cost effective compared to no VTE prophylaxis in the base case analysis. This was based on trials which included mainly cancer surgery patients. This result was consistent for all deterministic sensitivity analyses. In the probabilistic sensitivity analysis, LMWH was more cost-effective in 77% of the 5000 simulations of the probabilistic sensitivity analysis. To summarise, post-discharge VTE prophylaxis for this population was cost-effective and the result was insensitive to the parameters used in the sensitivity analysis. However, a major limitation of this model was that we assumed life expectancy was the same as the general population aged 60, whereas, having cancer patients' life expectancy is likely to be lower. In a sensitivity analysis it was found that life expectancy would have to be halved for it to no longer be cost-effective for these patients (Table 9-43).

9.5 Patient views

A total of six studies conducted among surgical patients were identified [33,78,429,430,510,626](Evidence Table 61, Appendix D). A summary of these studies is presented below. For patient views about specific thromboprophylaxis agents, see section 6.6.

Two studies looked into use of anti-embolism stockings / graduated compression stockings (GCS) [33,430,510]. One was a qualitative study which looked into the experience of patients who had recently worn GCS during their hospital stay [430]. This study found

that patients lacked information about how to wear the stockings and poor fitting was a problem (chapter 6 and chapter 32). Another observational study conducted in the UK found that overall, 39% of patients wore GCS in a correct manner, and only 4% adhered to the hospital policy of wearing thigh-length stockings [33,510].

One study randomised 207 women undergoing surgery for gynaecological malignancy to LMWH or IPCD[429]. Fewer patients (4%) receiving LMWH reported discomfort or side effects compared to the IPCD group (26%).

One study observed that adherence to IPCD in surgical wards was around 60% [626]. Another study where patients used both anti-embolism stockings and IPCD found that only 19% and 25.5% of patients surveyed were wearing correctly fitted IPCD and anti-embolism stockings respectively. In both of these studies, many patients were not wearing correctly fitted IPCDs or stockings (section 6.6).

For patient views about specific prophylaxis agents, see section 6.6.

9.6 Summary of evidence

Table 9-44: Summary of evidence from network meta-analysis results for DVT, symptomatic pulmonary embolism and major bleeding outcomes.

Intervention(s)	*Comparison(s)*	*Intervention favoured*		
		DVT	**PE**	**MB**
Prophylaxis vs no prophylaxis				
GCS	no prophylaxis	**GCS**	Not sig	-
IPCD/FID	no prophylaxis	**IPCD/FID**	Not sig	-
Fondaparinux	no prophylaxis	**Fondaparinux**	Not sig	**No prophylaxis**
LMWH	no prophylaxis	**LMWH**	**LMWH**	**No prophylaxis**
UFH	no prophylaxis	**UFH**	Not sig	**No prophylaxis**
VKA (adjusted dose)	no prophylaxis	**VKA**	Not sig	**No prophylaxis**
Aspirin (high-dose)	no prophylaxis	**Aspirin**	**Aspirin**	Not Sig
Fondaparinux + IPCD/FID	no prophylaxis	**Fondaparinux + IPCD/FID**	Not sig	**No prophylaxis**
LMWH + GCS	no prophylaxis	**LMWH + GCS**	-	**No prophylaxis**
UFH + GCS	no prophylaxis	**UFH + GCS**	Not sig	**No prophylaxis**
UFH + aspirin (high-dose)	no prophylaxis	**UFH + aspirin**	**UFH + aspirin**	**No prophylaxis**
Cost-effectiveness results **GCS was the most clinically effective and cost effective strategy. At lower levels of bleeding risk, combination prophylaxis (e.g. UFH+GCS) was most cost-effective.** **The re was one situation in the deterministic sensitivity analysis in which the most cost effective strategy changed was that high dose aspirin alone was the most cost effective strategy when the population specific pulmonary embolism relative risks were used.**				
Post discharge LMWH was cost effective in cancer surgery patients				

The VTE prophylaxis strategy which is significantly more effective in reducing DVT or PE, or resulting in significantly less major bleeding is stated in bold. Not sig = not statistically significant difference. No event= outcomes reported in study(ies) but no events were reported. '-'= not reported. MB = Major bleeding

9.7 Recommendations and link to evidence

Recommendation	**Offer VTE prophylaxis to patients undergoing gastrointestinal surgery who are assessed to be at increased risk of VTE (see section 5.9)** • **Start mechanical VTE prophylaxis at admission. Choose any one of:** - **anti-embolism stockings (thigh or knee length)** - **foot impulse devices** - **intermittent pneumatic compression devices (thigh or knee length)** **Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.** • **Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account patient factors and according to clinical judgement. Choose any one of:** - **fondaparinux sodium** - **LMWH** - **UFH (for patients with renal failure).** **Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).**
Recommendation	**Offer VTE prophylaxis to patients undergoing gynaecological, thoracic or urologic surgery who are assessed to be at increased risk of VTE (see section 5.9)** • **Start mechanical VTE prophylaxis at admission. Choose any one of:** - **anti-embolism stockings (thigh or knee length)** - **foot impulse devices** - **intermittent pneumatic compression devices (thigh or knee length)** **Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.** • **Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:**

	- LMWH **- UFH (for patients with renal failure).** **Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).**
Recommendation (From section 5.9)	**Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:** • **surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb** • **acute surgical admission with inflammatory or intra-abdominal condition** • **expected significant reduction in mobility** • **have one or more of the risk factors shown in Box 1.**
Box 1 – VTE risk factor box	• **Active cancer or cancer treatment** • **Age over 60 years** • **Critical care admission** • **Dehydration** • **Known thrombophilias** • **Obesity (BMI over 30 kg/m^2)** • **One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)** • **Personal history or a first degree relative with a history of VTE** • **Use of hormone replacement therapy** • **Use of oestrogen-containing contraceptive therapy** • **Varicose veins with phlebitis.** **For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).**
Relative values of different outcomes	The outcomes included in the economic model were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome). Each of these events had a cost and loss of quality adjusted life year associated with it, the details of which are provided in the methods of cost effectiveness

chapter.

Trade off between clinical benefit and harms

The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding. In the decision model base case, where the baseline risk of major bleeding was 1.4%, the number of deaths was the same for mechanical-only and combination prophylaxis but the QALYs gained were highest for mechanical-only. The QALY benefits from drug prophylaxis did not outweigh the QALYs lost due to bleeding. However, when the risk was lower, drug prophylaxis or combination prophylaxis increased QALYs.

Economic considerations

Mechanical-only prophlaxis was the most effective (at increasing QALYs) and most cost-effective strategy for general surgery patients. A combination of mechanical prophylaxis and heparin was cost-effective at a lower baseline risk of major bleeding (1.0% compared with 1.4%).

These results were extrapolated to the other patient groups on the basis that their baseline risks were similar.

Quality of evidence

There are 146 RCTs covering this group of patients. All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

Many of these are old, particularly the studies comparing prophylaxis with no prophylaxis. Surgical practice may have changed since these trials were published.

There was little direct evidence for pulmonary embolism as most the trials screened for DVT and may have reduced the risk of pulmonary embolism from developing.

Most of the pooled data investigated prophylaxis in general surgical patients; there were fewer studies in gynaecological patients and less still in urological and thoracic surgery patients. There was no evidence to suggest a difference in the effectiveness of prophylaxis in these groups but these data may not be directly applicable.

Other considerations

The average duration of VTE prophylaxis for 'general surgery' patients in the trials was 7 days. This concurs with the licensing conditions for pharmacological agents for surgical patients within the BNF where the recommended duration is 5-10 days, depending on the agent used. It is known in many cases surgical patients are discharged within 5 days of their operation. The guideline development group felt that the risk of VTE may still persist beyond this time period and prophylaxis may be effective after discharge. No economic

analysis was conducted for patients who were discharged before the full course of VTE prophylaxis had been given.

There are other considerations for each agent when choosing pharmacological prophylaxis (see section 6.8). UFH is not as widely used nowadays and is mainly used for patients with renal impairment. There are also practical considerations in that it requires 3 injections per day as oppose to one injection per day for LMWH or fondaparinux. Fondaparinux is a synthetic alternative to heparins which are derived from porcine products, although there may be concerns with an increased risk of bleeding. Fondaparinux only licensed in surgery for major orthopaedic procedures of the lower limb and patients undergoing major abdominal surgery. Consequently, it is not offered as an option for gynaecological, urological or thoracic surgery.

Recommendation	**Offer VTE prophylaxis to patients undergoing bariatric surgery.** • **Start mechanical VTE prophylaxis at admission. Choose any one of:** - **anti-embolism stockings (thigh or knee length)** - **foot impulse devices** - **intermittent pneumatic compression devices (thigh or knee length)** **Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.** • **Add pharmacological VTE prophylaxis for patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose any one of:** - **fondaparinux sodium** - **LMWH** - **UFH (for patients with renal failure).** **Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).**
Relative values of different outcomes	The outcomes included in the economic model for all general surgery patients were thromboembolic events (asymptomatic
Trade off between clinical benefit and harms	The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism

were considered against the risk of major bleeding. There is an increased risk of VTE in this group as all patients are obese.

Economic considerations

There is no relevant cost-effectiveness evidence specifically for this population subgroup. However, a combination of drug and mechanical prophylaxis was found to be cost-effective for general surgery patients where the risk of major bleeding is less than 1% (Chapter 9.4). It seems likely that combination prophylaxis will also be cost-effective for bariatric surgery patients who are at elevated risk of VTE and relatively low risk of major bleeding.

Quality of evidence

There are no studies specific to bariatric surgery. We extrapolated the results from the model investigating gastrointestinal, gynaecological, urological and thoracic surgery together. This included 146 RCTs. All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

Other considerations

The average duration of VTE prophylaxis for 'general surgery' patients in the trials was 7 days. This concurs with the licensing conditions for pharmacological agents for surgical patients within the BNF where the recommended duration is 5-10 days, depending on the agent used. It is known in many cases surgical patients are discharged within 5 days of their operation. The guideline development group felt that the risk of VTE may still persist beyond this time period and prophylaxis may be effective after discharge. No economic analysis was conducted for patients who were discharged before the full course of VTE prophylaxis had been given.

There are other considerations for each agent when choosing pharmacological prophylaxis. UFH is not as widely used nowadays and is mainly used for patients with renal impairment. There are also practical considerations in that it requires 3 injections per day as oppose to one injection per day for LMWH or fondaparinux sodium. Fondaparinux sodium is only licensed in surgery for major orthopaedic procedures of the lower limb and patients undergoing major abdominal surgery.

Recommendation	**Extend pharmacological prophylaxis to 28 days postoperatively for patients who have had major cancer surgery in the abdomen or pelvis.**

Relative values of different outcomes

The outcomes included in the economic model were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of

VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome). Each of these events had a cost and loss of quality adjusted life year associated with it, the details of which are provided in the methods of cost effectiveness chapter.

Trade off between clinical benefit and harms

The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding. Our decision model indicated that the QALYs lost due to major bleeding were outweighed by the QALYs gained from drug prophylaxis.

Economic considerations

In our economic analysis, post-discharge prophylaxis with LMWH was cost-effective for cancer surgery patients at £4,400 per QALY gained.

Quality of evidence

There are 3 RCTs covering this group of patients. All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

1 of the RCTs investigated cancer surgery patients, the other 2 were a mixture of cancer surgery patients. Overall, the majority of patients had cancer.

There was little direct evidence for pulmonary embolism as most the trials screened for DVT and may have reduced the risk of pulmonary embolism from developing.

Other considerations

Only trials for LMWH for extended duration prophylaxis in this population had been conducted. In these trial, the average duration of VTE prophylaxis was 28 days.

However, some patients may be contraindicated to LMWH and/or offered one of the other agents. The GDG still considered it important to extend pharmacological prophylaxis for 28 days postoperatively in these cases.

9.7.1 Other recommendations

The specific recommendations for patients undergoing gastrointestinal, gynaecological, thoracic and urological surgery in this chapter should be read in conjunction with other relevant recommendations in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)
- recommendations about patients in critical care (Section 29.7)

9.8 Summary of recommendations

- Offer VTE prophylaxis to patients undergoing **gastrointestinal surgery** who are assessed to be at increased risk of VTE (see section 5.9)
  - Start mechanical VTE prophylaxis at admission. Choose any one of:
    - anti-embolism stockings (thigh or knee length)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length)

    Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.
  - Add pharmacological VTE prophylaxis for patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose any one of:
    - fondaparinux sodium
    - LMWH
    - UFH (for patients with renal failure).

    Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).
- Offer VTE prophylaxis to patients undergoing **gynaecological, thoracic or urologic surgery** who are assessed to be at increased risk of VTE (see section 5.9)
  - Start mechanical VTE prophylaxis at admission. Choose any one of:
    - anti-embolism stockings (thigh or knee length)
    - foot impulse devices

- intermittent pneumatic compression devices (thigh or knee length)

Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:

  - LMWH

  - UFH (for patients with renal failure).

  Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

➢ Offer VTE prophylaxis to patients undergoing **bariatric surgery**.

- Start mechanical VTE prophylaxis at admission. Choose any one of:

  - anti-embolism stockings (thigh or knee length)

  - foot impulse devices

  - intermittent pneumatic compression devices (thigh or knee length)

  Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Add pharmacological VTE prophylaxis for patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose any one of:

  - fondaparinux sodium

  - LMWH

  - UFH (for patients with renal failure).

  Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

➢ Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:

- surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
- acute surgical admission with inflammatory or intra-abdominal condition
- expected significant reduction in mobility
- have one or more risk factors in Box 1.

Box 1. Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m^2)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).

- Extend pharmacological prophylaxis to 28 days postoperatively for patients who have had major cancer surgery in the abdomen or pelvis.

10 Elective hip replacement

10.1 Introduction

Elective total hip replacement is associated with an increased risk of VTE with a particular concern about the reported increased incidence of proximal DVT. The surgery covered in this section of the guideline is performed for primary or secondary degenerative joint disease. Other indications, for example, following fractures of the proximal femur are covered elsewhere. The all risk mortality after hip arthroplasty has been reported as 0.7% [481] with a base line risk of DVT in the absence of prophylaxis of 44% (chapter 5) and an incidence of pulmonary embolism of 3% (chapter 5).

An objection of using chemical VTE prophylaxis is the increased risk of bleeding as a result of anticoagulation. A balance of the benefit of VTE prophylaxis has to be weighed against the risks and consequences of a post-operative bleed. The baseline risk of major or significant bleeding in the absence of chemical VTE prophylaxis is 2% (chapter 5). However, the potential risks of major bleeding including re-operation and its possible link to infection are uncertain with the evidence available and should be clarified with further research.

This guideline is aimed at providing pre-, peri- and post-operative guidance for the reduction of VTE and its sequelae following elective hip replacement. The Guideline takes in to account the early complications of VTE and it's prophylaxis (e.g. bleeding, PE) and late complications including post-thrombotic symdrome and chronic thromboembolic pulmonary hypertension.

10.2 Evidence of methods of prophylaxis

There were 72 trials included in this section [12,26,28,47,51,126,129,132,142,151-153,174,188,190,193,195,198,201,202,207,209,243,249,259-261,272,293,296,299,327,330,377-380,400,410,420,421,433,465,476,479,507,523,526,527,534,565,573,574,582,587,605,612,619,627,635,638,650,651,659,673,675,684,702,705,708]. Most of RCTs had their data extracted from systematic reviews. Where applicable the study is cited in the evidence table for that review. Eight systematic reviews included RCTs covering patients having total hip replacement[15,21,125,294,355,451,557,719].

One paper reported on two trials [421] and 5 trials had compared 3 interventions [12,153,380,619,702]

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

10.2.1 Summary of comparisons identified for any main outcomes

	No prophylaxis	Post-discharge	GCS	IPCD/FID	Dabigatran	Fondaparinux	LMWH	Rivaroxaban	UFH	VKA	Asp (HD)	Asp (LD)	GCS + IPCD/FID	Mech + pharm	Other comparisons
GCS															
IPCD/FID	**2**														
Dabigatran															
Fondaparinux															
LMWH	**4**	**6**		**1**	**1 (a)**										
Rivaroxaban							**2 (b)**								
UFH	**11**	**1**					**10**								
VKA		**1**		**1**			**4**								
High dose aspirin	**6**								**1**						
Low dose aspirin	**1**								**1**		**2**				
GCS + IPCD/FID			**1**												
Mech + pharm			**5**				**1**		**1**				**4**	**5**	
Other comparisons				**3**					**1**				**2**	**2**	**1**

Figure 10-15: Number of studies which compared various types of prophylaxis methods.

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicates areas where no studies were identified.

GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) - low dose aspirin (≤ 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis

(a) Extended duration prophylaxis from surgery to 28-35 days

(b) One of these studies compared extended duration prophylaxis from surgery for 35 days, the other study investigated extended duration rivaroxaban (35 days) compared with standard duration LMWH (14 days)

10.2.2 Results from pairwise comparisons

Table 10-45: DVT – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
IPCD/FID vs nil [207,296]	2	51/ 195	102/ 205	0.53 (0.41, 0.70)	-0.24 (-0.33, -0.14)	ET: 24 FP: 4
LMWH vs nil [380,638,650,705]	4	49/ 252	100/ 240	0.40(a) (0.22, 0.71)	-0.22 (-0.33, -0.12)	ET: 26 FP: 13
UFH vs nil [51,151,153,209,249,410,659,684]	8	67/257	116/258	0.53 (b) (0.32, 0.89)	-0.20 (-0.31, -0.09)	ET: 27 FP: 17
High dose aspirin vs nil [12,153,261,433,587]	5	63/183	102/200	0.74 (c) (0.48, 1.14)	-0.16 (-0.29, -0.02)	ET: 29 FP: 28
Low dose aspirin vs nil [12]	1	1/30	11/30	0.09 (0.01, 0.66)	-0.33 (-0.52, -0.15)	ET: 29 FP: 32

Comparison	No. of studies	Interven -tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Single proph vs single						
IPCD/FID vs Vitamin K antagonist [507]	1	11/66	12/72	1.00 (0.47, 2.11)	0.00 (-0.12, 0.12)	ET: 37 FP: 95
Dabigatran vs LMWH(d) [476]	1	45/880	58/897	0.80 (0.55, 1.18)	-0.01 (-0.03, 0.01)	ET: [476] FP: 41
Rivaroxaban vs LMWH (e) [479]	2	26/ 2459	124/ 2427	0.21 (0.14, 0.32)	-0.05 (-0.09, 0.00)	ET: [479] FP: 261
LMWH vs UFH [26,129,152,174,198,243,327,380,400, 527]	10	191/ 1210	227/ 1045	0.76 (0.61, 0.93)	-0.05 (-0.08,-0.02)	ET: 32 FP: 48
VKA vs LMWH [195,293]	2	130/52 8	108/86 5	1.94 (1.53, 2.44)	0.12 (0.07, 0.16)	ET: 34 FP: 57
Aspirin (high dose) vs UFH [153]	1	10/20	1/20	10.0 (1.41,70.99)	0.45 (0.21, 0.69)	ET: 36 FP: 64
Aspirin (low dose) vs UFH [708]	1	7/19	10/25	0.92 (0.43, 1.97)	-0.03, (-0.32, 0.26)	ET: 36 FP: 68
Aspirin (high dose) vs. Aspirin (low dose) [12,259]	2	31/78	27/73	1.01 (0.73, 1.41)	0.03 (-0.07, 0.12)	ET: 56 FP: 78
Double proph vs single						
IPCD/FID + GCS vs GCS [190]	1	4/39	16/40	0.26 (0.09, 0.70)	-0.30 (-0.48, -0.12)	ET: 39 FP: 117
Asp (HD) + UFH vs UFH [188]	1	4/20	4/20	1.00 (0.29, 3.45)	0.00 (-0.25, 0.25)	ET: 42 FP: 162
UFH + GCS vs GCS [465]	1	8/35	19/32	0.38 (0.20, 0.75)	0.00 (-0.26, 0.26)	ET: 27 FP: 142
LMWH + GCS vs GCS [202,379,573,673]	4	128/50 0	141/ 336	0.62 (0.51, 0.76)	-0.17 (-0.23, -0.10)	ET: 26 FP: 134
Vitamin K antagonist + GCS vs GCS [299]	1	3/17	4/19	0.84 (0.22, 3.22)	-0.03 (-0.29, 0.22)	ET: 41 FP: 155
GCS + LMWH vs LMWH [330]	1	8/32	12/32	0.67 (0.32, 1.41)	-0.13 (-0.35, 0.10)	ET: 38 FP: 107
IPCD/FID + UFH vs UFH [605]	1	6/35	10/35	0.60 (0.24, 1.47)	-0.11 (-0.31, 0.08)	ET: 39 FP: 120
Double proph vs double						
IPCD/FID + GCS vs UFH + GCS [582]	1	9/67	23/65	0.38 (0.19, 0.76)	-0.22 (-0.36, -0.08)	ET: 50 FP: 200
IPCD/FID + GCS vs LMWH + GCS [675]	1	24/136	18/138	1.35 (0.77, 2.38)	0.05 (-0.04, 0.13)	ET: 49 FP: 202
IPCD/FID + GCS vs VKA + GCS [28,193]	2	29/148	44/148	0.49(f) (0.13, 1.89)	-0.12 (-0.28, 0.04)	ET: 48 FP: 207
Fondaparinux + GCS vs LMWH + GCS [377,651]	2	80/169 2	148/ 1714	0.55(g) (0.35, 0.85)	-0.04 (-0.06, -0.01)	ET: 44 FP: 172
LMWH + GCS vs UFH + GCS [635]	1	45/136	47/137	0.96 (0.69, 1.35)	-0.01 (-0.12, 0.10)	ET: 45 FP: 174
VKA + GCS vs Asp (HD) + GCS [260]	1	10/55	18/51	0.52 (0.26, 1.01)	-0.17 (-0.34, -0.01)	ET: 35 FP: 196
Other Comparisons						
FID vs UFH then Asp (HD) [619]	1	0/25	5/25	0.09 (0.01, 1.56)	-0.20 (-0.37, 0.03	ET: 37 FP: 93
UFH then Asp (HD) + FID vs FID + [619]	1	0/25	0/25	Not Estimable	0.00 (-0.07, 0.07)	ET: 37 FP: 153
FID + UFH then Asp (HD) vs UFH then Asp (HD) [619]	1	0/25	5/25	0.09 (0.01, 1.56)	-0.20 (-0.37, 0.03)	ET: 39 FP: 129
LMWH then FID + GCS vs LMWH + GCS [523]	1	3/100	6/100	0.50 (0.13, 1.94)	-0.03 (-0.09, 0.03)	ET: 51 FP: 214
Post Discharge						

Comparison	No. of studies	Interven -tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
LMWH [47,132,142,378,526]	5	58/560	136/533	0.41 (0.31, 0.55)	-0.14 (-0.19, -0.09)	ET: 58 FP: 225
UFH [420]	1	4/33	6/28	0.57 (0.18, 1.81)	-0.09 (-0.28, 0.10)	ET: 59 FP: 229

** FP – forest plot number in Appendix E; ET – evidence table number in Appendix D, Proph - prophylaxis*

(a) *There is substantial statistical heterogeneity between studies for this population (I^2 =54.4%, χ^2 on 3 df =6.58, p=0.09).*

(b) *There is substantial statistical heterogeneity between studies for this population (I^2 =65.9%, χ^2 on 7 df =20.52, p=0.005).*

(c) *There is substantial statistical heterogeneity between studies for this population (I^2 =53.9%, χ^2 on 4 df =8.67, p=0.07).*

(d) *Extended prophylaxis study. Patients were randomized at surgery and prophylaxis continued for 28-35 days in both arms. Only the results relating to the 220mg dose of Dabigatran was included in this analysis.*

(e) *Extended prophylaxis study. Patients were randomized at surgery and Rivaroxaban continued for 35 days Enoxaparin was continued for 35 days in one study and 14 days.*

(f) *There is substantial statistical heterogeneity between studies for this population (I^2 =77.0%, χ^2 on 1 df =4.35, p=0.04).*

(g) *There is substantial statistical heterogeneity between studies for this population (I^2 =63.8%, χ^2 on 1 df =2.76, p=010).*

Table 10-46: Pulmonary embolism – summary of results from RCTs

Comparison	No. of studies	Interven -tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
IPCD/FID vs nil [296]	1	1/152	1/158	1.04 (0.07, 16.47)	0.00 (-0.02, 0.02)	ET: 24 FP: 5
LMWH vs nil [638,650,705]	3	1/158	4/154	0.33 (0.05, 2.02)	-0.01 (-0.04, 0.02)	ET: 26 FP: 14
UFH vs nil [51,410,684]	3	20/143	19/140	0.88 (0.30, 2.61)	-0.01 (-0.08, 0.05)	ET: 27 FP: 18
High dose aspirin vs nil [12,261,433,587,612]	6	2/189	7/209	0.42 (0.11, 1.56)	-0.02 (-0.05, 0.01)	ET: 29 FP: 29
Low dose aspirin vs nil [12]	1	0/30	1/30	0.33 (0.01, 7.87)	-0.03 (-0.12, 0.05)	ET: 29 FP: 33
Single proph vs single						
IPCD/FID vs LMWH [627]	1	0/25	0/25	Not Estimable	0.01 (-0.01, 0.03)	ET: 37 FP: 88
IPCD/FID vs Vitamin K antagonist [507]	1	0/66	0/72	Not Estimable	0.00 (-0.03, 0.03)	ET: 37 FP: 96
Dabigatran vs LMWH(a) [476]	1	5/880	3/897	1.70 (0.41, 7.09)	0.00 (0.00, 0.01)	ET: [476] FP: 42
Rivaroxaban vs. LMWH(b) [479]	2	5/2459	6/2427	0.79 (0.11, 5.87)	0.00 (-0.01, 0.00)	ET: [479] FP: 262
LMWH vs UFH [26,198,243,327,400,527]	6	1/793	8/791	0.34 (0.10, 1.15)	-0.01 (-0.02, 0.00)	ET: 32 FP: 49
VKA vs LMWH [126]	1	12/1495	15/1516	0.81 (0.38, 1.73)	0.00 (-0.01, 0.00)	ET: 34 FP: 58
Aspirin (high dose) vs. Aspirin (low dose) [12,259]	2	0/78	2/73	0.18 (0.01, 3.64)	-0.02 (-0.07, 0.03)	ET : 56 FP : 79
Double proph vs single						
LMWH + GCS vs GCS [202,573,673]	3	2/414	2/249	0.65 (0.10, 4.37)	0.00 (-0.01, 0.01)	ET: 26 FP: 135
GCS + LMWH vs LMWH [330]	1	2/32	3/32	0.67 (0.12, 3.73)	-0.03 (-0.16, 0.10)	ET: 38 FP: 108
IPCD/FID + UFH vs UFH [605]	1	0/35	0/35	Not Estimable	0.00 (-0.05, 0.05)	ET: 39 FP: 121

Comparison	No. of studies	Interven -tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Double proph vs double						
IPCD/FID + GCS vs LMWH + GCS [675]	1	1/136	0/138	3.04 (0.13, 74.07)	0.01 (-0.01, 0.03)	ET: 49 FP: 203
Fondaparinux + GCS vs LMWH + GCS [377,651]	2	7/2255	3/2251	2.10 (0.43, 10.37)	0.00 (0.00, 0.01)	ET: 44 FP: 172
IPCD + Asp (HD) vs GCS Asp (HD) [565]	1	0/50	0/50	Not Estimable	0.00 (-0.04, 0.04)	ET: 30 FP: 170
LMWH + GCS vs UFH + GCS [635]	1	2/167	6/168	0.34 (0.07, 1.64)	-0.02 (-0.06, 0.01)	ET: 45 FP: 175
VKA + GCS vs Asp (HD) + GCS [260]	1	0/55	0/51	Not Estimable	0.00 (-0.04, 0.04)	ET: 35 FP: 197
Other Comparisons						
Asp (HD) + IPCD + GCS vs IPCD + GCS [702]	1	1/72	0/75	3.16 (0.13, 76.44)	0.01 (-0.02, 0.05)	ET: 42 FP: 253
VKA + GCS + IPCD vs GCS + IPCD [702]	1	0/69	0/75	Not Estimable	0.00 (-0.03, 0.03)	ET: 41 FP: 254
VKA + IPCD + GCS vs Asp + IPCD + GCS [702]	1	0/69	1/72	0.35 (0.01, 8.39)	-0.01 (-0.05, 0.02)	ET: 35 FP:199
LMWH then FID + GCS vs LMWH + GCS [523]	1	0/100	0/100	Not Estimable	0.00 (-0.02, 0.02)	ET: 51 FP: 215
Post Discharge						
LMWH [47,132,142,272,378,526]	6	0/923	5/894	0.16 (0.02, 1.35)	0.00 (-0.01, 0.01)	ET: 58 FP: 226
Vitamin K antagonist [534]	1	0/184	1/176	0.32 (0.01, 7.78)	0.01 (-0.02, 0.01)	ET: 60 FP: 231

** FP – forest plot number in Appendix E; ET – evidence table number in Appendix D*
Proph – prophylaxis
(a) – Extended prophylaxis study. Patients were randomized at surgery and prophylaxis continued for 28-35 days in both arms. Only the results relating to the 220mg dose of Dabigatran was included in this analysis.
(b) - Extended prophylaxis study. Patients were randomized at surgery and Rivaroxaban continued for 35 days Enoxaparin was continued for 35 days in one study and 14 days in the other.

Table 10-47: Major bleeding – summary of results from RCTs

Comparison	No. of studies	Interven -tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
LMWH vs nil [380,650]	2	2/168	4/166	0.50 (0.09, 2.66)	-0.01 (-0.04, 0.02)	ET: 26 FP: 15
UFH vs nil [51,151,153,249,410,421,659,684]	9	26/342	19/345	1.42 (0.84, 2.41)	0.00 (-0.01, 0.02)	ET: 27 FP: 19
High dose aspirin vs nil [12,153,261,587]	4	0/162	0/178	Not Estimable	0.00 (-0.02, 0.02)	ET: 29 FP: 30
Single proph vs single						
IPCD/FID vs Vitamin K antagonist [507]	1	0/66	0/72	Not Estimable	0.00 (-0.03, 0.03)	ET: 37 FP: 97
Dabigatran vs LMWH(a) [476]	1	23/1146	18/1154	1.29 (0.70, 2.37)	0.00 (-0.01, 0.02)	ET: [476] FP: 43
Rivaroxaban vs LMWH(b) [479]	2	7/3437	3/3453	2.29 (0.57, 9.16)	0.00 (0.00, 0.00)	ET: [479] FP: 263
LMWH vs UFH [129,174,243,380,400,527]	6	29/1119	39/926	0.59 (0.34, 1.01)	-0.01 (-0.03, 0.01)	ET: 32 FP: 50
VKA vs LMWH [126,195,293]	4	30/2288	91/2794	0.57 (0.38, 0.85)	-0.01 (-0.04, 0.01)	ET: 34 FP: 59
Aspirin (high dose) vs UFH [153]	1	0/20	1/21	0.33 (0.01, 7.72)	-0.05 (-0.18, 0.08)	ET: 36 FP: 66

Comparison	No. of studies	Interven -tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Aspirin (high dose) vs. Aspirin (low dose) [12]	1	0/30	0/30	Not Estimable	0.00 (-0.06, 0.06)	ET: 56 FP: 80
Double proph vs single						
Asp (HD) + UFH vs UFH [188]	1	1/20	0/20	3.00 (0.13,69.52)	0.05 (-0.08, 0.18)	ET: 42 FP: 164
LMWH + GCS vs GCS [573]	2	7/391	1/186	2.02 (0.28,14.72)	0.01 (0.00, 0.03)	ET: 26 FP: 136
Fondaparinux + GCS vs GCS [201]	1	2/81	0/82	5.06 (0.25, 103.81)	0.02 (-0.02, 0.07)	ET: 40 FP:130
Vitamin K antagonist + GCS vs GCS [299]	1	1/17	1/19	1.12 (0.08,16.52)	0.01 (-0.14, 0.16)	ET: 41 FP: 156
Double proph vs double						
IPCD/FID + GCS vs Warfarin + GCS [28]	1	0/50	0/45	Not Estimable	0.00 (-0.04, 0.04)	ET: 48 FP: 208
Fondaparinux + GCS vs LMWH + GCS [377,651]	2	67/2268	43/2262	1.55 (1.06, 2.26)	0.01 (0.00, 0.02)	ET: 44 FP: 173
LMWH + GCS vs UFH + GCS [635]	1	2/167	2/168	0.75 (0.32, 1.77)	0.00 (-0.01, 0.01)	ET: 45 FP: 176
VKA + GCS vs Asp (HD) + GCS [260]	1	10/55	1/51	9.27 (1.23,69.90)	0.16 (0.05, 0.27)	ET: 35 FP: 198
Other Comparisons						
LMWH then FID + GCS vs LMWH + GCS [523]	1	0/100	0/100	Not Estimable	0.00 (-0.02, 0.02)	ET: 51 FP: 216
Post Discharge						
LMWH [132,272,526]	6	0/555	1/531	0.32 (0.01, 7.80)	0.00 (-0.01, 0.01)	ET: 58 FP: 227
UFH [420]	1	0/33	0/28	Not Estimable	0.00 (-0.06, 0.06)	ET: 59 FP: 230
Vitamin K antagonist [534]	1	1/184	0/176	2.87 (0.12,69.99)	0.01 (-0.01, 0.02)	ET: 60 FP:232

** FP – forest plot number in Appendix E; ET – evidence table number in Appendix D*

Proph - prophylaxis

(a) – Extended prophylaxis study. Patients were randomized at surgery and prophylaxis continued for 28-35 days in both arms. Only the results relating to the 220mg dose of Dabigatran was included in this analysis.

(b) - Extended prophylaxis study. Patients were randomized at surgery and Rivaroxaban continued for 35 days Enoxaparin was continued for 35 days in one study and 14 days in the other.

10.2.3 Additional information

10.2.3.1 All cause mortality

All cause mortality was not identified as a key outcome during the development of the surgical guideline. Much of the data were identified from systematic reviews where all cause mortality was not reported. There was not time during the development of this guideline to review all cause mortality for this population. In the National Joint Registry data[481] the mortality at 3 months after total hip replacement was 0.7% not adjusting for prophylaxis method. It is estimated that at this event rate, a sample size of 200,000 patients in each arm is required to detect a 10% reduction in mortality with 80% power and a p value of 0.05 (α=0.05, two sided). Smaller reductions in mortality would require even larger sample sizes. None of the published studies nor the total sample size in the meta-analysis was powered to detect a difference in mortality.

10.2.3.2 Other outcomes

No studies reported chronic thromboembolic pulmonary hypertension, post thrombotic syndrome or heparin induced thrombocytopenia

10.2.3.3 Additional studies

Eighteen (18) RCTs reported evidence for both hip and knee replacement patients without distinguishing between the two groups [20,27,69,127,200,220,242,250,290,292,299,322,402,408,514,531,541,601]. The results of these studies are presented in the evidence tables (Appendix D) and forest plots (Appendix E).

10.3 Network meta-analysis results

10.3.1 Introduction

A network meta-analysis was completed for DVT, pulmonary embolism and major bleeding. Details on the network meta-analysis methods can be found in section 3.10.

For elective total hip replacement the studies for standard duration prophylaxis (e.g. prophylaxis given for a maximum of 21 days) were analysed in the network meta-analysis. Prophylaxis extending beyond this period were analysed separately. As the only studies for dabigatran and rivaroxaban extended prophylaxis for 28-35 days it is not included in the network meta-analyses of DVT and PE (the network meta-analysis of major bleeding is conducted for all population subgroups pooled together).

10.3.2 Results

DVT results

There were 46 studies included in the network meta-analysis for DVT [12,26,51,129,151-153,174,188,195,198,202,207,209,243,249,259-261,293,296,299,327,330,377,379,380,400,410,433,465,507,527,573,587,605,619,635,638,650,651,659,673,684,705,708]

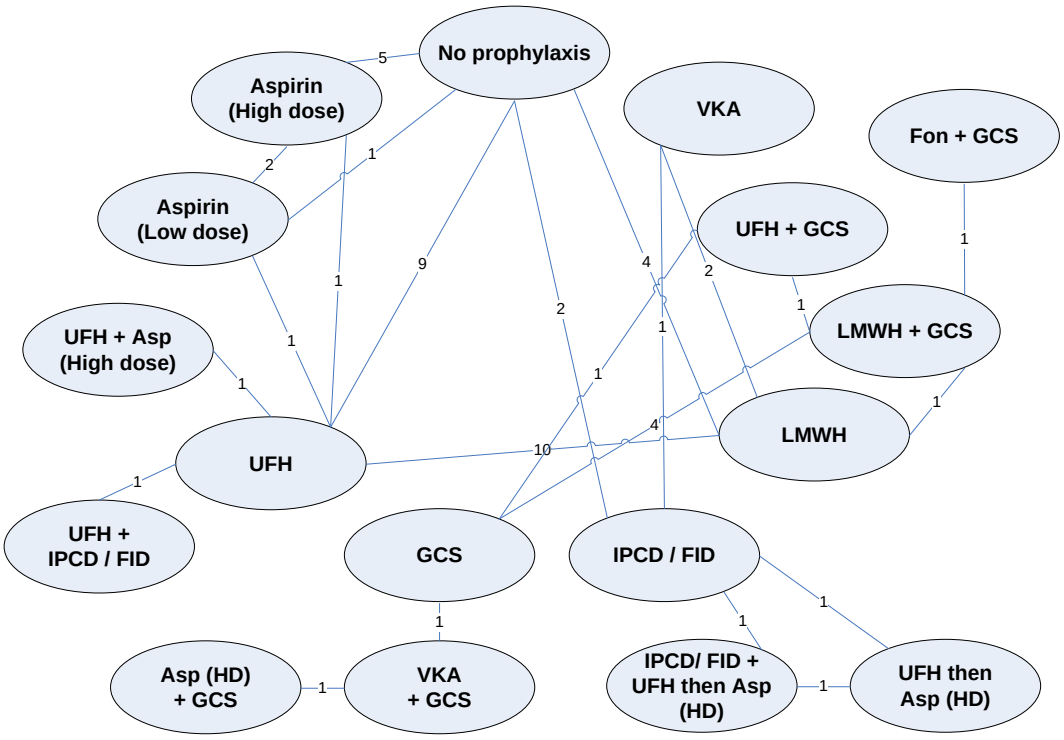


Figure 10-16: Network diagram for DVT. Numbers indicate the number of studies which contributed results for each comparison

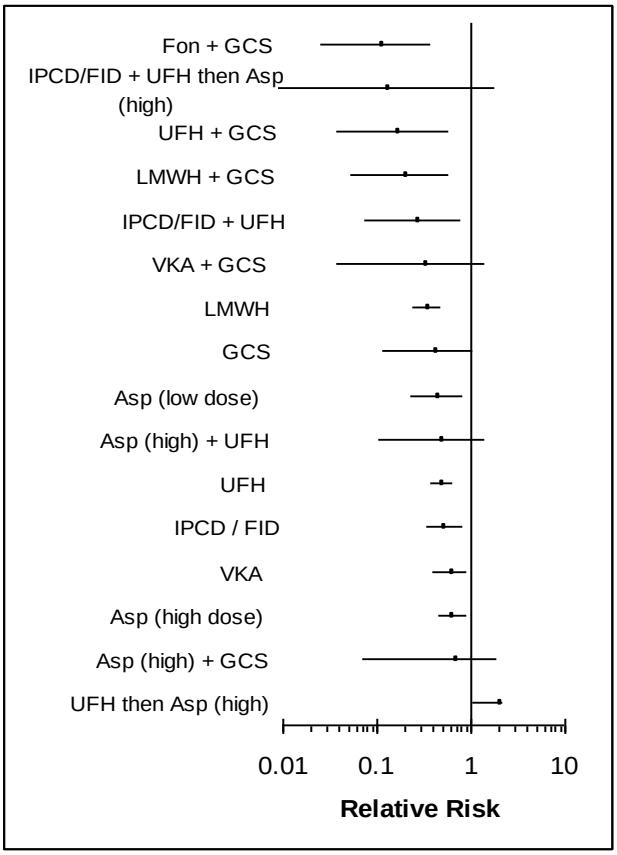


Figure 10-17: DVT results – network meta-analysis results of interventions compared to no prophylaxis

Table 10-48: DVT – network meta-analysis results

Intervention (compared with no prophylaxis)	Relative Risk (95% credible intervals)
Fon + GCS	0.11 (0.03, 0.38)
IPCD/FID + UFH then Asp high	0.13 (0.00, 1.81)
UFH + GCS	0.17 (0.04, 0.57)
LMWH + GCS	0.21 (0.05, 0.59)
IPCD/FID + UFH	0.28 (0.08, 0.79)
VKA + GCS	0.35 (0.04, 1.44)
LMWH	0.36 (0.25, 0.48)
GCS	0.43 (0.11, 1.05)
Asp (low dose)	0.47 (0.22, 0.81)
Asp (high) + UFH	0.50 (0.10, 1.39)
UFH	0.50 (0.37, 0.64)
IPCD / FID	0.54 (0.34, 0.81)
VKA	0.64 (0.39, 0.92)
Asp (high dose)	0.66 (0.45, 0.91)
Asp (high) + GCS	0.71 (0.07, 1.91)
UFH then Asp (high)	2.06 (1.04, 2.19)

Credible intervals are the Bayesian equivalent of confidence intervals.
The residual deviance was 106.1, which is quite close to the number of data points of 96, implying that the model fits the data well.

When comparing these results with the direct meta-analysis evidence, we did notice some evidence of inconsistency between comparisons. The direct comparison of low-dose aspirin with nil (one study n=60) indicated a relative risk of 0.09, whereas these results indicate a relative risk of 0.47. This seems to be due to the weight of the indirect evidence which finds that low-dose aspirin has a similar level of effectiveness to unfractionated heparin.

Pulmonary embolism results

There were 24 studies included in the network meta-analysis for PE[12,26,51,126,198,202,243,259,261,296,327,330,377,400,410,527,587,619,635,638,651,673,684,705]

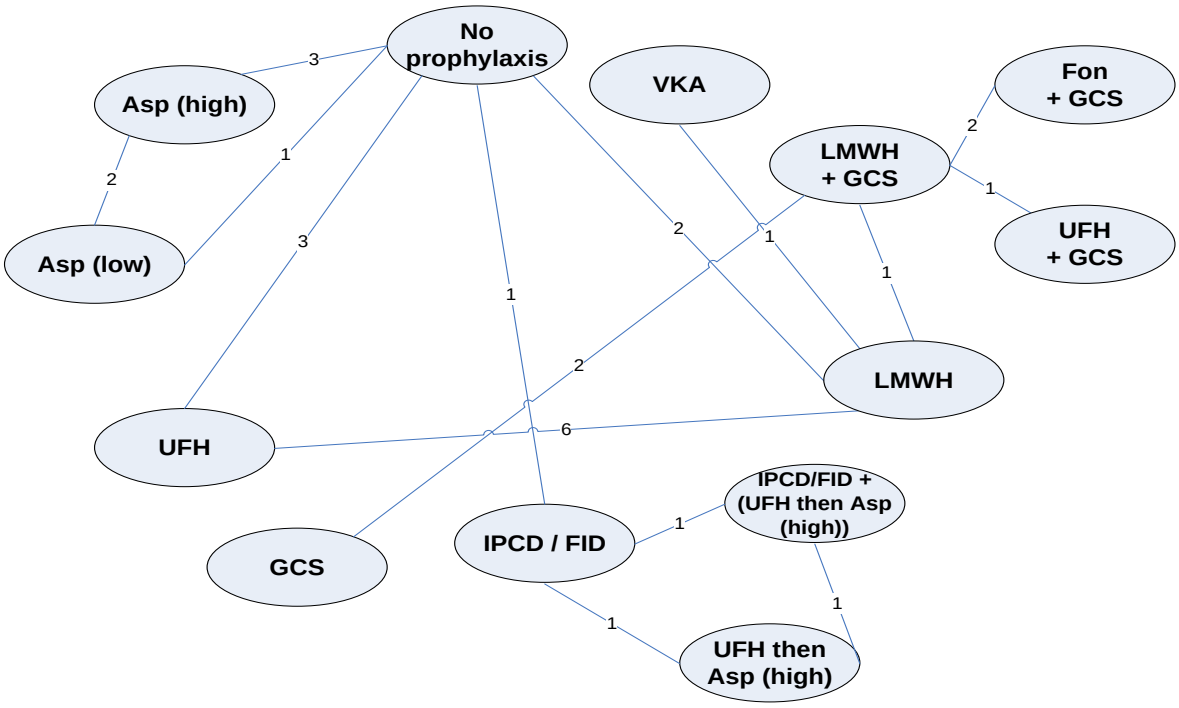


Figure 10-18: Network diagram for pulmonary embolism. Numbers indicate the number of studies which contributed results for each comparison

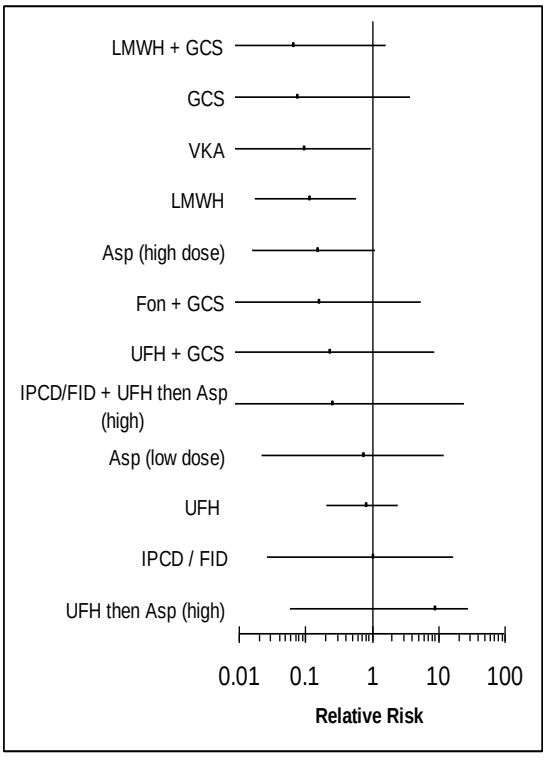


Figure 10-19: Pulmonary embolism – network meta-analysis results of interventions compared to no prophylaxis

Table 10-49: Pulmonary embolism – network meta-analysis results

Intervention (compared with no prophylaxis)	Relative Risk (95% credible intervals)
LMWH + GCS	0.07 (0.00, 1.62)
GCS	0.08 (0.00, 3.74)
VKA	0.10 (0.01, 0.96)
LMWH	0.12 (0.02, 0.59)
Aspirin (high dose)	0.16 (0.02, 1.12)
Fon + GCS	0.17 (0.00, 5.43)
UFH + GCS	0.25 (0.00, 8.83)
IPCD/FID + UFH then Asp (high)	0.26 (0.00, 24.61)
Aspirin (low dose)	0.77 (0.02, 11.93)
UFH	0.86 (0.21, 2.52)
IPCD/FID	1.09 (0.03, 16.74)
UFH then Aspirin (high)	9.31 (0.06, 28.91)

Credible intervals are the Bayesian equivalent of confidence intervals.

The residual deviance was 47.7, which is quite close to the number of data points of 50, implying that the model fits the data well.

Major bleeding results

A network meta-analysis for major bleeding was conducted using studies across hip fracture surgery, hip replacement surgery, knee replacement surgery, general medical patients and general surgical patients.

One hundred and twenty eight (128) studies were included in the analysis of which:

- 10 studies were in **medical patients**[45,121,191,256,257,350,387,390,394,579],
- 48 studies were in **general surgery patients**[10,14,29,40,50,52,72,75,76,92,113,199,210,227,230,238,262,266,267,269,280,283,321,324,329,358,366,385,439,496,499,503,504,516,517,530,552,553,570,575,588,589,633,639,641,645,657,667,703,711,713],
- 28 studies were in **elective hip replacement patients**[126,129,151,153,174,188,195,201,202,243,260,293,299,377,380,400,409,421,465,527,573,574,635,650,651,659,684],
- 9 studies were in patients undergoing **hip fracture surgery**[175,178,204,248,463,533,609,704,715]
- 15 studies were in **elective knee replacement patients** [36,66,130,186,201,202,274,388,389,399,436,476,479].
- 7 studies were in **mixed orthopaedic surgery patients**[69,200,242,250,292,459,531]
- 11 studies were in **mixed surgery patients**[54,166,270,271,340-344,396,416,486,568,569,575,585,655].

Seven of these studies included three comparison arms[153,299,380,504,533,633,655].

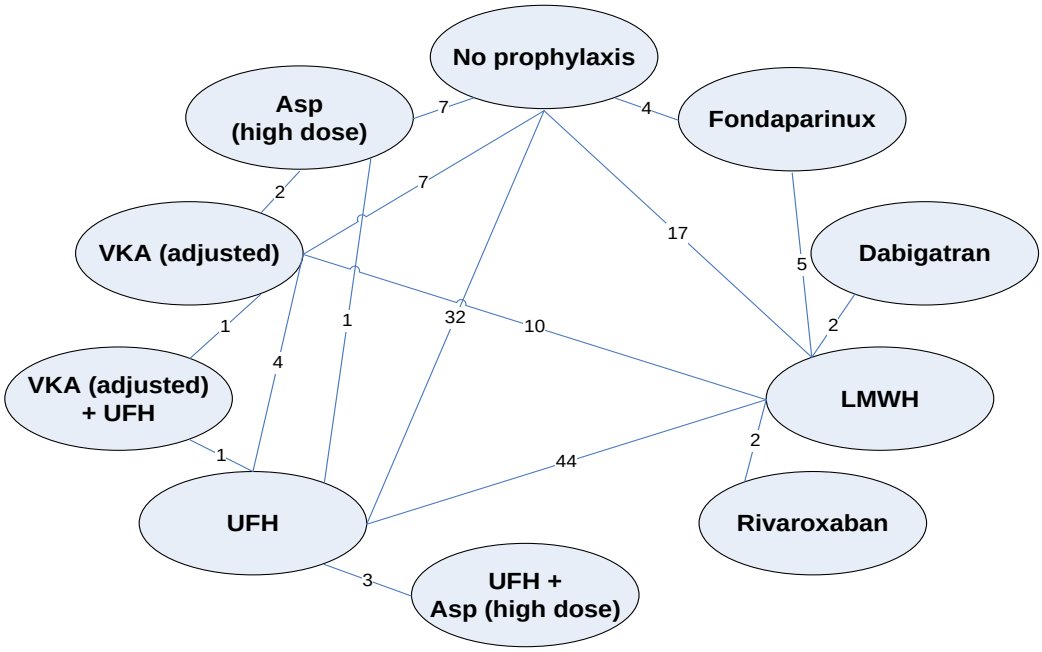


Figure 10-20: Network diagram for major bleeding. Numbers indicate the number of studies which contributed results for each comparison

Only the results for interventions included in the network meta-analysis for DVT were included in the results.

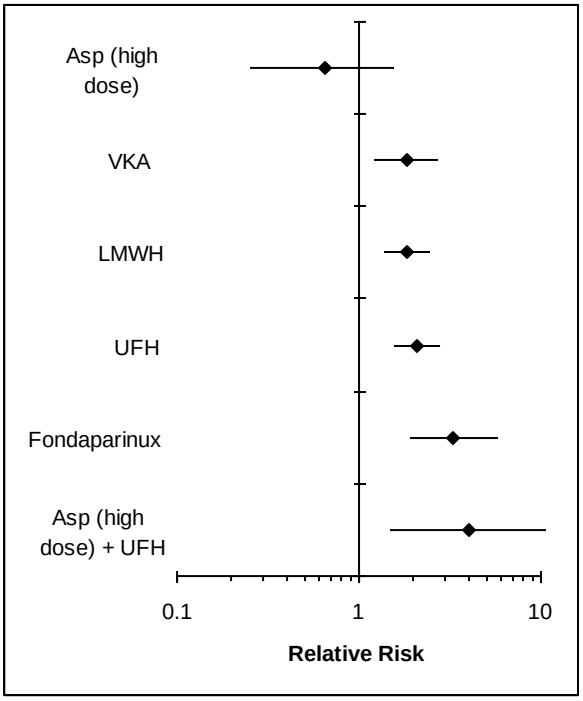


Figure 10-21: Major bleeding – network meta-analysis results of interventions compared to no prophylaxis

Table 10-50: Major bleeding – network meta-analysis results

Intervention (compared with no prophylaxis)	Relative Risk (95% credible intervals)
Asp (high dose)	0.68 (0.26, 1.57)
VKA	1.82 (1.22, 2.73)
LMWH	1.85 (1.37, 2.73)
UFH	2.11 (1.58, 2.83)
Fondaparinux	3.29 (1.91, 5.83)
Asp (high dose) + UFH	4.00 (1.50, 10.68)

Credible intervals are the Bayesian equivalent of confidence intervals.
The residual deviance was 291.5, which is quite close to the number of data points of 263, implying that the model fits the data well.

10.4 Cost-effectiveness evidence

10.4.1 Introduction

General assumptions and methods for model are described in chapter 4.

The results are driven by the network meta-analysis, above. Other data used for the cost-effectiveness analysis, which are specific to elective total hip replacement patients can be found in Table 10-51 and Table 10-52

Table 10-51: Baseline risk and other population specific parameters used in the economic model for total hip replacement patients

Baseline Characteristics	*Source*	*Value*
Mean age (years)	Hospital Episode Statistics Data (2005-6)[159]	70
% Male		38%
Standardised Mortality Ratio (a)	Ramiah, 2007 [543]	Men: 85% Women: 98% (10 years)
Mean duration of prophylaxis	Systematic review of RCTs (b)	10 days
Proportion of DVTs that are symptomatic (Ratio of symptomatic DVTs to all DVTs)	Published systematic review [542]	21.0%
Major Bleed Fatality Rate (c)	Systematic review of RCTs[467]	0.8%
PE Fatality Rate (d)	Systematic review of RCTs[557] (all elective surgery)	6.0% =11/184
Re-operation rate	Review of fondaparinux and dabigatran studies [36,175,377,476,651]	13%
DVT risk	Systematic review of RCTs (b)	45.0%
Symptomatic PE risk	Systematic review of RCTs (b)	3.4%
Major bleeding risk	Systematic review of RCTs (b)	1.6%

(a) Ratio of the death rate in the surgical group compared with the death rate in the general population, adjusting for age and sex
(b) This refers to the systematic review of RCTs for the current guideline
(c) Fatal major bleeds divided by all major bleeds
(d) Fatal PEs divided by all symptomatic PEs

Table 10-52: Weights used for events in the base case analysis

Event	*Cost (£)*	*QALYs lost*	*Net loss (£) (a)*
DVT Asymptomatic	0	0.0000	0
DVT Symptomatic	576	0.0035	645
Post-thrombotic syndrome	7,565	0.1997	11,559
Chronic pulmonary hypertension	69,123	6.1647	192,417
Pulmonary embolism - fatal	0	9.5019	190,039
Pulmonary embolism - symptomatic	2,521	0.0041	2,603
Major bleeding - No long-term sequalae	908	0.0267	1,441
Major bleeding - Stroke	23,877	7.4385	172,647
Major bleeding - fatal	0	9.5019	190,039
Heparin-induced thrombocytopaenia (sensitivity analysis only)	2,615	1.4176	30,966

QALY=quality-adjusted life-year
(a) Net loss is the sum of the resource cost plus the QALY loss: Net loss=cost+ (20,000 x QALYs lost)

10.4.2 Results for elective total hip replacement patients

Event rates by strategy can be found in Appendix G.

10.4.2.1 Base case results (standard duration prophylaxis)

Table 10-53: Base case results (standard duration prophylaxis) – deterministic and probabilistic results

	Deterministic INB	*Probabilistic INB*	
Intervention	*Mean*	*Mean*	*% of simulations where strategy was most cost-effective*
LMWH_plus_GCS	971	964	12.6%
UFH_plus_GCS	962	957	15.9%
Fondaparinux_plus_GCS	916	910	11.8%
LMWH	818	818	1.7%
AspirinLD	802	799	13.0%
GCS	793	784	11.2%
UFH_plus_IPCD-FID	764	765	9.7%
IPCD-FID	644	639	1.4%
WarfarinAD_plus_GCS	620	603	8.9%
UFH	538	541	0.0%
AspirinHD	516	515	0.2%
WarfarinAD	360	357	0.0%
AspirinHD_plus_GCS	268	257	11.8%
UFH_plus_AspirinHD	117	121	1.9%

INB = Incremental Net Benefit. The strategy with the highest probabilistic mean INB is the most cost effective overall

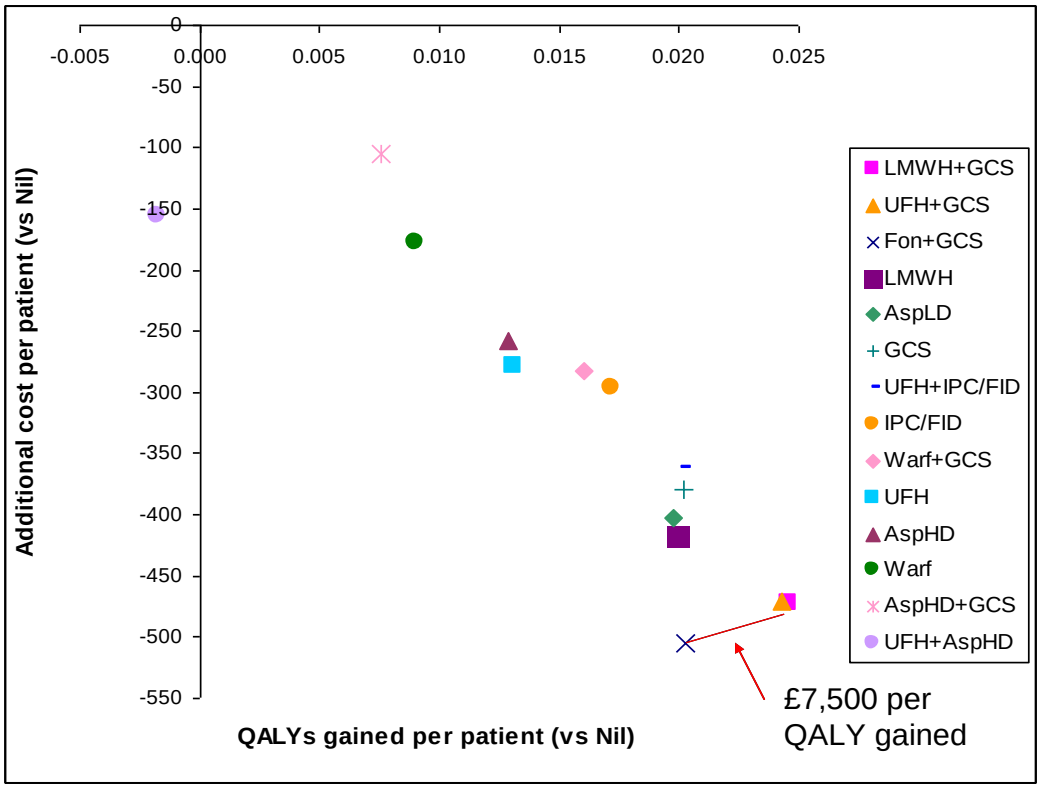


Figure 10-22: Base case results of the cost-effectiveness analysis for total hip replacement patients (probabilistic analysis): standard duration(a)

Fon = fondaparinux, Asp HD = High dose Aspirin, Warf = Warfarin,

(a) UFH+AspHD has been omitted for ease of presentation. Due to increased bleeding this strategy lies in the top left quadrant of the cost-effectiveness plane (that is it increases cost and reducers QALYs compared with no prophylaxis).

10.4.2.2 Base case results (post - discharge)

Six studies [47,132,142,272,378,526] randomised patients at discharge to receive LMWH or no prophylaxis and evaluated only events occurring after the initial hospital stay.

Table 10-54: Base case results for post-discharge prophlaxis comparing LMWH with no prophylaxis

	Deterministic INB	Probabilistic INB	
Intervention	Mean	Mean	% of simulations where strategy was most cost-effective
LMWH	238	250	98.9%
Nil	0	0	1.1%

INB = Incremental Net Benefit. The strategy with the highest probabilistic mean INB is the most cost-effective overall

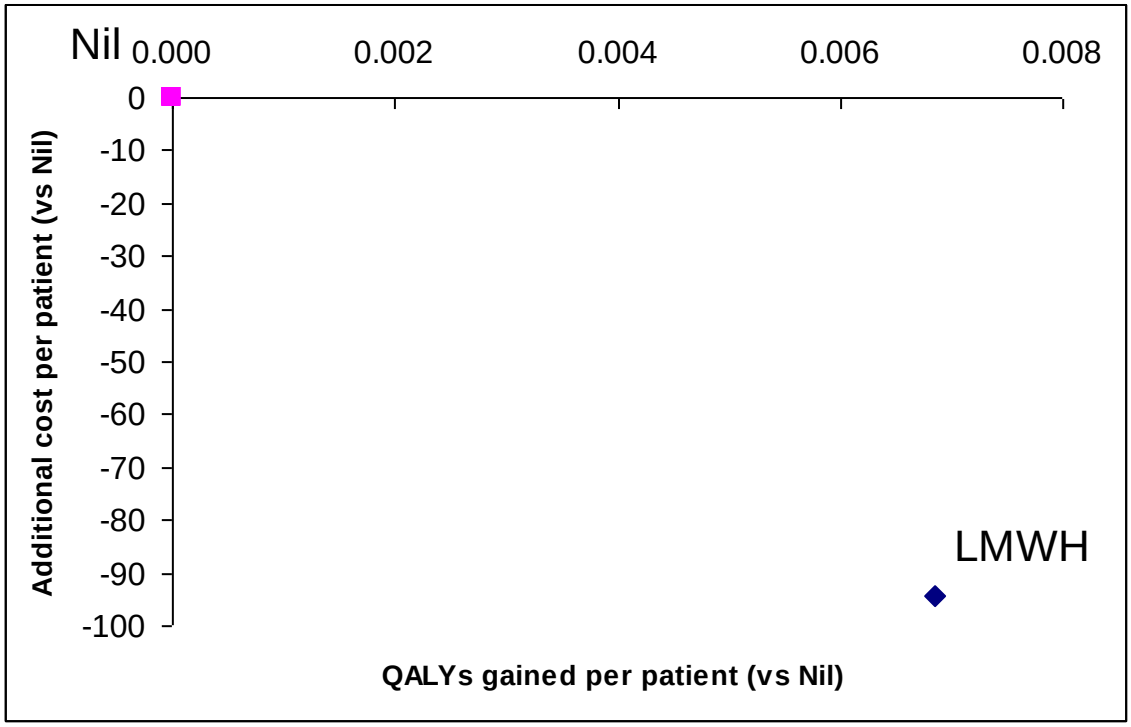


Figure 10-23: Base case results of the cost-effectiveness analysis for total hip replacement patients (probabilistic analysis): post-discharge prophylaxis

10.4.2.3 Base case results (extended duration)

One study[476] randomised patients to either LMWH or dabigatran at the time of surgery and evaluated all events occurring from that point. Two studies[479] compared Rivaroxaban with LMWH. Rivaroxaban was found to be the most cost-effective intervention in the base case analysis.

Table 10-55: Base case results for extended duration prophylaxis comparing LMWH with Dabigatran and Rivaroxaban

	Deterministic INB	Probabilistic INB	
Intervention	Mean	Mean	% of simulations where strategy was most cost-effective
Rivaroxaban	208	121	80.7%
Dabigatran	37	27	16.0%
LMWH	0	0	3.4%

INB = Incremental Net Benefit. The strategy with the highest probabilistic mean INB is the most cost effective overall

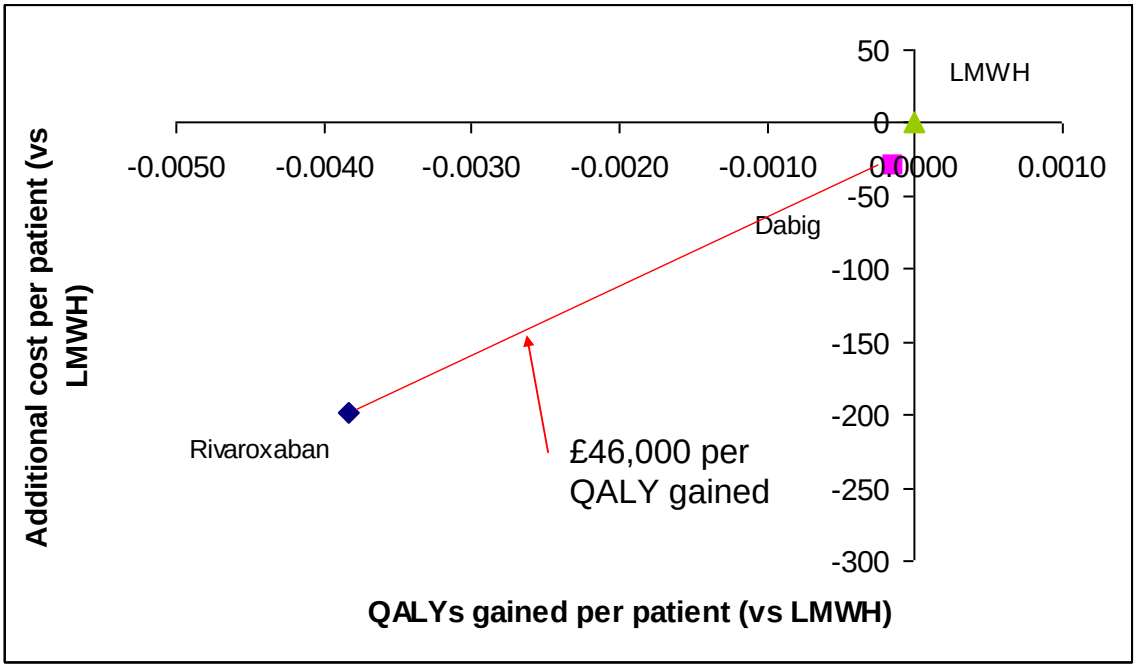


Figure 10-24: Base case results of the cost-effectiveness analysis for total hip replacement patients (probabilistic analysis): extended duration prophylaxis

10.4.2.4 Deterministic sensitivity analysis

Table 10-56: Deterministic sensitivity analysis results

Factors changed within the Model	*Most Cost-effective Strategy*		
	Standard duration prophylaxis	*Post Discharge (LMWH vs nil)*	*Extended Duration (LMWH vs dabigatran vs Rivaroxaban)*
Base case	LMWH + GCS	LMWH	Rivaroxaban
Base case (probabilistic)	LMWH + GCS	LMWH	Rivaroxaban
Chronic Thromboembolic Pulmonary Hypertension and Post Thrombotic Syndrome			
0% Chronic Thromboembolic Pulmonary Hypertension	LMWH + GCS	LMWH	Rivaroxaban
0.5% Chronic Thromboembolic Pulmonary Hypertension	LMWH + GCS	LMWH	Rivaroxaban
1% Chronic Thromboembolic Pulmonary Hypertension	LMWH + GCS	LMWH	Rivaroxaban
0% Chronic Thromboembolic Pulmonary Hypertension and 0% Post Thrombotic Syndrome	Low-dose aspirin	LMWH	Rivaroxaban
High Post Thrombotic Syndrome rate (e.g. 30% after symptomatic DVT and 21% after asymptomatic DVT)	LMWH + GCS	LMWH	Rivaroxaban
Low Post Thrombotic Syndrome (e.g. 15% after symptomatic DVT and 8% after asymptomatic DVT)	LMWH + GCS	LMWH	Rivaroxaban
Low cost for Post Thrombotic Syndrome	LMWH + GCS	LMWH	Rivaroxaban
High cost for Post Thrombotic Syndrome	LMWH + GCS	LMWH	Rivaroxaban
High cost for Chronic Thromboembolic Pulmonary Hypertension	LMWH + GCS	LMWH	Rivaroxaban
Other Sensitivity Analyses			
Explicitly include Heparin Induced Thrombocytopenia (LMWH=0.5%, UFH=5%)	Fon+GCS	N/A	N/A
Explicitly include Heparin Induced Thrombocytopenia (LMWH=0.2%, UFH=2.6%)	Fon+GCS	N/A	N/A
Using population specific pulmonary embolism result	LMWH+GCS	LMWH	Rivaroxaban
Using population specific major bleeding relative risks	Fon+GCS	N/A	N/A
Low aspirin major bleeding relative risk from Network Meta-analysis (RR = 0.49)	LMWH + GCS	N/A	N/A
High aspirin major bleeding relative risk from aspirin vs. nil arms (RR = 1.3)	LMWH + GCS	N/A	N/A
Discounted LMWH/Dabigatran cost = £1	LMWH + GCS	LMWH	Rivaroxaban
Fatality after pulmonary embolism = 10%	LMWH + GCS	LMWH	Rivaroxaban
Fatality after Major Bleeding = 5%	LMWH + GCS	LMWH	Rivaroxaban
Foot Impulse Device (consumable: £18, pump: £0)	LMWH + GCS	N / A	N / A
Increased NICE threshold (£30,000/ QALY)	LMWH + GCS	LMWH	Rivaroxaban

QALY=quality-adjusted life-year, fon=fondaparinux

Table 10-57: Most cost-effective strategy by baseline risk of pulmonary embolism and major bleeding: standard duration prophylaxis

PE risk	Major bleeding risk												
	0%	0.5%	1%	1.5%	2%	2.5%	3%	3.5%	4%	4.5%	5%	5.5%	6%
0%	Fon +GCS	Fon +GCS	LMWH +GCS	LMWH +GCS	AspLD	AspLD	AspLD	AspLD	AspLD	AspLD	AspLD	AspLD	AspLD
0.5%	Fon +GCS	Fon +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	AspLD	AspLD	AspLD	AspLD	AspLD	AspLD	AspLD	AspLD
1%	Fon +GCS	Fon +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	AspLD	AspLD	AspLD	AspLD	AspLD	AspLD	AspLD
1.5%	Fon +GCS	Fon +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	AspLD	AspLD	AspLD	AspLD	AspLD	AspLD	AspLD
2%	Fon +GCS	Fon +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	AspLD	AspLD	AspLD	AspLD	AspLD	AspLD
2.5%	Fon +GCS	Fon +GCS	Fon +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	AspLD	AspLD	AspLD	AspLD	AspLD	AspLD
3%	Fon +GCS	Fon +GCS	Fon +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	AspLD	AspLD	AspLD	AspLD	AspLD
3.5%	Fon +GCS	Fon +GCS	Fon +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	AspLD	AspLD	AspLD	AspLD
4%	Fon +GCS	Fon +GCS	Fon +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	AspLD	AspLD	AspLD	AspLD
4.5%	Fon +GCS	Fon +GCS	Fon +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	AspLD	AspLD	AspLD
5%	Fon +GCS	Fon +GCS	Fon +GCS	UFH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	AspLD	AspLD
5.5%	Fon +GCS	Fon +GCS	Fon +GCS	UFH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	AspLD	AspLD
6%	Fon +GCS	Fon +GCS	Fon +GCS	UFH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	LMWH +GCS	AspLD

Fon=fondaparinux; Asp LD = Low dose aspirin (<300mg/day)

Table 10-58: Most cost-effective strategy by baseline risk of pulmonary embolism and major bleeding: post discharge prophylaxis

PE risk	Major bleeding risk												
LMWH	0%	0.5%	1%	1.5%	2%	2.5%	3%	3.5%	4%	4.5%	5%	5.5%	6%
0%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
0.5%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
1%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
1.5%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
2%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
2.5%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
3%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
3.5%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
4%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
4.5%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
5%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
5.5%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
6%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH

Table 10-59: Most cost-effective strategy by baseline risk of pulmonary embolism and major bleeding: extended duration prophylaxis

	Major bleeding risk													
PE risk	Rivar	0%	0.5%	1%	1.5%	2%	2.5%	3%	3.5%	4%	4.5%	5%	5.5%	6%
0%	Rivar	Rivar	Rivar	Rivar	Dabig	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
0.5%	Rivar	Rivar	Rivar	Rivar	Rivar	Dabig	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
1%	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Dabig	Dabig	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
1.5%	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Dabig	Dabig	LMWH	LMWH	LMWH	LMWH	LMWH
2%	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Dabig	Dabig	Dabig	Dabig	LMWH	LMWH	LMWH
2.5%	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Dabig	Dabig	Dabig	Dabig	LMWH	LMWH
3%	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Dabig	Dabig	Dabig	Dabig	Dabig
3.5%	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Dabig	Dabig	Dabig	Dabig
4%	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Dabig	Dabig	Dabig	Dabig
4.5%	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Dabig	Dabig	Dabig
5%	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Dabig	Dabig
5.5%	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Dabig
6%	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Rivar	Dabig

Rivar=Rivaroxaban, Dabig = Dabigatran

In a threshold sensitivity analysis, we found that post-discharge LMWH prophylaxis was no longer cost-effective if greater than 60% of patients require district nurse visits to deliver their prophylaxis.

10.4.3 Conclusion of cost-effectiveness analysis

A combined strategy of low molecular weight heparin and GCS was the most clinically effective and cost-effective standard duration prophylaxis strategy in the deterministic base case and in the probabilistic analysis. A combination of pharmacological and mechanical (GCS, IPCD or FID) prophylaxis was found to be the most cost-effective strategy in over 70% of the simulations in the standard duration prophylaxis probabilistic sensitivity analysis.

Most of the results in the deterministic sensitivity analysis did not differ from the base case of LMWH + GCS. The following analyses returned different results:

- Fondaparinux + GCS was the most cost-effective strategy when heparin Induced thrombocytopenia was considered.
- Fondaparinux + GCS was the most cost-effective strategy when the major bleeding relative risks for only the total hip replacement population were used to estimate the incidence of major bleeding rather than the relative risks estimated using the network meta-analysis across all populations.
- Low-dose aspirin was most cost-effective when the risk of chronic thromboembolic pulmonary hypertension and post thrombotic syndrome are zero

At the lowest levels of bleeding risk, fondaparinux + GCS was most cost-effective but as bleeding risk increases LMWH+GCS became the optimal strategy. At the highest levels of bleeding risk, low-dose aspirin was the most cost-effective strategy – this might be an artefact since we did not have an estimate of bleeding increase for

aspirin. If we exclude low-dose aspirin then mechanical-only prophylaxis is most cost-effective for patients at highest risk of bleeding.

Low molecular weight heparin was more cost-effective than no prophylaxis post hospital discharge. This remained the most cost-effective strategy in all sensitivity analyses.

Rivaroxaban was more cost-effective than either dabigatran or LMWH on the basis of the extended duration prophylaxis trials. In all of the deterministic sensitivity analyses completed for extended duration prophylaxis, rivaroxaban was most cost-effective. In a 2-way sensitivity analysis comparing the effect of different baselines risks of pulmonary embolism and major bleeding, LMWH and dabigatran became cost-effective at higher levels of major bleeding risk.

10.5 Patient views

A total of 7 studies included patients with hip replacement procedures [16,102,128,247,506,525,555] (Evidence tables 61-3, Appendix D). All these studies involved a mixture of elective hip and knee replacement patients [16,102,128,506,525,555], except one [247]. Another study also had trauma patients [506]. More information about patient views and adherence from these studies are presented in Section 6.6. The following is a summary of the main findings.

Haddad et al [247] observed the adherence to IPCD (% time used, measure using an external device) among elective hip replacement patient to be around 80%, both before and after the education initiative.

Four studies looked at the adherence and patient views of FID[16,102,525,555]. The adherence reported ranged from 30% to 95%, depending on timing of observation and definitions used. Although the majority of patients found FID comfortable, interference with sleep was quite widely reported (28% to 58%) among studies where patients were required to wear the devices continuously.

One of these FID studies compared the acceptability of FID to subcutaneous LMWH injections [16]. All patients received both prophylaxes, and were generally comfortable with them. Slightly more patients found LMWH painful (14.1% vs 11% in FID). However, significantly more patients would rather not have FIDs (37%) compared to LMWH (14.0%) or continue prophylaxis for 4 weeks (76.7% vs. 51.2%).

In another study, the FID (n=120) was compared to IPCD plus (GCS) (n=104) [555]. Significantly more patients were "comfortable" or had no complaints with the FID (71% vs. 55%). Among 35 participants in the FID group who had used an IPCD in a previous surgery, more (69%) preferred the FID than IPCD (20%). The rest had no preference.

One study looked into the ability to self-administer subcutaneous LMWH and adhere to the injection regimen for 21 days in 51 patients[128]. Patients received instructions and a demonstration by the staff nurses. On discharge, written and video instructional materials were provided. Among the 40 patients who completed the study, most (86%) performed self-injections while 14% were assisted by a family or friend. Most patients (98%) understood the importance of heparin and 68% (34/ 50) felt comfortable with self-injection.

For patient views about specific prophylaxis agents, see Section6.6.

10.6 Summary of evidence

Intervention(s)	Comparison(s)	Intervention favoured		
		DVT	PE	MB
Prophylaxis vs no prophylaxis				
GCS	No prophylaxis	Not sig	Not sig	-
IPCD / FID	No prophylaxis	**IPCD / FID**	Not sig	-
Asp (low dose)	No prophylaxis	**Asp (low dose)**	Not sig	-
Asp (high dose)	No prophylaxis	**Asp (high dose)**	Not sig	Not sig
VKA (adusted dose)	No prophylaxis	**VKA (adjusted dose)**	**VKA (adjusted dose)**	**No prophylaxis**
UFH	No prophylaxis	**UFH**	Not sig	**No prophylaxis**
LMWH	No prophylaxis	**LMWH**	**LMWH**	**No prophylaxis**
Aspirin (high) + GCS	No prophylaxis	Not sig	-	Not sig
VKA + GCS	No prophylaxis	Not sig	-	Not sig
UFH + GCS	No prophylaxis	**UFH + GCS**	Not sig	**No prophylaxis**
LMWH + GCS	No prophylaxis	**LMWH + GCS**	Not sig	**No prophylaxis**
Fon + GCS	No prophylaxis	**Fon + GCS**	Not sig	**No prophylaxis**
IPCD/ FID + UFH	No prophylaxis	**IPCD/FID + UFH**	-	**No prophylaxis**
IPCD/FID + UFH then Asp (high)	No prophylaxis	Not sig	Not sig	-
Aspirin (high) + UFH	No prophylaxis	Not sig	-	**No prophylaxis**
UFH then Aspirin (high)	No prophylaxis	Nil	Not sig	-
Post Discharge (from direct evidence)				
LMWH	No prophylaxis post discharge	**LMWH**	Not sig	Not sig
UFH	No prophylaxis post discharge	Not sig	-	No events
VKA	No prophylaxis post discharge	-	Not sig	Not sig
Extended Prophylaxis (randomised at surgery for 28 days) (from direct evidence)				
Dabigatran	LMWH	Not sig	Not sig	Not sig
Rivaroxaban	LMWH	**Rivaroxaban**	Not sig	Not sig
There were no statistical significant difference of effectiveness between LMWH, UFH and Fondaparinux in reducing DVT, PE or major bleeding outcomes				
Cost-effectiveness				
LMWH in combination with GCS was the most clinically effective and cost-effective strategy in the deterministic base case and in the probabilistic analysis. Most of the results in the deterministic sensitivity analysis did not differ from the base case, i.e. LMWH+GCS was still most cost-effective.				
Post-discharge, LMWH was more cost-effective than no prophylaxis and remained -effective in all deterministic sensitivity analyses.				
Rivaroxaban was more cost-effective than LMWH or dabigatran for extended duration prophylaxis (that is in-hospital plus post-discharge) and remained so in all of the deterministic sensitivity analyses completed				

The prophylaxis strategy, which is significantly more effective in reducing DVT or PE; or resulting in significantly less major bleeding is stated in bold. Not sig = not statistically significant difference. '-'= not reported
nil – no prophylaxis; GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; VKA – vitamin K antagonist; asp – aspirin; high dose aspirin is >300mg. MB = Major bleeding

10.7 Recommendations and link to evidence

Recommendation	**Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing elective hip replacement surgery :** • **Start mechanical VTE prophylaxis at admission. Choose any one of the following based, on individual patient factors:** - **anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)** - **foot impulse devices** - **intermittent pneumatic compression devices (thigh or knee length)** **Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.** • **Provided there are no contraindications, start pharmacological VTE prophylaxis after surgery. Choose any one of:** – **dabigatran etexilate, starting 1-4 hours after surgery*** – **fondaparinux sodium, starting 6 hours after surgical closure provided haemostasis has been established** – **LMWH, starting 6–12 hours after surgery** – **rivaroxaban, starting 6-10 hours after surgery)$** – **UFH (for patients with renal failure), starting 6–12 hours after surgery.** **Continue pharmacological VTE prophylaxis for 28-35 days, according to the summary of product characteristics for the individual agent being used.** ****Dabigatran etexilate, within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 157 (2008).[476]*** ***$ Rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 170 (2009).[479]***
Relative values of different outcomes	The orthopaedic subgroup noted that although all cause mortality is the most important outcome for this population the studies were not powered to detect a difference in mortality for

any of the interventions under consideration. The next most important outcome was thought to be the risk of symptomatic venous thromboembolism balanced against the risk of major bleeding. The relative risk reduction for all DVT events was used as a surrogate for symptomatic VTE events as the orthopaedic subgroup group accepted that there was a relationship between the risk reduction in DVT and PE.

Trade off between clinical benefit and harms

The benefit of reducing VTE events was balanced with the potential harms of bleeding. The economic model included consideration of long-term sequelae such as the cost of reoperation due to bleeding, post thrombotic syndrome, chronic thromboembolic pulmonary hypertension and stroke. Our decision model indicated that the QALYs lost due to major bleeding were outweighed by the QALYs gained from drug prophylaxis.

Economic considerations

An original economic model was developed for this population. This model concluded that anti-embolism stockings (GCS) in combination with LMWH, UFH or fondaparinux were the most cost-effective interventions for reducing the risk of VTE for the period of hospitalisation within the standard duration prophylaxis trials (approximately 10 days) – dabigatran could not be compared in this analysis.

The economic model showed that extending thromboprophylaxis after hospitalisation with LMWH for 4 weeks post-discharge was cost-effective for total hip replacement patients. In addition, rivaroxaban was found to be cost-effective compared with dabigatran and LMWH as thromboprophylaxis from surgery for 4-5 weeks.

Quality of evidence

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which themselves had been critically appraised to be of a high quality (level 1+ or level 1++).

Overall the quality of the evidence is good. There is a large body of evidence for this population comprising 72 RCTs providing thromboprophylaxis for between 7-21days, of which 46 were included in the network meta-analysis. The remaining 25 were not included as they did not contain interventions that linked into the main network. In addition, there were 9 studies investigating extended duration in hip replacement patients for 28-35 days. These studies were all published since 1996.

There was an inconsistency across studies in the definition of major bleeding outcomes used. The definition as used within each paper was accepted.

Other considerations

Initiation of pharmaceutical thromboprophylaxis: The orthopaedic subgroup were mindful of the increase in bleeding risk in the period immediately after surgery and agreed that prophylaxis should be started only once the immediate bleeding risk had reduced.

Only one RCT compared pre-op start times with post-op start for LMWH and this showed no significant difference in major bleeding.

The summary of product characteristics states a postoperative start time for dabigatran, rivaroxaban and fondaparinux, and a preoperative start time for most LMWHs although the actual start times vary depending on the specific LMWH. In this guideline it is recommended that LMWH is started postoperatively which is off-label because concerns about the risk of bleeding into the joint. Patients would be protected preoperatively against VTE by mechanical prophylaxis. Some of the LMWH studies included in our analyses also started LMWH post-operatively. Further information should be sought from the summary of product characteristics for each anticoagulant.

Mechanical thromboprophylaxis: There was a discussion within the orthopaedic subgroup about the practicality of using anti-embolism stockings after hip replacement surgery. Patients are likely to have swollen legs post-operatively and it was felt important to ensure that patient's legs are re-measured after surgery to confirm that the stockings remained correctly fitted. The evidence demonstrates that IPCD/FID was effective in reducing DVT and was a more practical solution in these patients. The orthopaedic subgroup therefore recommended that IPCD/FID were available as an alternative to anti-embolism stockings. The orthopaedic subgroup was aware of potential patient compliance issues with the use of IPC devices and difficulty in their use when patients regained mobility but agreed that they should be continued until the patient was discharged or no longer significantly immobile.

Mechanical prophylaxis (GCS, IPCD or FID) was felt to be particularly important in the period around the operation where patients were not protected by chemical prophylaxis. The orthopaedic subgroup agreed that by providing mechanical methods from admission the risk of developing DVT in the peri-operative period was reduced.

10.7.1 Other recommendations of relevance

The specific recommendations for patients having elective hip replacements in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information including when patients are discharged with prophylaxis(Section 32.5)

10.8 Summary of recommendations

- Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing elective hip replacement surgery :

    - Start mechanical VTE prophylaxis at admission. Choose any one of the following based on individual patient factors:

        - anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)
        - foot impulse devices
        - intermittent pneumatic compression devices (thigh or knee length)

        Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

    - Provided there are no contraindications, start pharmacological VTE prophylaxis after surgery. Choose any one of the following:

        - dabigatran etexilate, starting 1-4 hours after surgery*
        - fondaparinux sodium, starting 6 hours after surgical closure provided haemostasis has been established
        - LMWH, starting 6–12 hours after surgery
        - rivaroxaban, starting 6-10 hours after surgery$
        - UFH (for patients with renal failure), starting 6–12 hours after surgery.

        Continue pharmacological VTE prophylaxis for 28-35 days, according to the summary of product characteristics for the individual agent being used.

* Dabigatran etexilate, within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 157 (2008).[476]

$ Rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 170 (2009).[479]

11 Elective knee replacement

11.1 Introduction

Elective total knee replacement for primary or secondary degenerative joint disease is a highly successful procedure involving a large number of patients per annum, usually in an elderly population but with an increasing application in younger age groups. The general risks of this surgery including infection are well documented. The baseline risk for VTE is not as significant as that reported in THR, particularly, with fatal and non-fatal pulmonary embolism (probably less than 1%). Regrettably there is no significant evidence on the effects of thromboprophylaxis on fatal and non fatal PE in TKR, there is only evidence which relates to DVT and these studies suggest that DVT rates including asymptomatic DVT may be as high as 60%.

Uncertainties remain therefore as to whether the studies which show a reduction in DVT rates by thromboprophylaxis can be extrapolated to PE rates and whether there is sufficient morbidity from DVT apart from PE to merit prophylaxis. There is some evidence that links DVT in TKR to morbidity related to post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension but there has been minimal reporting of these morbidities in the British and American literature and many knee surgeons rarely, if ever, see these problems in their clinics. There is discrepancy between this view and the experience of other specialities involved in the subsequent management of DVT sequelae.

The other uncertainty in chemical VTE prophylaxis in TKR is that of "major bleeding" and its potential association with an increased risk of wound haematoma, re-operation and deep infection. Current evidence in this area is weak but suggests a risk in the order of 1%.

Clearly further research is required to try to resolve these uncertainties and extremely large numbers of patients will be needed to provide statistically significant data on risks less than 1%. Until this evidence is available, these patients should be offered the most effective thromboprophylaxis available with the minimum of side effects. A fatal and non fatal PE rate of less than 1% cannot be ignored as this involves several hundred deaths or emergency admissions each year. A high DVT rate cannot be ignored even if the morbidity rates are unclear. Equally, a possible bleeding complication rate of 1% cannot be ignored and thromboprophylaxis must be as safe as possible in this respect.

The VTE prophylaxis recommendation will therefore attempt to meet as many of their concerns as possible by paying attention to the timing of chemical prophylaxis and its duration plus the best means of combining chemical and mechanical (GCS, IPCD or FID) prophylaxis.

11.2 Evidence of methods of thromboprophylaxis

There were 23 RCTs identified for knee replacement patients [36,66,130,132,183,186,201,202,245,274,291,388,389,399,436,476,479,493,676,686,697] which included one study with comparing 3 interventions [436]. Most of RCTs had their data extracted from systematic reviews. Where applicable the study is cited in the evidence table for that review. Seven systematic reviews included RCTs covering patients having total knee replacement[15,21,125,355,451,557,719].

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

11.2.1 Summary of comparisons identified for any outcome

	No prophylaxis	Post-discharge	GCS	IPCD/FID	Dabigatran	Fondaparinux	LMWH	Rivaroxaban	UFH	VKA	Asp (HD)	Asp (LD)	GCS + IPCD/FID	Mech + pharm	
GCS															
IPCD/FID	**2**														
Dabigatran															
Fondaparinux															
LMWH	**1**	**2**		**2**	**2**										
Rivaroxaban							**2**								
UFH							**1**								
VKA							**3**								
High dose aspirin	**1**			**2**											
Low dose aspirin															
GCS + IPCD/FID							**1**								
Mech + pharm			**3**								**1**				
Other comparisons															**3**

Figure 11-25: Number of studies which compared various types of prophylaxis methods.

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicates areas where no studies were identified.

GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) - low dose aspirin (≤ 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis

11.2.2 Results from pairwise comparisons

Table 11-60: DVT – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
IPCD/FID vs nil [436,697]	2	6/38	28/44	0.26 (0.12, 0.57)	-0.51 (-.074, -0.28)	ET: 24 FP: 4
LMWH vs nil [388]	1	11/65	37/64	0.29 (0.16, 0.52)	-0.41 (-0.56, -0.26)	ET: 26 FP: 13
High dose aspirin vs. nil [436]	1	8/21	9/12	0.51 (0.27, 0.96)	-0.37 (-0.69, -0.05)	ET: 29 FP: 28
Single proph vs single						
IPCD/FID vs LMWH [66,676]	2	91/162	64/156	1.51(a) (0.71, 3.20)	0.17 (-0.09, 0.43)	ET: 37 FP: 87
IPCD/FID vs High dose aspirin [245,436]	2	21/71	40/79	0.59 (0.40, 0.88)	-0.25 (-0.39, -0.10)	ET: 37 FP: 98
VKA vs. LMWH [186,274,389]	3	274/609	182/611	1.50 (1.29, 1.74)	0.15 (0.10, 0.20)	ET: 34 FP: 57
Dabigatran vs LMWH [476]	2	363/ 1107	350/ 1155	1.08 (b) (0.86, 1.36)	0.02 (-0.04, 0. 09)	ET: [476] FP: 41
Rivaroxaban vs LMWH [479]	2	140/178 9	246/183 7	0.38 (c) (0.22, 0.65)	-0.06 (-0.12, 0.01)	ET: [479] FP: 261
LMWH vs. UFH[130]	1	54/145	74/143	0.72 (0.55, 0.94)	-0.15 (-0.26, -0.03)	ET: 32 FP: 48
Double proph vs single						
IPCD/FID + Asp high dose vs Aspirin high dose [291]	1	1/13	4/14	0.27 (0.03, 2.11)	-0.21 (-0.49, 0.07)	ET: 39 FP: 114
LMWH + GCS vs GCS [202,399]	2	113/332	108/182	0.56 (0.46, 0.69)	-0.27 (-0.36, -0.18)	ET: 26 FP: 134
IPCD + FID vs LMWH [493]	1	4/15	0/14	8.44 (0.50, 144)	0.27 (0.03, 0.50)	ET: 37 FP: 104
Double proph vs double						
Fon + GCS vs LMWH + GCS [36]	1	45/361	98/361	0.46 (0.33, 0.63)	-0.15 (-0.20, -0.09)	ET: 44 FP: 171
LMWH + IPCD/FID vs Asp High dose + IPCD/FID [686]	1	17/135	18/129	0.90 (0.49, 1.67)	-0.01 (-0.10, 0.07)	ET: 46 FP: 190
LMWH + GCS vs UFH + GCS [183]	1	21/92	25/93	0.85 (0.51, 1.40)	-0.04 (-0.16, 0.08)	ET: 45 FP: 174
Post discharge						
LMWH [132]	1	33/155	37/144	0.83 (0.55, 1.25)	-0.04 (-0.14, 0.05)	ET: 58 FP: 225

** FP – forest plot number in Appendix E; ET – evidence table number in Appendix D*

Proph - prophylaxis

a) *There is substantial statistical heterogeneity between studies for this population (I^2=86.8%, χ^2 on 1 df = 7.56, p= 0.006).*

b) *There is substantial statistical heterogeneity between studies for this population (I^2=72.1%, χ^2 on 1 df = 3.58, p= 0.06).*

c) *There is substantial heterogeneity between studies for this population population (I^2=50.3%, χ^2 on 1 df = 32.01, p= 0.16).*

Table 11-61: Pulmonary embolism – summary of results from RCTs

Comparison	No. of studies	Interven -tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
IPCD/FID vs nil [436,697]	2	1/38	4/44	0.30 (0.04, 2.27)	-0.09 (-0.45, 0.26)	ET: 24 FP: 5
High dose aspirin vs. nil [436]	1	3/21	4/12	0.43 (0.11, 1.60)	-0.19 (-0.50, 0.12)	ET: 29 FP: 29
Single proph vs single						
IPCD/FID vs LMWH [66]	1	0/63	0/67	N/A	0.00 (-0.03, 0.03)	ET: 37 FP: 88
IPCD/FID vs High dose aspirin [245,436]	2	4/71	4/79	1.34 (0.32, 5.49)	0.03 (-0.04, 0.09)	ET: 37 FP: 99
VKA vs. LMWH [186,274,389]	3	3/609	2/611	1.39 (0.19, 10.16)	0.00 (-0.00, 0.01)	ET: 34 FP: 58
Dabigatran vs LMWH [476]	2	6/1107	5/1155	1.28 (0.39, 4.16)	0.00 (0.00, 0.00)	ET: [476] FP: 42
Rivaroxaban vs LMWH [479]	2	4/2727	12/2725	0.54 (0.19, 1.50)	0.00 (-0.01, 0.00)	ET: [479] FP: 262
LMWH vs. UFH[130]	1	0/145	1/143	0.33 (0.01, 8.00)	-0.01 (-0.02, 0.01)	ET: 32 FP: 49
Double proph vs single						
LMWH + GCS vs GCS [202,399]	2	3/358	1/203	1.15 (0.17, 7.80)	0.01 (-0.01, 0.02)	ET: 26 FP: 135
Double proph vs double						
Fon + GCS vs LMWH + GCS [36]	1	1/517	4/517	0.25 (0.03, 2.23)	-0.01 (-0.01, 0.00)	ET: 44 FP: 172
LMWH + IPCD/FID vs Asp High dose + IPCD/FID [686]	1	0/135	1/129	0.32 (0.01, 7.75)	-0.01 (-0.03, 0.01)	ET: 46 FP: 191
LMWH + GCS vs UFH + GCS [183]	1	0/92	0/93	N/A	0.00 (-0.02, 0.02)	ET: 45 FP: 175
Extended duration						
LMWH [132,272]	2	3/583	4/578	0.80 (0.13, 4.86)	0.00 (-0.01, 0.01)	ET: 58 FP: 226

FP – forest plot number in Appendix E; ET – evidence table number in Appendix D
Proph – prophylaxis

Table 11-62: Major bleeding – summary of results from RCTs

Comparison	No. of studies	Interven -tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
LMWH vs nil [388]	1	0/66	1/65	0.33 (0.01, 7.92)	-0.02 (-0.06, 0.03)	ET: 26 FP: 15
High dose aspirin vs. nil [436]	1	1/21	0/12	1.77 (0.08, 40.40)	0.05 (-0.10, 0.20)	ET: 29 FP: 30
Single proph vs single						
IPCD/FID vs LMWH [66]	1	0/63	1/67	0.35 (0.01, 8.54)	-0.01 (-0.06, 0.03l)	ET: 37 FP: 89
IPCD/FID vs High dose aspirin [436]	1	0/10	1/21	0.67 (0.03, 15.06)	-0.05 (-0.21, 0.11)	ET: 37 FP: 100
VKA vs. LMWH [186,274,389]	3	22/789	38/786	0.58 (0.34, 0.97)	-0.02 (-0.04, 0.01)	ET: 34 FP: 59
Dabigatran vs LMWH [476]	2	15/ 1536	21/ 1562	0. 72 (a) (0.27, 1.89)	0.00 (-0.01, 0.01)	ET: [476] FP: 43
Rivaroxaban vs LMWH [479]	2	17/276 4	10/274 7	1.67 (0.76, 3.69)	0.00 (0.00, 0.01)	ET: [479] FP: 263
LMWH vs. UFH[130]	1	3/228	3/225	0.99 (0.20, 4.84)	0.00 (-0.02, 0.02)	ET: 32 FP: 50
Double proph vs single						
Fon + GCS vs GCS [201]	1	1/84	1/87	1.04 (0.07,16.29)	0.00 (-0.03, 0.03)	ET: 40 FP: 132
LMWH + GCS vs GCS [202,399]	2	7/397	7/214	0.53 (0.17, 1.63)	-0.01 (-0.04, 0.02)	ET: 26 FP: 136
Double proph vs double						
Fon + GCS vs LMWH + GCS [36]	1	11/517	1/ 517	11.00 (1.43, 84.89)	0.02 (0.01, 0.03)	ET: 44 FP: 173
LMWH + IPCD/FID vs Asp high dose + IPCD/FID [686]	1	0/135	0/129	N/A	0.00 (-0.01, 0.01)	ET: 46 FP: 192
Extended duration						
LMWH [132,272]	2	2/583	3/568	0.72 (0.14, 3.83)	0.00 (-0.01, 0.01)	ET: 58 FP: 227

** FP – forest plot number in Appendix E; ET – evidence table number in Appendix D*
Proph - prophylaxis

a) *There is substantial statistical heterogeneity between studies for this population (I^2=50.2%, χ^2 on 1 df = 2.01, p= 0.16).*

11.2.3 Additional information

11.2.3.1 All cause mortality

All cause mortality was not identified as a key outcome during the development of the surgical guideline. Much of the data were identified from systematic reviews where all cause mortality was not reported. There was not enough time during the development of this guideline to review all cause mortality for this population. In the national joint registry data[481] the mortality rate at 3 months after total knee replacement was 0.5%, not adjusting for thromboprophylaxis method. It is estimated that at this event rate, a sample size of 300,000 patients in each arm is required to detect a 10% reduction in mortality with 80% power and a p value of 0.05 (α=0.05, two sided) Smaller reductions in mortality would require even larger sample sizes. None of the published

studies nor the total sample size in the meta-analysis was powered to detect a difference in mortality.

11.2.3.2 Other outcomes

No RCTs or systematic reviews reported results post thrombotic syndrome, chronic thromboembolic pulmonary hypertension, heparin induced thrombocytopenia, quality of life or length of stay as outcomes for this population.

11.2.3.3 Additional studies

Eighteen (18) RCTs reported evidence for both hip and knee replacement patients without distinguishing between the two groups [20,27,69,127,200,220,242,250,290,292,299,322,402,408,514,531,541,601]. The results of these studies are presented in evidence tables (Appendix D) and forest plots (Appendix E) for those comparisons.

11.3 Network meta-analysis

A network meta-analysis was completed for DVT and major bleeding. Details on the network meta-analysis methods can be found in section 3.10.

DVT results

There were 18 studies included in the network meta-analysis for asymptomatic and symptomatic DVT [36,66,130,186,245,274,291,388,389,436,476,479,676,686,697]. One study compared three interventions[436]

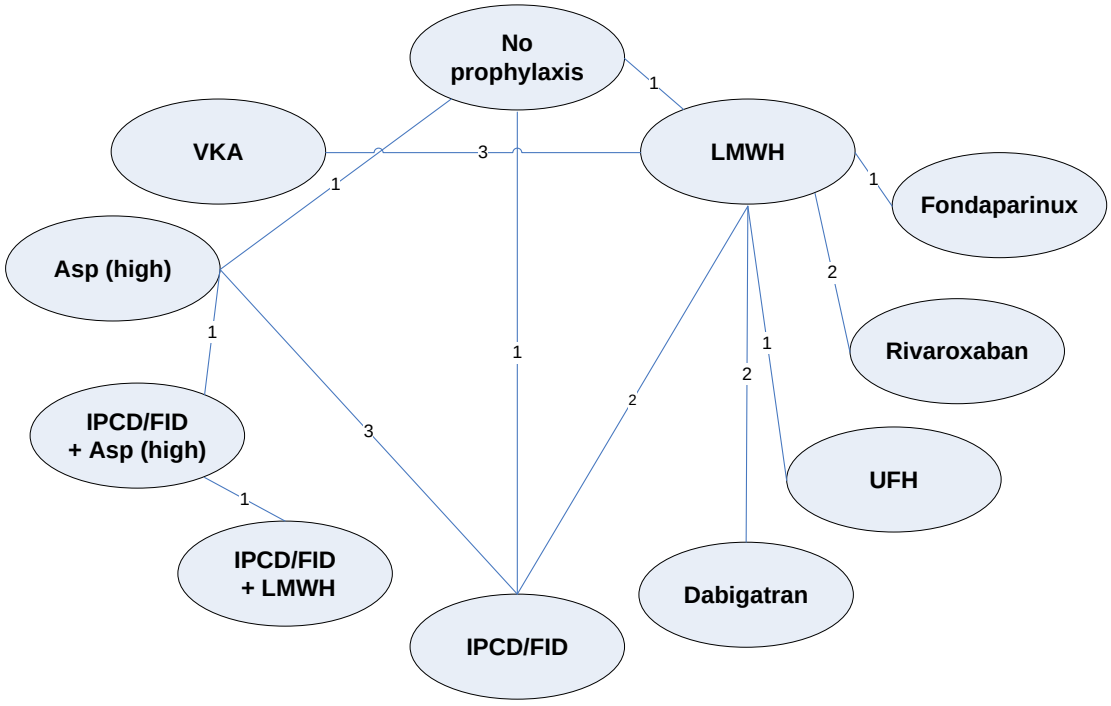


Figure 11-26: Network diagram for all DVT. Numbers indicate the number of studies which contributed results for each comparison

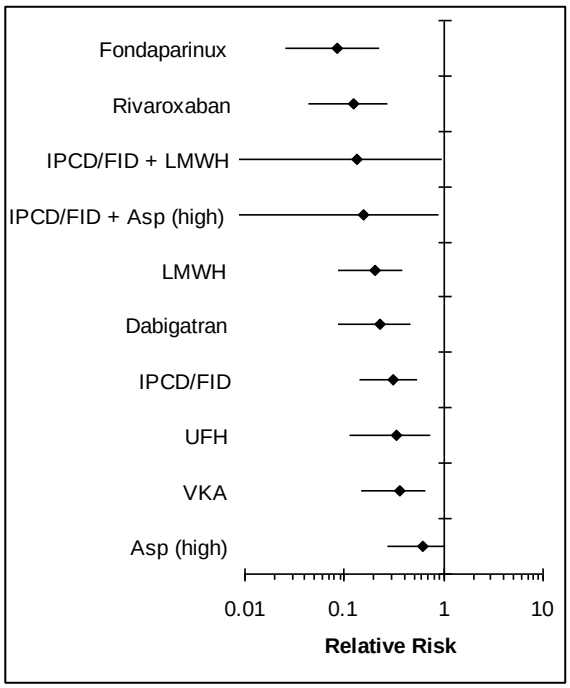


Figure 11-27: DVT– network meta-analysis results of interventions compared to no prophylaxis

Table 11-63: DVT – network meta-analysis results

Intervention (compared with no prophylaxis)	Relative Risk (95% credible intervals)
Fondaparinux	0.08 (0.03, 0.23)
Rivaroxaban	0.12 (0.04, 0.28)
IPCD/FID + LMWH	0.14 (0.01, 0.97)
IPCD/FID + Asp (high dose)	0.15 (0.01, 0.91)
LMWH	0.20 (0.09, 0.39)
Dabigatran	0.22 (0.09, 0.47)
IPCD/FID	0.31 (0.14, 0.55)
UFH	0.34 (0.11, 0.73)
VKA	0.36 (0.15, 0.67)
Asp (high dose)	0.62 (0.28, 1.04)

Credible intervals are the Bayesian equivalent of confidence intervals.

The residual deviance was 37.9, which is quite close to the number of data points of 30, implying that the model fits the data well.

Pulmonary embolism results

There was not enough evidence to complete a network meta-analysis for this outcome.

Major bleeding results

A network meta-analysis for major bleeding was conducted using studies across hip fracture surgery, hip replacement surgery, knee replacement surgery, general medical patients and general surgical patients.

One hundred and twenty eight (128) studies were included in the analysis of which:

- 10 studies were in **medical patients**[45,121,191,256,257,350,387,390,394,579],
- 48 studies were in **general surgery patients**[10,14,29,40,50,52,72,75,76,92,113,199,210,227,230,238,262,266,267,269,280,283,321,324,329,358,366,385,439,496,499,503,504,516,517,530,552,553,570,575,588,589,633,639,641,645,657,667,703,711,713],
- 28 studies were in **elective hip replacement patients**[126,129,151,153,174,188,195,201,202,243,260,293,299,377,380,400,409,421,465,527,573,574,635,650,651,659,684],
- 9 studies were in patients undergoing **hip fracture surgery**[175,178,204,248,463,533,609,704,715]

- 15 studies were in **elective knee replacement patients**[36,66,130,186,201,202,274,388,389,399,436,476,479].
- 7 studies were in **mixed orthopaedic surgery patients**[69,200,242,250,292,459,531]
- 11 studies were in **mixed surgery patients**[54,166,270,271,340-344,396,416,486,568,569,575,585,655].

Seven of these studies included three comparison arms[153,299,380,504,533,633,655].

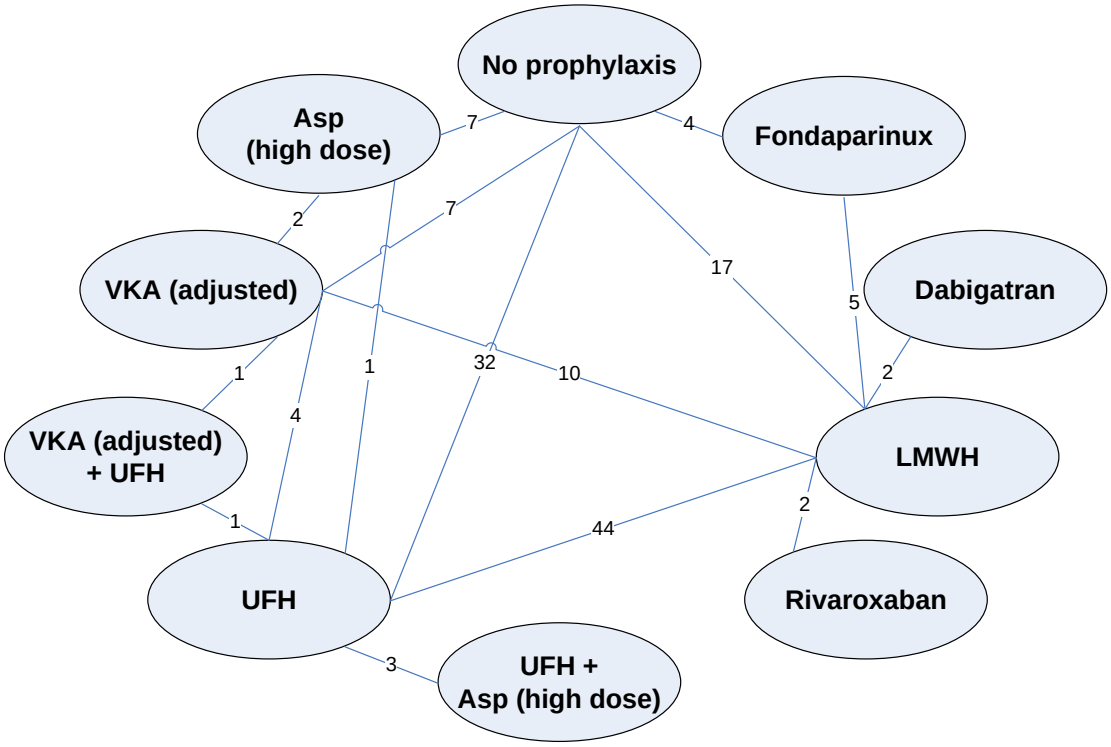


Figure 11-28: Network diagram for major bleeding. Numbers indicate the number of studies which contributed results for each comparison

Only the results for interventions included in the network meta-analysis for DVT were included in the results.

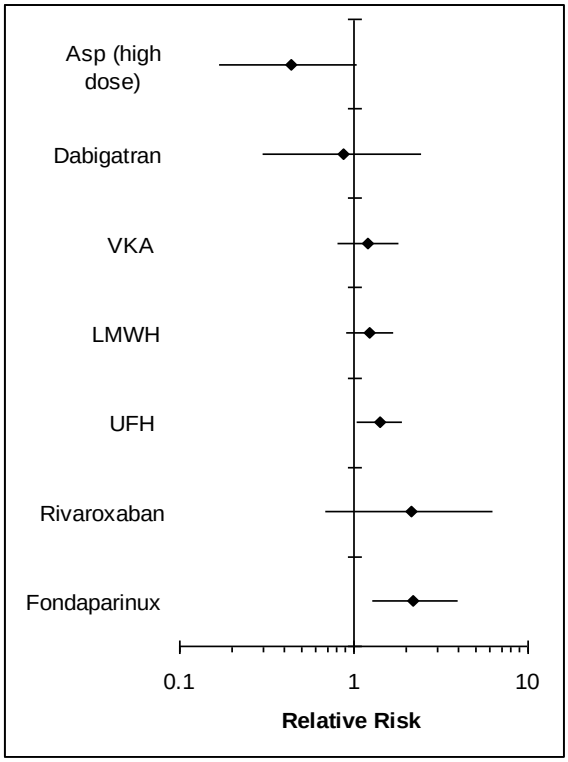


Figure 11-29: Major Bleeding – network meta-analysis results of interventions compared to no prophylaxis

Table 11-64: Major bleeding – network meta-analysis results

Intervention (compared with no prophylaxis)	Relative Risk (95% credible intervals)
Aspirin (high dose)	0.44 (0.17, 1.04)
Dabigatran	0.87 (0.30, 2.45)
VKA	1.21 (0.81, 1.82)
LMWH	1.23 (0.91, 1.68)
UFH	1.40 (1.05, 1.89)
Rivaroxaban	2.12 (0.70, 6.29)
Fondaparinux	2.21 (1.27, 3.94)

Credible intervals are the Bayesian equivalent of confidence intervals.

The residual deviance was 291.5, which is quite close to the number of data points of 263, implying that the model fits the data well.

11.4 Cost-effectiveness evidence

11.4.1 Introduction

The general assumptions and methods for the cost-effectiveness model are described in chapter 4.

The results are driven by the network meta-analysis, above. Other data used for the cost-effectiveness analysis which are specific to knee replacement patients can be found in Table 11-65 and Table 11-66.

Table 11-65: Baseline risk and other population specific parameters used in the economic model for knee replacement patients

Baseline Characteristics	*Source*	*Value*
Mean age (years)	Hospital Episode Statistics Data (2005-6) [159]	70
% Male	Hospital Episode Statistics Data (2005-6) [159]	42
Standardised Mortality Ratio (a)	Nunley 2003 [494]	52% (1 year)
Mean duration of prophylaxis	Systematic review of RCTs (b)	10 days
Proportion of DVTs that are symptomatic (Ratio of symptomatic DVTs to all DVTs)	Published systematic review [542]	5.0%
Major Bleed Fatality Rate (c)	Muntz (2004)[467] systematic review of thromboprophylaxis RCTs	0.8%
PE Fatality Rate (d)	Systematic review of RCTs[557] (all elective surgery)	6.0% =11/184
Re-operation rate	From a review of recent fondaparinux and dabigatran trials [36,175,377,476,651]	13%
DVT risk	No prophylaxis/placebo arms of RCTs from systematic review (b)	60.0%
Symptomatic PE risk	This figure is an estimate as no studies have presented results for symptomatic PE in the absence of prophylaxis. Symptomatic PE in cohort studies with prophylaxis range from 0.2-1.9% [422,674,678,689]	1.0%
Major bleeding risk	No prophylaxis/placebo arms of RCTs from systematic review (b)	1.9%

a) *Ratio of the death rate in the surgical group compared with the death rate in the general population, adjusting for age and sex*
b) *This refers to the systematic review of RCTs for the current guideline*
c) *Fatal major bleeds divided by all major bleeds*
d) *Fatal PEs divided by all symptomatic PEs*

Table 11-66: Weights used for events in the base case analysis

Event	Cost (£)	QALYs lost	Net loss (a)(£)
DVT Asymptomatic	0	0.0000	0
DVT Symptomatic	576	0.0035	645
Post-thrombotic syndrome	7,475	0.1971	11,417
Chronic pulmonary hypertension	69,123	6.0517	190,156
Pulmonary embolism - fatal	0	9.3889	187,778
Pulmonary embolism - symptomatic	2,521	0.0041	2,603
Major bleeding - No long-term sequalae	908	0.0267	1,441
Major bleeding - Stroke	23,877	7.3254	170,386
Major bleeding - fatal	0	9.3889	187,778
Heparin-induced thrombocytopaenia (sensitivity analysis only)	2,610	1.4006	30,623

QALY=quality-adjusted life-year
(a) *Net loss is the sum of the resource cost plus the QALY loss:*
Net loss=cost+ (20,000 x QALYs lost)

Event rates by strategy can be found in Appendix G.

11.4.2 Results for knee replacement patients

Table 11-67: Base case results – deterministic and probabilistic results

	Deterministic INB	*Probabilistic INB*	
Intervention	*Mean*	*Mean*	*% of simulations where strategy was most cost-effective*
Fondaparinux	864	910	17.2%
Dabigatran	902	904	15.8%
LMWH	881	890	1.9%
AspirinHD_plus_IPCD-FID	884	890	44.7%
Rivaroxaban	815	869	16.5%
LMWH_plus_IPCD-FID	800	815	3.0%
IPCD-FID	792	790	0.8%
WarfarinAD	675	680	0.0%
UFH	652	669	0.2%

INB = Incremental Net Benefit. The strategy with the highest probabilistic mean INB is the most cost effective overall

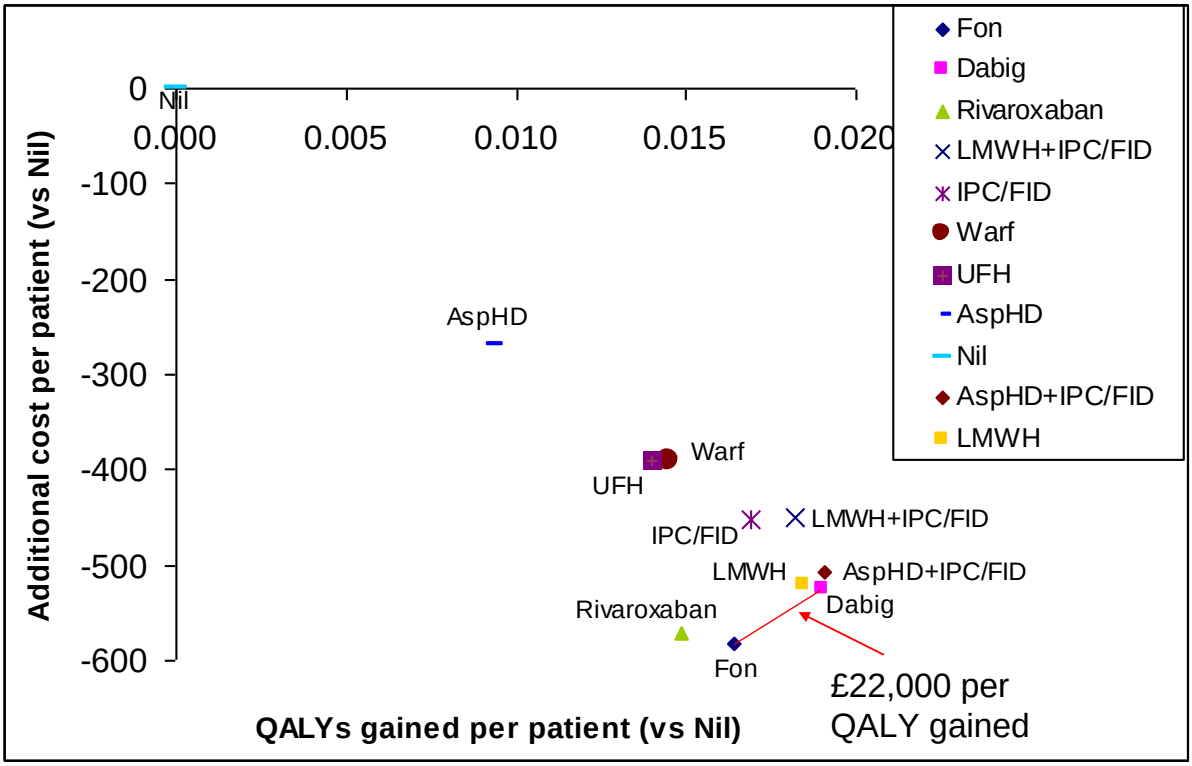


Figure 11-30: Base case results of the cost-effectiveness analysis for total knee replacement patients (probabilistic analysis)

Fon = fondaparinux, Asp HD = High dose Aspirin, Warf = Warfarin, Dabig= Dabigatran

11.4.3 Deterministic sensitivity analysis

Table 11-68: Deterministic sensitivity analysis results

Factors changed within the Model	*Most Cost-effective Strategy*
Base case	Dabigatran
Base case (probabilistic)	Fondaparinux
Chronic Thromboembolic Pulmonary Hypertension and Post Thrombotic Syndrome	
0% Chronic Thromboembolic Pulmonary Hypertension	Dabigatran
0.5% Chronic Thromboembolic Pulmonary Hypertension	Dabigatran
1% Chronic Thromboembolic Pulmonary Hypertension	Dabigatran
0% Chronic Thromboembolic Pulmonary Hypertension and 0% Post Thrombotic Syndrome	Dabigatran
High Post Thrombotic Syndrome rate (e.g. 30% after symptomatic DVT and 21% after asymptomatic DVT)	Fondapainux
Low Post Thrombotic Syndrome (e.g. 15% after symptomatic DVT and 8% after asymptomatic DVT)	Dabigatran
Low cost for Post Thrombotic Syndrome	Dabigatran
High cost for Post Thrombotic Syndrome	Fondapainux
High cost for Chronic Thromboembolic Pulmonary Hypertension	Dabigatran
Other Sensitivity Analyses	
Explicitly include Heparin Induced Thrombocytopenia (LMWH=0.5%, UFH=5%)	Dabigatran
Explicitly include Heparin Induced Thrombocytopenia (LMWH=0.2%, UFH=2.6%)	Dabigatran
Using population specific major bleeding relative risks	LMWH
Discounted LMWH / Dabigatran cost = £1	LMWH
Fatality after PE = 10%	Dabigatran
Fatality after Major Bleeding = 5%	Dabigatran
Low aspirin major bleeding relative risk from Network Meta-analysis (RR = 0.49)	Dabigatran
Higher aspirin & dabigatran major bleeding relative risk	LMWH
Foot Impulse Device (consumable: £18, pump: £0)	Dabigatran
Increased NICE threshold (£30,000/ QALY)	Dabigatran

QALY=quality-adjusted life-year

Table 11-69: Most cost-effective strategy by baseline risk of pulmonary embolism and major bleeding: standard duration prophylaxis

		Major bleeding risk												
PE risk		0%	0.5%	1%	1.5%	2%	2.5%	3%	3.5%	4%	4.5%	5%	5.5%	6%
	0%	Fon	Fon	Fon	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig
	0.5%	Fon	Fon	Fon	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig
	1%	Fon	Fon	Fon	Fon	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig
	1.5%	Fon	Fon	Fon	Fon	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig
	2%	Fon	Fon	Fon	Fon	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig
	2.5%	Fon	Fon	Fon	Fon	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig
	3%	Fon	Fon	Fon	Fon	Fon	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig
	3.5%	Fon	Fon	Fon	Fon	Fon	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig
	4%	Fon	Fon	Fon	Fon	Fon	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig
	4.5%	Fon	Fon	Fon	Fon	Fon	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig
	5%	Fon	Fon	Fon	Fon	Fon	Fon	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig
	5.5%	Fon	Fon	Fon	Fon	Fon	Fon	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig
	6%	Fon	Fon	Fon	Fon	Fon	Fon	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig	Dabig

Fon = Fondaparinux; Dabig = Dabigatran

11.4.4 Conclusion of cost-effectiveness results

It was noted that for total knee replacement surgery dabigatran was the most cost-effective strategy in the deterministic analysis. However, fondaparinux was more cost-effective in the probabilistic analysis..

Dabigatran and fondaparinux were the most cost-effective strategies in the base case and in most of the deterministic sensitivity analyses. LMWH was the most cost-effective strategy when

- discounted drug costs were used or
- when population specific major bleeding relative risks or
- when the major bleeding risk for dabigatran was assumed the same as for LMWH.

Rivaroxaban had a similar level of cost-effectiveness to LMWH, dabigatran and fondaparinux, as was found in the NICE Technology Appraisal TA170. In the manufacturers model, rivaroxaban was slightly more cost-effective than the others but the TA committee noted that the model had inappropriately ignored non-significant differences and had not taken account of health loss attributable to intra-cranial bleeding.

AspirinHD_plus_IPCD-FID also came out as relatively cost-effective in the base case analysis but this was on the basis that aspirin does not increase the risk of major bleeding. When an increased risk of bleeding similar to LMWH was assumed then aspirin was no longer cost-effective.

A cost-effectiveness analysis of post discharge prophylaxis or extended duration prophylaxis has not been completed for this population.

11.5 Patient views

A total of eight studies included some patients undergoing knee replacement surgery[16,102,128,506,525,555,614,687] (Evidence tables 61-63, Appendix D). More information about patient views and adherence from these studies are presented in section 6.6. The following is a summary of the main findings.

Two studies investigated the patient views and adherence of self injection with LMWH[128,614]. Spahn et al[614] evaluated postoperative self-injection of LMWH for about 10 days in 300 patietns. Fully completed questionnaires from 207 patients showed that after training for self-injection, most (92.2%) chose self-administration rather than a nursing service. Of those who chose self-administration, 16% required family or friends to help. Fewer patients who self-injected without any help found it 'very unpleasant' compared to those who received help. Overall, adherence was incomplete in 28.3% patients who did not use the nursing service.

Colwell et al[128] looked into the ability to self-administer subcutaneous LMWH and adhere to the injection regimen for 21 days in 51 patients. Patients received instructions and a demonstration by the staff nurses. On discharge, written and video instructional materials were provided. Among the 40 patients who completed the study, 86% performed self-injections while 14% were assisted by a family or friend. Most patients (98%) understood the importance of heparin and 68% felt comfortable with self-injection.

Five studies looked at the adherence and patient views of foot impulse devices (FID)[16,102,525,555,687]. The adherence reported ranged from 30% to 95%, depending on timing of observation and definitions used. Although the majority of patients found FID comfortable, interference with sleep was quite widely reported (28% to 58%) among studies where patients were required to wear the devices continuously.

The study on FID which recruited only knee replacement patients reported patient comfort and adherence[687]. Given a choice of options ranging from extremely uncomfortable to extremely comfortable, on average, patients found the foot wrap to be between "moderately comfortable" to "very comfortable" and the pumping action "slightly" comfortable".

One of these FID studies compared the acceptability of FID to subcutaneous LMWH injections[16]. All patients received both prophylaxis methods, and were generally comfortable with them. Slightly more patients found LMWH painful (14.1% vs 11% in FID). However, significantly more patients would rather not have FIDs (37%) compared to LMWH (14.0%) or continue prophylaxis for 4 weeks (76.7% vs. 51.2%).

In another study, FID (n=120) were compared to intermittent pneumatic compression devices (IPCD) plus graduated compression stockings (GCS) (n=104) [555]. Significantly more patients were "comfortable" or had no complaints with FID (71% vs. 55%). Among 35 participants in the FID group who had used IPCD in a previous surgery, more (69%) preferred FID than IPCD (20%). The rest had no preference.

For patient views on specific interventions from all population subgroups (surgical and medical), are presented in section 6.6.

11.6 Summary of evidence

Table 11-70: Summary of evidence from network meta-analysis results for DVT, pulmonary embolism and major bleeding outcomes.

Intervention(s)	*Comparison(s)*	*Intervention favoured*		
		DVT	**PE**	**MB**
Prophylaxis vs no prophylaxis				
IPCD/FID	no prophylaxis	**IPCD/FID**	-	-
Aspirin (high dose)	no prophylaxis	Not sig	-	Not sig
VKA (adjusted dose)	no prophylaxis	**VKA**	-	Not sig
UFH	no prophylaxis	**UFH**	-	**No prophylaxis**
LMWH	no prophylaxis	**LMWH**	-	Not sig
Fondaparinux	no prophylaxis	**Fondaparinux**	-	**No prophylaxis**
Dabigatran	no prophylaxis	**Dabigatran**	-	Not sig
Rivaroxaban	no prophylaxis	**Rivaroxaban**	-	Not sig
Asp (HD) + IPCD/FID	no prophylaxis	**Asp (HD) + IPCD/FID**	-	Not sig
LMWH + IPCD/FID	no prophylaxis	**LMWH + IPCD/FID**	-	Not sig
Cost-effectiveness				
Dabigatran and fondaparinux were the most cost-effective strategies in the base case and in most of the deterministic sensitivity analyses. LMWH was the most cost-effective strategy when **• discounted drug costs were used or** **• when population specific major bleeding relative risks or** **• when the major bleeding risk for dabigatran was assumed the same as for LMWH.** **In TA170, the Committee concluded that, on balance, rivaroxaban, enoxaparin and dabigatran had very similar costs and benefits in the prevention of VTE.** **Rivaroxaban had a similar level of cost-effectiveness to LMWH, dabigatran and fondaparinux**				
A cost-effectiveness analysis of post discharge prophylaxis was not completed for this population.				

The prophylaxis strategy which is significantly more effective in reducing DVT or PE; or resulting in significantly less major bleeding is stated in bold. Not sig = not statistically significant difference. '-'= not reported.

nil – no prophylaxis; GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; VKA – vitamin K antagonist; asp (HD) – high dose aspirin; high dose aspirin is >300mg MB = Major bleeding

11.7 Recommendations and link to evidence

Recommendation	**Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing elective knee replacement surgery.** • **Start mechanical VTE prophylaxis at admission. Choose any one of the following, based on individual patient factors:** - **anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)** - **foot impulse devices** - **intermittent pneumatic compression devices (thigh or knee length)** **Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.** • **Provided there are no contraindications, start pharmacological VTE prophylaxis after surgery. Choose any one of:** – **dabigatran etexilate, starting 1-4 hours after surgery *** – **fondaparinux sodium, starting 6 hours after surgical closure provided haemostasis has been established** – **LMWH, starting 6–12 hours after surgery** – **rivaroxaban, starting 6-10 hours after surgery$** – **UFH (for patients with renal failure), starting 6–12 hours after surgery.** **Continue pharmacological VTE prophylaxis for 10-14 days, according to the summary of product characteristics for the individual agent being used.** **** Dabigatran etexilate, within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 157 (2008).[476]*** ***$ Rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 170 (2009).[479]***
Relative values of different	The orthopaedic subgroup noted that although all cause

outcomes

mortality is the most important outcome for this population the studies were not powered to detect a difference in mortality for any of the interventions under consideration. The next most important outcome was thought to be the risk of symptomatic venous thromboembolism balanced against the risk of major bleeding. The relative risk reduction for all DVT events was used as a surrogate for symptomatic VTE events as the orthopaedic subgroup accepted that there was a relationship between the risk reduction in DVT and PE.

Trade off between clinical benefit and harms

The benefit of reducing VTE events was balanced with the potential harms of bleeding. The economic model includes consideration of long term sequelae such as the cost of reoperation due to bleeding, post thrombotic syndrome, chronic thromboembolic pulmonary hypertension and stroke.

Our decision model indicated that the QALYs lost due to major bleeding were outweighed by the QALYs gained from drug prophylaxis.

Economic considerations

An economic model was developed for this population which found that fondaparinux, dabigatran, LMWH and rivaroxaban were the most cost-effective strategies.

AspirinHD_plus_IPCD-FID also came out as relatively cost-effective in the base case analysis but this was on the basis that aspirin does not increase the risk of major bleeding. When an increased risk of bleeding similar to LMW H was assumed then aspirin was no longer cost-effective. The GDG felt that the base case assumption was not plausible and therefore concluded that AspirinHD_plus_IPCD-FID was not sufficiently cost-effective.

Quality of evidence

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

The clinical evidence consisted of 23 RCTs in knee replacement surgery of which 18 were included in the network meta-analysis for DVT. The studies tended to be relatively large and only 17% (4/23) had less than 100 patients. Additionally they were relatively recent studies with only9% (2/23) published before 1990 and 52% (11/23) published since 2000.

Other considerations

Pharmacological prophylaxis: The orthopaedic subgroup were mindful of the increase in bleeding risk in the period immediately after knee surgery and agreed that prophylaxis should be started only after the immediate bleeding risk had reduced.

Only one RCT compared pre op start times with post-op start for LMWH and this showed no significant difference in major bleeding.

The summary of product characteristics states a postoperative

start time for dabigatran, rivaroxaban and fondaparinux, and a preoperative start time for most LMWHs although the actual start times vary depending on the specific LMWH. In this guideline it is recommended that LMWH is started postoperatively which is off-label because concerns about the risk of bleeding into the joint. Patients would be protected preoperatively against VTE by mechanical prophylaxis. Some of the LMWH studies included in our analyses also started LMWH postoperatively. Further information should be sought from the summary of product characteristics for each anticoagulant.

The LMWH dose used in the comparison of LMWH with rivaroxaban is higher than that recommended for use in the UK. This was taken into account when considering which pharmacological agents to use.

Mechanical prophylaxis:

There was no evidence in knee replacement patients for the use of stockings alone. Because there were no trials which used stockings they could not be included in the network meta-analysis for knee replacement patients, and were not included in the cost-effectiveness model. There was a discussion within the orthopaedic subgroup about the practicality of using anti-embolism stockings after knee replacement surgery. Patients are likely to have swollen legs after surgery and so it was felt important to ensure that patient's legs are re-measured after surgery to ensure stockings remained correctly fitted correctly.

The evidence demonstrates that IPCD/FID devices were effective at reducing DVT and were a more practical solution in these patients. The orthopaedic subgroup therefore recommended that IPCD/FID were available as an alternative to anti-embolism stockings. The orthopaedic subgroup were aware of potential patient compliance issues with the use of IPCD and difficulty of their use when patients regained mobility but agreed that either anti-embolism stockings or IPCD devices should be continued until the patient was discharged or no longer had significantly reduced mobility.

Mechanical prophylaxis was felt to be particularly important in the period around the operation where patients were not protected by chemical prophylaxis. The orthopaedic subgroup agreed that by providing mechanical methods from admission the risk of developing DVT in the peri-operative period was reduced.

Duration of prophylaxis: The duration of pharmacological prophylaxis from the trials and on which the cost-effectiveness model was based was between 7-14 days. The orthopaedic subgroup noted that the length of stay for knee replacement patients is likely to be around 5-7 days. The orthopaedic subgroup decided that the duration of prophylaxis should be for 10-14 days (as per licensing conditions), in order to reflect

the evidence from trials. This may require prophylaxis outside the hospital period. If the patient is discharged with prophylaxis, their GP should be notified to ensure that appropriate after care is provided. A suitable regime might be LMWH whilst in hospital followed by oral agents once discharged home.

11.7.1 Other recommendations of relevance

The specific recommendations for patients having elective total knee replacement in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information including when patients are discharged with prophylaxis (section 32.5)

11.8 Summary of recommendations

- Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing elective knee replacement surgery.
    - Start mechanical VTE prophylaxis at admission. Choose any one of the following based on individual patient factors:
        - anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)
        - foot impulse devices
        - intermittent pneumatic compression devices (thigh or knee length)

      Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.
    - Provided there are no contraindications, start pharmacological VTE prophylaxis after surgery. Choose one of the following:
        - dabigatran etexilate, starting 1-4 hours after surgery*
        - fondaparinux sodium, starting 6 hours after surgical closure provided haemostasis has been established
        - LMWH, starting 6–12 hours after surgery

- rivaroxaban, starting 6-10 hours after surgery$
- UFH (for patients with renal failure), starting 6–12 hours after surgery.

Continue pharmacological VTE prophylaxis for 10-14 days, according to the summary of product characteristics for the individual agent being used.

* Dabigatran etexilate, within its marketing authorisation, is recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 157(2008).[476]

$ Rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery. NICE technology appraisal guidance 170 (2009).[479]

12 Hip fracture surgery

12.1 Introduction

Fractures of the proximal femur (commonly known as neck of femur or hip fractures) are very common in the elderly population and carry significant morbidity and mortality. They occur mainly as osteoporotic or fragility fractures but a small proportion may result from major trauma in a younger age group. The latter is covered under the section on major trauma (Section 22).

We have estimated from the incidence of RCTs that the risk of developing DVT, pulmonary embolism and major bleeding in patients with fractures of the proximal femur not receiving thromboprophylaxis is:

- DVT (symptomatic and asymptomatic) - 37% (95% CI: 35% to 40%)
- Symptomatic pulmonary embolism – 6% (95% CI: 4% to 7%)
- Major bleeding events – 2% (95% CI: 1% to 3%)

It is likely from the evidence available that the incidence of each is greater in this patient group with an additional impact mainly from cardiovascular, respiratory and cerebrovascular disease. Therefore, the risks of adding mechanical and pharmacological VTE prophylaxis have to be weighed very carefully against any potential adverse effects of this treatment. However, there is some evidence from the studies evaluated for this guideline that there is a reduction in VTE events if thromboprophylaxis is used. This effect is greater in proportion than the risk of adverse events, in particular, major bleeding.

12.2 Evidence of methods of prophylaxis

12.2.1 Summary of comparisons identified for any outcome

Thirty randomised controlled trials which reported at least one of the three main outcomes were identified[51,74,172,175-178,185,204,209,248,316,370,381,458,463-465,470,533,541,590,609,613,621,630,631,700,704,715]. Some of these investigated more than two methods of thromboprophylaxis. Most of RCTs had their data extracted from systematic reviews. Where applicable the study is cited in the evidence table for that review. Six systematic reviews included RCTs covering patients with hip fracture[21,125,355,451,557,719].

Another two studies investigated thromboprophylaxis in a mixed population of both hip fracture and elective hip replacement patients[122,459].

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

	No prophylaxis	Post-discharge	GCS	IPCD/FID	Dabigatran	Fondaparinux	LMWH	UFH	VKA	Asp (HD)	Asp (LD)	GCS + IPCD/FID	Mech + pharm
GCS													
IPCD/FID	**1**												
Dabigitran													
Fondaparinux		**1**											
LMWH	**2**					**1**							
UFH	**7**						**2**						
VKA	**6**												
High dose aspirin	**7**							**3**	**1**				
Low dose aspirin													
GCS + IPCD/FID				**1**									
Mech + pharm								**1**					
Other comparisons							**1**				**1**		

Figure 12-31: Number of studies which compared various types of prophylaxis methods.

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicates areas where no studies were identified.

GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) - low dose aspirin (≤ 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis

12.2.2 Results from pairwise comparisons

Table 12-71: DVT – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
IPCD/FID vs nil[185]	1	4/145	9/159	0.49 (0.15, 1.55)	-0.03 (-0.07, 0.02)	ET: 24 FP: 4
LMWH vs nil[316,613]	2	33/102	78/116	0.48 (035, 0.65)	-0.35 (-0.48, -0.23)	ET: 26 FP: 13
UFH vs nil[51,209,370,464,631,704]	6	63/236	115/228	0.56 (0.39, 0.81) (a)	-0.23 (-0.35, -0.12)	ET: 27 FP: 17
VKA vs nil[74,248,463,470,533]	5	57/245	132/240	0.44 (0.34, 0.56)	-0.32 (-0.40, -0.24)	ET: 28 FP: 21
High dose asp vs nil[172,464,533,590,609,700,715]	7	117/385	116/338	0.85 (0.62, 1.15) (b)	-0.15 (-0.05, 0.05)	ET: 29 FP: 28
Single proph vs single						
Fon vs LMWH[175]	1	49/624	117/623	0.42 (0.31, 0.57)	-0.11 (-0.15, -0.07)	ET: 31 FP: 44
LMWH vs UFH[381,458]	1	14/53	23/54	0.62 (0.36, 1.07)	-0.16 (-0.34, 0.02)	ET: 32 FP: 48
VKA vs high dose asp[533]	1	13/65	27/66	0.49 (0.28, 0.86)	-0.21 (-0.36, -0.06)	ET: 35 FP: 60
Double proph vs single						
UFH + GCS vs GCS[465]	1	10/29	8/23	0.99 (0.47, 2.10)	0.00 (-0.26, 0.26)	ET: 27 FP: 142
Other prophylaxis strategies						
IPCD then LMWH vs LMWH[177]	1	2/21	4/24	0.57 (0.12, 2.81)	-0.07 (-0.27, 0.12)	ET: 51 FP: 209
Post discharge						
Fondaparinux[176]	1	3/208	74/218	0.04 (0.01, 0.13)	-0.33 (-0.39, -0.26)	ET: 57 FP: 221

** FP – forest plot number in Appendix E; ET – evidence table number in Appendix D*
Proph - prophylaxis
(a) Significant statistical heterogeneity within the results (I^2 = 54%, p=0.03)
(b) Significant statistical heterogeneity within the results (I^2 = 60.3%, p=0.02)

Table 12-72: Pulmonary embolism – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
IPCD/FID vs nil[185] (a)	1	6/145	9/159	0.73 (0.27, 2.00)	-0.02 (-0.06, 0.03)	ET: 24 FP: 5
UFH vs nil[204,464]	2	1/74	2/74	0.50 (0.05, 5.34)	-0.01 (-0.06, 0.04)	ET: 27 FP: 18
VKA vs nil[74,178,463,470,533]	5	4/307	28/303	0.21 (0.08, 0.53)	-0.07 (-0.11, -0.03)	ET: 28 FP: 22
High dose asp vs nil[172,464,533,590,609,700,715]	7	12/385	26/338	0.44 (0.22, 0.88)	-0.03 (-0.06, -0.01)	ET: 29 FP: 29
Single proph vs single						
Fon vs LMWH[175]	1	3/831	3/840	1.01 (0.20, 4.99)	0.01 (-0.01, 0.01)	ET: 31 FP: 45

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
LMWH vs UFH[458]	1	6/46	0/42	11.89 (0.69, 204.91)	0.13 (0.03, 0.23)	ET: 32 FP: 49
VKA vs high dose asp[533]	1	0/65	1/66	0.34 (0.01, 8.16)	-0.02 (-0.06, 0.03)	ET: 35 FP: 61
Double proph vs single						
UFH + GCS vs GCS[465]	1	2/29	1/23	1.59 (0.15, 16.42)	0.03 (-0.10, 0.15)	ET: 27 FP: 143
Aspirin + other prophylaxis vs other prophylaxis (b)[541]	1	46 /6679	81 /6677	0.57 (0.40, 0.81)	-0.01 (-0.01, 0.00)	ET: 42 FP: 165
Other prophylaxis strategies						
IPCD then LMWH vs LMWH[177]	1	1/21	0/24	3.41 (0.15, 79.47)	0.05 (-0.07, 0.17)	ET: 51 FP: 210
Extended duration						
Fondaparinux[176]	1	0/326	3/330	0.14 (0.01, 2.79)	-0.01 (-0.02, 0.00)	ET: 57 FP: 222

** FP – forest plot number in Appendix E; ET – evidence table number in Appendix D*
Proph - prophylaxis
(a) Asymptomatic and symptomatic pulmonary embolism

Table 12-73: Major bleeding – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
LMWH vs nil[316]	1	0/41	0/41	not estimable	0.00 (-0.05, 0.05)	ET: 26 FP: 15
UFH vs nil[51,204,464,704]	4	4/129	6/123	0.69 (0.23, 2.13)	-0.01 (-0.05, 0.03)	ET: 27 FP: 19
VKA vs nil[74,178,248,463,533]	5	26/312	18/310	1.35 (0.70, 2.62)	0.02 (-0.03, 0.06)	ET: 28 FP: 23
High dose asp vs nil[172,464,533,590,609,700,715]	87	8/385	10/338	0.52 (0.14, 1.96) (b)	-0.01 (-0.03, 0.01)	ET: 29 FP: 30
Single proph vs single						
Fon vs LMWH[175]	1	18/831	19/842	0.96 (0.51, 1.82)	0.00 (-0.02, 0.01)	ET: 31 FP: 46
VKA vs high dose asp[533]	1	5/65	1/66	5.08 (0.61, 42.28)	0.06 (-0.01, 0.13)	ET: 35 FP: 62
Double proph vs single						
UFH + GCS vs GCS[465]	1	0/29	0/23	not estimable	0.00 (-0.07, 0.07)	ET: 27 FP: 144
Other prophylaxis strategies	-	-	-	-	-	
Post discharge						
Fondaparinux[176]	1	8/327	2/329	4.02 (0.86, 18.81)	0.02 (0.00, 0.04)	ET: 57 FP: 223

** FP – forest plot number in Appendix E; ET – evidence table number in Appendix D*
Proph - prophylaxis

12.2.3 Additional information

12.2.3.1 All cause mortality

Table 12-74: Mortality – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
LMWH vs nil[316]	1	3/30	4/38	0.95 (0.23, 3.92)	-0.01 (-0.15, 0.14)	ET: 26 FP: 16
UFH vs nil[51,204,631]	3	20/193	20/187	0.96 (0.55, 1.67)	-0.01 (-0.08, 0.07)	ET: 27 FP: 20
VKA vs nil[74,178,248,463,470,533]	6	47/362	62/365	0.76 (0.54, 1.07)	-0.01 (-0.05, 0.03)	ET: 28 FP: 24
High dose asp vs nil[172,464,533,590,609,700,715]	7	23/385	25/338	0.75 (0.42, 1.34)	-0.01 (-0.04, 0.03)	ET: 29 FP: 31
Single proph vs single						
Fon vs LMWH[175]	1	38/831	42/842	0.92 (0.60, 1.41)	-0.00 (-0.02, 0.02)	ET: 31 FP: 47
LMWH vs UFH[381,458]	2	6/99	5/98	1.17 (0.35, 3.90)	0.01 (-0.05, 0.07)	ET: 32 FP: 51
VKA vs high dose asp[533]	1	2/65	3/66	0.68 (0.12, 3.92)	-0.01 (-0.08, 0.05)	ET: 35 FP: 63
Double proph vs single						
UFH + GCS vs GCS[465]	1	0/29	3/23	0.11 (0.01, 2.11)	-0.13 (-0.28, 0.02)	ET: 27 FP: 145
Post discharge						
Fondaparinux[176]	1	6/327	8/329	0.75 (0.26, 2.15)	-0.01 (-0.03, 0.02)	ET: 57 FP: 224

** FP – forest plot number in Appendix E; ET – evidence table number in Appendix D*
Proph - prophylaxis

12.2.3.2 Additional outcomes

No RCTs or systematic reviews reported results for post thrombotic syndrome, chronic thromboembolic pulmonary hypertension, heparin induced thrombocytopenia, quality of life or length of stay as outcomes for this population.

12.2.3.3 Additional studies

Two RCTs investigated thromboprophylaxis in a mixed group of hip fracture and elective hip replacement patients. These have not been included in the above section and were not included in the economic model for either hip fracture or elective hip replacement:

- Cohen et al[122] found there was no significant difference in DVT or pulmonary embolism when stockings for 35 days were added to fondaparinux for five to nine days. (Appendix D, Evidence table 40; Appendix E, Forest plots 170-172)

- Monreal et al[459] found there was no significant difference in DVT or major bleeding when aspirin was added to UFH. (Appendix D, Evidence table 42; Appendix E, Forest plots 161, 163)

12.3 Network meta-analysis results

12.3.1 Introduction

A network meta-analysis was completed for DVT, major bleeding and all cause mortality. Details on the network meta-analysis methods can be found in section 3.10.

For patients undergoing surgery for fractures of the proximal femur the studies of standard duration prophylaxis (e.g. prophylaxis given for a maximum of 21 days) were analysed in the network meta-analysis. Prophylaxis extending beyond this period was analysed in a separate cost-effectiveness analysis.

12.3.2 Results

DVT results

There were 23 studies included in the network meta-analysis for DVT [51,74,172,175,177,185,209,248,316,370,381,463,464,470,533,590,609,613,631,700,704,715]. One study compared three interventions[533].

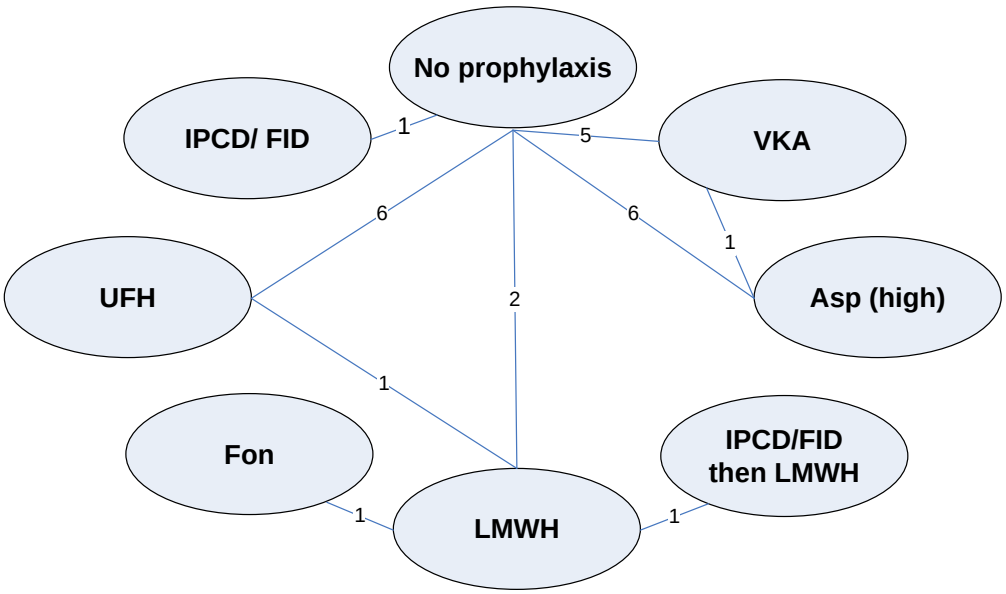


Figure 12-32: Network diagram for DVT. Numbers indicate the number of studies, which contributed results for each comparison

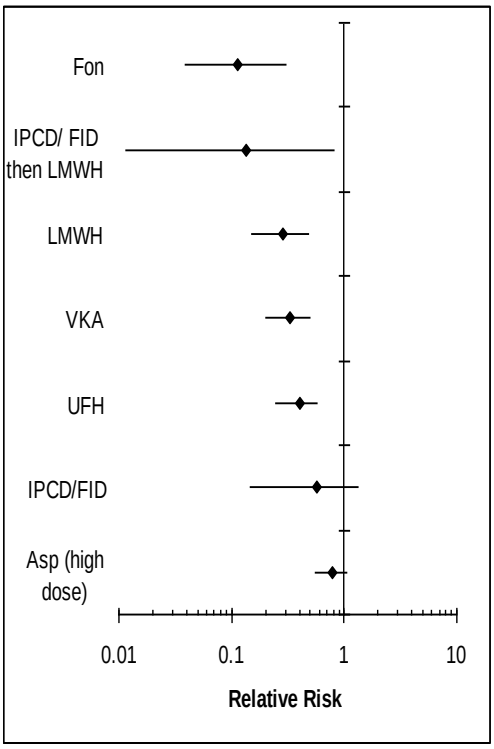


Figure 12-33: DVT – network meta-analysis results of interventions compared to no prophylaxis

Table 12-75: DVT – network meta-analysis results

Intervention (compared with no prophylaxis)	Relative Risk (95% credible intervals)
Fondaparinux	0.11 (0.04, 0.31)
IPCD/FID then LMWH	0.14 (0.01, 0.82)
LMWH	0.29 (0.15, 0.50)
VKA (adjusted-dose)	0.33 (0.20, 0.51)
UFH	0.41 (0.25, 0.59)
IPCD / FID	0.58 (0.15, 1.37)
Asp (high dose)	0.79 (0.56, 1.07)

Credible intervals are the Bayesian equivalent of confidence intervals.
The residual deviance was 56.0, which is quite close to the number of data points of 47, implying that the model fits the data well.

Pulmonary embolism results

There were not enough data to complete a network analysis for this outcome

Major bleeding results

A network meta-analysis for major bleeding was conducted using studies across hip fracture surgery, hip replacement surgery, knee replacement surgery, general medical patients and general surgical patients.

One hundred and twenty eight (128) studies were included in the analysis of which:

- 10 studies were in **medical patients**[45,121,191,256,257,350,387,390,394,579],
- 48 studies were in **general surgery patients**[10,14,29,40,50,52,72,75,76,92,113,199,210,227,230,238,262,266,267,269,280,283,321,324,329,358,366,385,439,496,499,503,504,516,517,530,552,553,570,575,588,589,633,639,641,645,657,667,703,711,713],
- 28 studies were in **elective hip replacement patients**[126,129,151,153,174,188,195,201,202,243,260,293,299,377,380,400,409,421,465,527,573,574,635,650,651,659,684],
- 9 studies were in patients undergoing **hip fracture surgery**[175,178,204,248,463,533,609,704,715]

- 15 studies were in **elective knee replacement patients**[36,66,130,186,201,202,274,388,389,399,436,476,479].
- 7 studies were in **mixed orthopaedic surgery patients**[69,200,242,250,292,459,531]
- 11 studies were in **mixed surgery patients**[54,166,270,271,340-344,396,416,486,568,569,575,585,655].

Seven of these studies included three comparison arms[153,299,380,504,533,633,655].

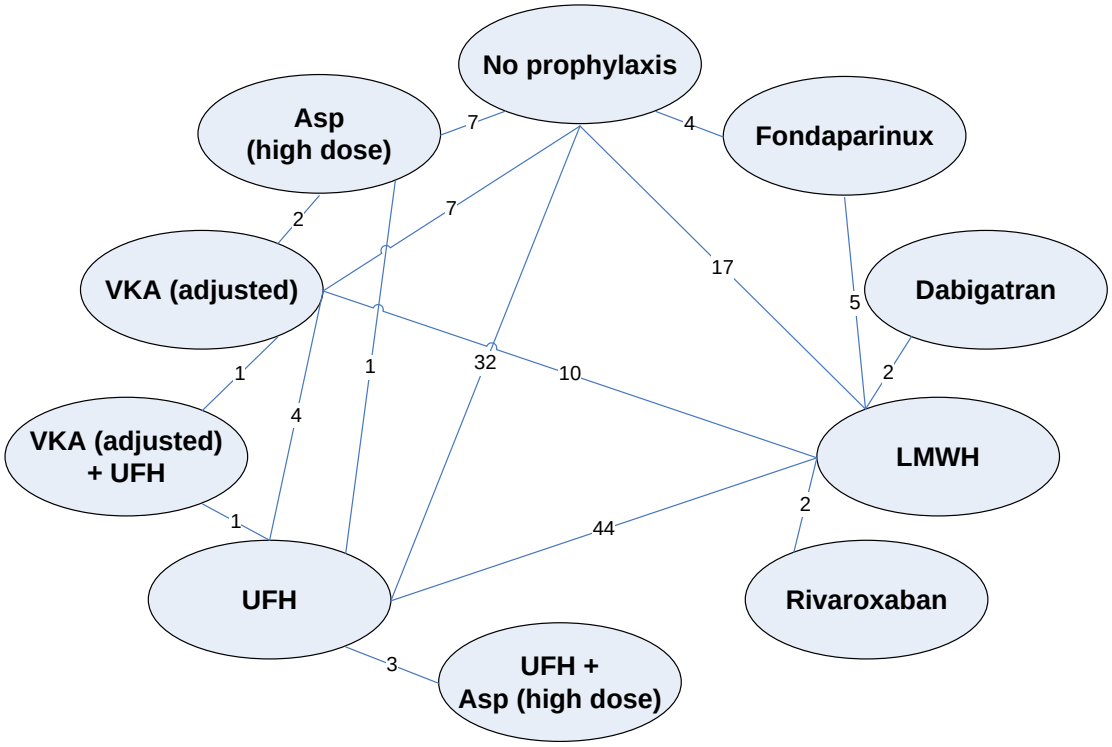


Figure 12-34: Network diagram for major bleeding. Numbers indicate the number of studies which contributed results for each comparison

Only the results for interventions included in the network meta-analysis for DVT were included in the results.

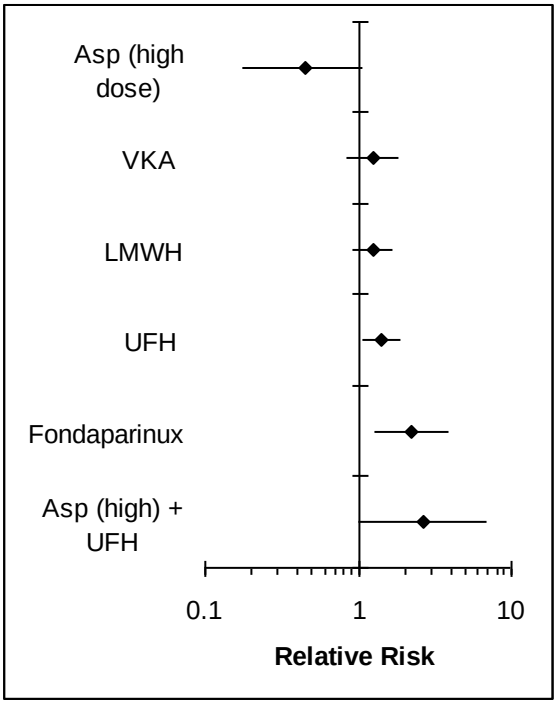


Figure 12-35: Major bleeding – network meta-analysis results of interventions compared to no prophylaxis

Table 12-76: Major bleeding – network meta-analysis results (pooled across all population subgroups)

Intervention (compared with no prophylaxis)	Relative Risk (95% credible intervals)
Asp (high dose)	0.45 (0.18, 1.07)
VKA	1.24 (0.83, 1.85)
LMWH	1.26 (0.94, 1.71)
UFH	1.43 (1.08, 1.92)
Fondaparinux	2.22 (1.30, 3.88)
Aspirin + UFH	2.69 (1.02, 6.91)

Credible intervals are the Bayesian equivalent of confidence intervals.

The residual deviance was 291.5, which is quite close to the number of data points of 263, implying that the model fits the data quite well.

All cause mortality

There were 18 studies included in the network meta-analysis for all cause mortality[51,74,172,175,178,204,248,316,380,458,463,470,533,590,609,631,700,715]. One study compared three interventions[533].

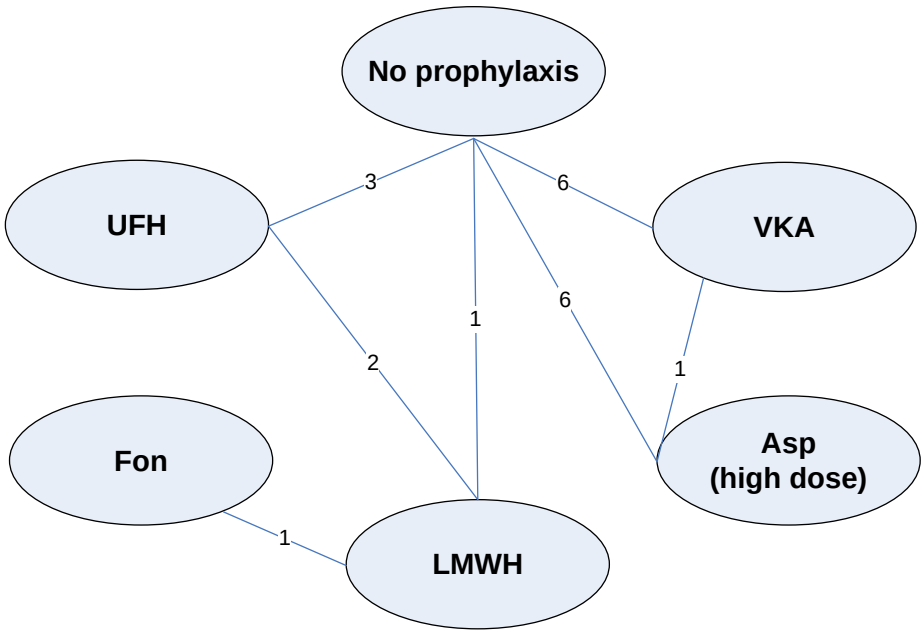


Figure 12-36: Network diagram for all cause mortality. Numbers indicate the number of studies which contributed results for each comparison

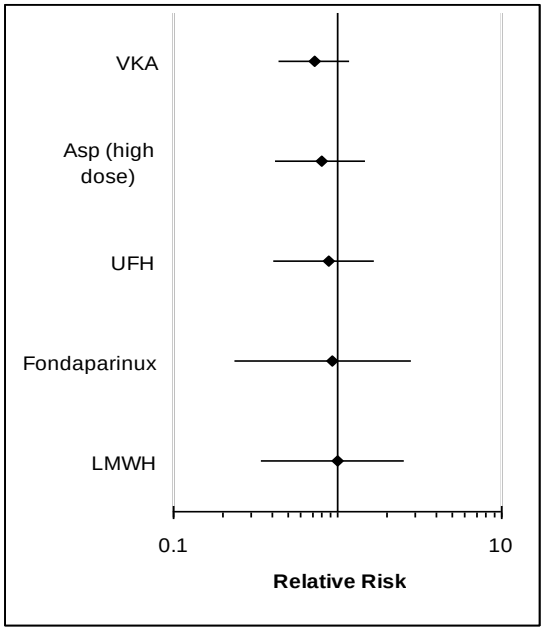


Figure 12-7: All cause mortality – network meta-analysis results of interventions compared to no prophylaxis

Table 12-77: All cause mortality – network meta-analysis results

Intervention (compared with no prophylaxis)	Relative Risk (95% credible intervals)
VKA	0.73 (0.44, 1.18)
Asp (high dose)	0.81 (0.42, 1.47)
UFH	0.88 (0.41, 1.68)
Fondaparinux	0.93 (0.24, 2.85)
LMWH	1.00 (0.35, 2.55)

Credible intervals are the Bayesian equivalent of confidence intervals.

The residual deviance was 33.5, which is quite close to the number of data points of 37, implying that the model fits the data well.

12.4 Cost-effectiveness evidence

12.4.1 Introduction

The general assumptions and methods for the cost-effectiveness model are described in chapter 4.

The results are driven by the network meta-analysis, above. Other data used for the cost-effectiveness analysis which are specific to hip fracture patients can be found in Table 12-76, Table 12-78 and Table 12-79.

Table 12-78: Baseline risk and other population specific parameters used in the economic model for hip fracture patients

Baseline Characteristics	*Source*	*Value*
Mean age (years)	Hospital Episode Statistics data 2005-6[159]	82
% Male	Hospital Episode Statistics data 2005-6[159]	23%
Standardised Mortality Ratio(a)	Seagroatt, 1994 [595]	461% (1 year)
Mean duration of prophylaxis	Systematic review of RCTs(b)	10 days
Proportion of DVTs that are symptomatic (Ratio of symptomatic DVTs to all DVTs)	Assumed to be the same as elective hip replacement.	21.0%
Major Bleed Fatality Rate (c)	Muntz (2004) systematic review of thromboprophylaxis RCTs[467]	0.8% (5/632)
PE Fatality Rate (d)	Systematic review of RCTs (b)	31.0% (9/21)
DVT risk	Systematic review of RCTs (b)	39.8%
Symptomatic PE risk	Systematic review of RCTs (b)	7.9%
Major bleeding risk	Systematic review of RCTs (b)	3.2%

a) *Ratio of the death rate in the surgical group compared with the death rate in the general population, adjusting for age and sex*
b) *This refers to the systematic review of RCTs for the current guideline*
c) *Fatal major bleeds divided by all major bleeds*
d) *Fatal PEs divided by all symptomatic PEs*

Table 12-79: Weights used for events in the base case analysis

Event	Cost (£)	QALYs lost	Net loss* (£)
DVT Asymptomatic	0	0.0000	0
DVT Symptomatic	576	0.0035	645
Post-thrombotic syndrome	3,427	0.0801	5,030
Chronic pulmonary hypertension	69,123	0.9672	88,467
Pulmonary embolism - fatal	0	4.3044	86,089
Pulmonary embolism - symptomatic	2,521	0.0041	2,603
Major bleeding - No long-term sequalae	908	0.0267	1,441
Major bleeding - Stroke	23,877	2.2410	68,696
Major bleeding - fatal	0	4.3044	86,089
Heparin-induced thrombocytopaenia (sensitivity analysis only)	2,428	0.6395	15,219

QALY=quality-adjusted life-year
** Net loss is the sum of the resource cost plus the QALY loss:*
Net loss=cost+ (20,000 x QALYs lost)

Event rates by strategy can be found in Appendix G.

12.4.2 Results: standard duration prophylaxis

12.4.2.1 Base case results

Table 12-80: Base case results – deterministic and probabilistic results

	Deterministic INB	*Probabilistic INB*	
Intervention (ordered by mean probabilistic INB)	*Mean*	*Mean*	*% of simulations where strategy was most cost-effective*
Fondaparinux	2151	2148	85.0%
WarfarinAD	1835	1830	4.2%
LMWH	1713	1711	4.5%
UFH	1470	1465	0.6%
IPCD-FID	979	999	5.7%
AspirinHD	560	558	0.0%
Nil	0	0	0.0%

INB = Incremental Net Benefit. The strategy with the highest probabilistic mean INB is the most cost-effective overall

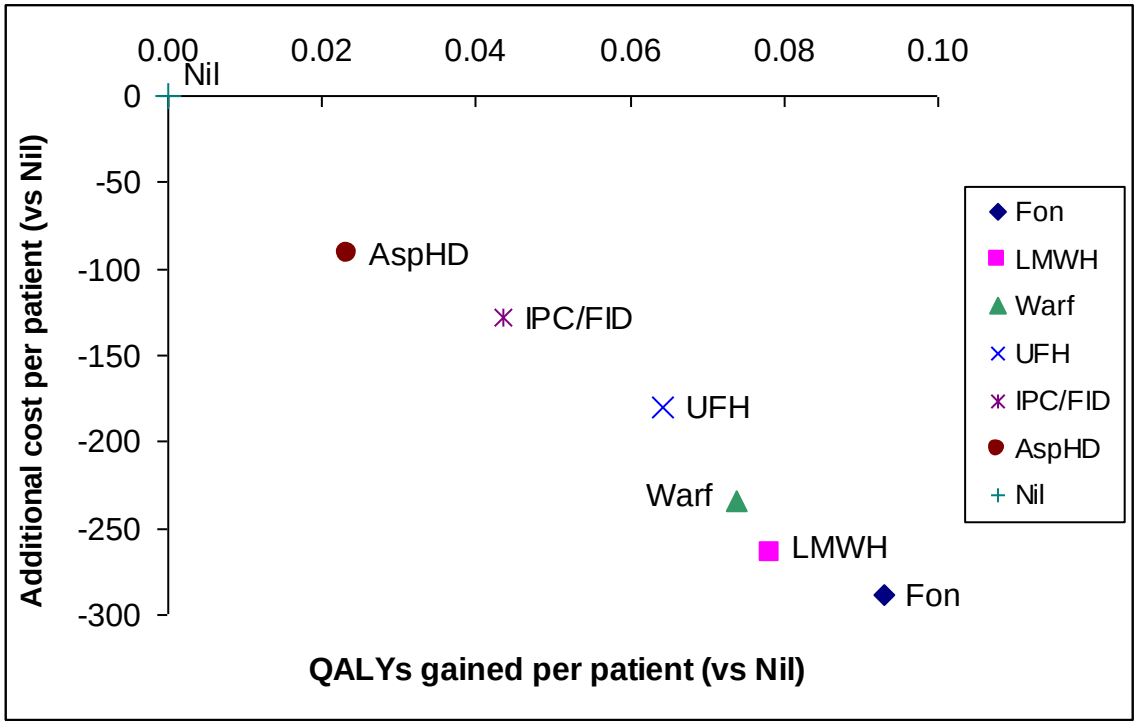


Figure 12-7: Base case results of the cost-effectiveness analysis for hip fracture patients: standard duration prophylaxis

Fon = fondaparinux, Warf = warfarin, QALY=quality-adjusted life-year

12.4.3 Base case results – post discharge prophylaxis

Table 12-81: Results for study post discharge comparing LMWH with no prophylaxis

	Deterministic INB	*Probabilistic INB*	
Intervention (ordered by mean probabilistic INB)	**Mean**	**Mean**	**% of simulations where strategy was most cost-effective**
Fondaparinux	262	239	92.0%
Nil	0	0	8.0%

INB = Incremental Net Benefit. The strategy with the highest probabilistic mean INB is the most cost-effective overall

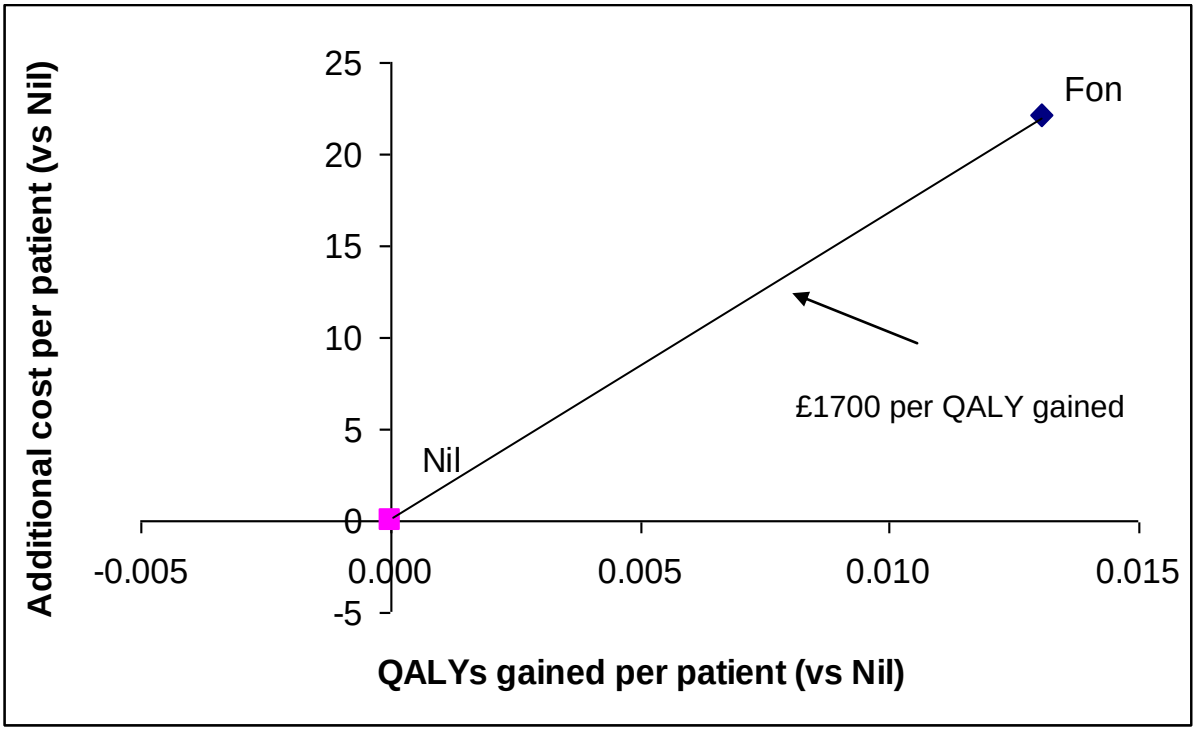


Figure 12-7: Base case results of the cost-effectiveness analysis for hip fracture patients: post-discharge prophylaxis
Fon = fondaparinux

12.4.4 Deterministic sensitivity analysis

Table 12-82: Deterministic sensitivity analysis results

Factors changed within the Model	*Most Cost-effective Strategy*	
	Standard duration prophylaxis	*Post Discharge (fondaparinux vs nil)*
Base case	Fondaparinux	Fondaparinux
Base case (probabilistic)	Fondaparinux	Fondaparinux
Chronic Thromboembolic Pulmonary Hypertension and Post Thrombotic Syndrome		
0% Chronic Thromboembolic Pulmonary Hypertension	Fondaparinux	Fondaparinux
0.5% Chronic Thromboembolic Pulmonary Hypertension	Fondaparinux	Fondaparinux
1% Chronic Thromboembolic Pulmonary Hypertension	Fondaparinux	Fondaparinux
0% Chronic Thromboembolic Pulmonary Hypertension and 0% Post Thrombotic Syndrome	Fondaparinux	Fondaparinux
High Post Thrombotic Syndrome rate (e.g. 30% after symptomatic DVT and 21% after asymptomatic DVT)	Fondaparinux	Fondaparinux
Low Post Thrombotic Syndrome (e.g. 15% after symptomatic DVT and 8% after asymptomatic DVT)	Fondaparinux	Fondaparinux
Low cost for Post Thrombotic Syndrome	Fondaparinux	Fondaparinux
High cost for Post Thrombotic Syndrome	Fondaparinux	Fondaparinux
High cost for Chronic Thromboembolic Pulmonary Hypertension	Fondaparinux	Fondaparinux
Other Sensitivity Analyses		
Explicitly include Heparin Induced Thrombocytopenia (LMWH=0.5%, UFH=5%)	Fondaparinux	N/A
Explicitly include Heparin Induced Thrombocytopenia (LMWH=0.2%, UFH=2.6%)	Fondaparinux	N/A
Using population specific major bleeding relative risks	N / A	N/A
Low aspirin major bleeding relative risk from Network Meta-analysis (RR = 0.49)	Fondaparinux	N/A
High aspirin major bleeding relative risk from aspirin vs. nil arms (RR = 1.3)	Fondaparinux	N/A
Discounted LMWH cost = £1	Fondaparinux	N/A
Fatality after PE = 10%	Fondaparinux	Fondaparinux
Fatality after Major Bleeding = 5%	Fondaparinux	Fondaparinux
Foot Impulse Devicecost (consumable: £40, pump: £0)	Fondaparinux	N/A
Increased NICE threshold (£30,000/ QALY)	Fondaparinux	Fondaparinux

QALY=quality-adjusted life-year

Table 12-83: Most cost-effective strategy by baseline risk of pulmonary embolism and major bleeding: standard duration prophylaxis

		Major bleeding risk												
PE risk	Fon	0%	0.5%	1%	1.5%	2%	2.5%	3%	3.5%	4%	4.5%	5%	5.5%	6%
	0%	Fon	Fon	Fon	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
	0.5%	Fon	Fon	Fon	Fon	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
	1%	Fon	Fon	Fon	Fon	Fon	Fon	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
	1.5%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
	2%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	LMWH	LMWH	LMWH	LMWH	LMWH
	2.5%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	LMWH	LMWH	LMWH	LMWH
	3%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	LMWH	LMWH	LMWH
	3.5%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	LMWH	LMWH
	4%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon
	4.5%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon
	5%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon
	5.5%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon
	6%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon

Fon=fondaparinux,

Table 12-84: Most cost-effective strategy by baseline risk of pulmonary embolism and major bleeding: post-discharge

		Major bleeding risk												
PE risk		0%	0.5%	1%	1.5%	2%	2.5%	3%	3.5%	4%	4.5%	5%	5.5%	6%
	0%	Fon	Fon	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
	0.5%	Fon	Fon	Fon	Fon	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
	1%	Fon	Fon	Fon	Fon	Fon	Fon	Nil	Nil	Nil	Nil	Nil	Nil	Nil
	1.5%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Nil	Nil	Nil	Nil
	2%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Nil	Nil
	2.5%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon
	3%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon
	3.5%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon
	4%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon
	4.5%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon
	5%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon
	5.5%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon
	6%	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon	Fon

Fon=fondaparinux, Nil=no post-discharge prophylaxis

In a threshold sensitivity analysis, we found that post-discharge fondaparinux prophylaxis was no longer cost-effective if greater than 55% of patients require district nurse visits to deliver their prophylaxis.

12.4.5 Conclusion

For standard duration prophylaxis, fondaparinux was the most effective at increasing quality-adjusted life-years and the most cost-effective strategy.

For patients with a very low bleeding risk fondaparinux was the most cost-effective strategy. LMWH tended to be more cost-effective as the risk of major bleeding increased.

Fondaparinux was the most cost-effective strategy in all other deterministic sensitivity analyes conducted.

In the post discharge period fondaparinux was found to be cost-effective compared to no post-discharge prophylaxis. It remained the most cost-effective strategy in all of the deterministic sensitivity analyses conducted.

12.5 Patient views

No studies on patient views or adherence conducted specifically among patients undergoing hip fracture surgery were found.

For patient views from all patient groups (medical and surgical) about specific prophylaxis agents, see section 6.6**Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.**.

12.6 Summary of evidence

Table 12-85: Summary of evidence from network meta-analysis results for DVT, symptomatic pulmonary embolism and major bleeding outcomes.

Intervention(s)	Comparison(s)	Intervention favoured		
		DVT	Mortality	MB
Prophylaxis vs no prophylaxis				
IPCD/FID	no prophylaxis	Not sig	-	-
Fondaparinux	no prophylaxis	**Fondaparinux**	Not sig	**No prophylaxis**
LMWH	no prophylaxis	**LMWH**	Not sig	Not sig
UFH	no prophylaxis	**UFH**	Not sig	**No prophylaxis**
VKA (adjusted dose)	no prophylaxis	**VKA**	Not sig	Not sig
Aspirin (high-dose)	no prophylaxis	Not sig	Not sig	Not sig
IPCD then LMWH	no prophylaxis	**IPCD then LMWH**	-	-
Post Discharge **(from direct evidence)**				
Fondaparinux	No prophulaxis	**Fondaparinux**	Not sig	Not sig
Cost-effectiveness results				
Fondaparinux was the most cost-effective strategy for standard duration prophylaxis except when major bleeding rate risk was high in which case LMWH was most cost-effective.				
In the post discharge period fondaparinux was found to be cost-effective. No data were available for post-discharge use of LMWH in hip fracture patients.				

The prophylaxis strategy which is significantly more effective in reducing DVT or PE ; or resulting in significantly less major bleeding is stated in bold. Not sig = not statistically significant difference. No event= outcomes reported in study(ies) but no events were reported. '-'= not reported. MB = Major bleeding

12.7 Recommendations and link to evidence

Recommendation	**Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing hip fracture surgery.** • **Start mechanical VTE prophylaxis at admission. Choose any one of the following based on individual patient factors:** – **anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)** – **foot impulse devices** – **intermittent pneumatic compression devices (thigh or knee length).** **Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.** • **Provided there are no contraindications, add pharmacological VTE prophylaxis. Choose any one of:** – **fondaparinux sodium, starting 6 hours after surgical closure, provided haemostasis has been established and there is no risk of bleeding (see Box 2)** – **LMWH, starting at admission, stopping 12 hours before surgery and restarting 6–12 hours after surgery.** – **UFH (for patients with renal failure), starting at admission, stopping 12 hours before surgery and restarting 6–12 hours after surgery.** **Continue pharmacological VTE prophylaxis for 28-35 days, aaccording to the summary of product characteristics for the individual agent being used.**
Recommendation	**Fondaparinux sodium is not recommended for use preoperatively for patients undergoing hip fracture surgery. If it has been used preoperatively it should be stopped 24 hours before surgery and restarted 6 hours after surgical closure, provided haemostasis has been established and there is no risk of bleeding (see Box 2).**
Box 2-Bleeding Risk Factors	**Regard hospitalised patients as being at risk of bleeding if they have any of the following risk factors:** • **Active bleeding** • **Acquired bleeding disorders (such as acute liver failure)** • **Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR higher than 2)** • **Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours**

	• **Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours** • **Acute stroke** • **Thrombocytopenia (platelets < 75 x 10^9/l)** • **Uncontrolled systolic hypertension (230/120 mmHg or higher)** **Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease).**
Relative values of different outcomes	The orthopaedic subgroup noted that although all-cause mortality is the most important outcome for this population the studies were not powered to detect a difference in mortality for any of the interventions under consideration. The next most important outcome was thought to be the risk of symptomatic venous thromboembolism balanced against the risk of major bleeding. The relative risk reduction for all DVT events was used as a surrogate for symptomatic VTE events as the orthopaedic subgroup accepted that there was a relationship between the risk reduction in DVT and PE.
Trade off between clinical benefit and harms	The benefit of reducing VTE events is balanced with the potential harms of bleeding. The economic model includes consideration of long-term sequelae such as the cost of reoperation due to bleeding, post thrombotic syndrome, chronic thromboembolic pulmonary hypertension and stroke. Our decision model indicated that the QALYs lost due to major bleeding were outweighed by the QALYs gained from drug prophylaxis.
Economic considerations	An economic model was developed for this population. This model indicated that fondaparinux was the most effective and most cost-effective prophylaxis method for standard duration prophylaxis. LMWH was the next most-cost-effective strategy and became more cost-effective as the baseline risk of bleeding increases. The economic model showed that extending prophylaxis with fondaparinux for 35 days post-surgery was cost-effective for this population. No data were available for determining the cost-effectiveness of extended LMWH prophylaxis used in this population, although results from elective hip replacement surgery indicated it was cost-effective for this population. No evidence for combination prophylaxis in this population was included in the economic model. Evidence for the effectiveness of combination prophylaxis for fractures of the proximal femur is extrapolated from elective hip replacement evidence. As patients with fractures of the proximal femur have an increased DVT and PE risk compared with elective hip replacement surgery and that mechanical prophylaxis had no impact on the bleeding risk the orthopaedic subgroup felt that it was likely to be cost-effective in this population.

Quality of evidence

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

The clinical evidence consisted of 30 RCTs of which 23 were included in the network meta-analysis for DVT. These studies tended to be small, 61% (14/23) and had less than 100 patients. In addition, 78% (18/23) were published before 1990. Some studies reported bleeding outcomes using different criteria. After a review of the techniques used for fixation of the fractures of the proximal femur used within individual studies it was noted that there was a wide variety of techniques including some which were no longer used in current practice. This may limit the applicability of the evidence.

Other considerations

Many patients undergoing surgery for fracture of the proximal femur are likely to be elderly and may have comorbidities that increase the risk of developing deep vein thrombosis and pulmonary emboli.

Initiation of prophylaxis: The orthopaedic subgroup noted that in this population, individual patient risk factors for VTE (e.g. advanced age and immobility) were likely to be present at admission. It was also noted that surgery for these cases might not occur immediately due to time taken to stabilise the patient or availability of surgical resources. The orthopaedic subgroup agreed that prophylaxis should be initiated at admission once the bleeding risks had been established and it had been confirmed that patients did not have contraindications. The orthopaedic subgroup were concerned about pre-operative bleesding and noted that if the bleeding risks were unknown at admission, mechanical prophylaxis should be initiated until the risk of bleeding had been established.

The summary of product characteristics states a postoperative start time for dabigatran, rivaroxaban and fondaparinux, and a preoperative start time for most LMWHs although the actual start times vary depending on the specific LMWH. In this guideline it is recommended that LMWH is started postoperatively which is off-label because concerns about the risk of bleeding into the joint. Patients would be protected preoperatively against VTE by mechanical prophylaxis. Some of the LMWH studies included in our analyses also started LMWH postoperatively.

Use of fondaparinux: Although the results of the economic model found fondaparinux to be cost-effective both for standard duration and post discharge prophylaxis, the orthopaedic subgroup were aware of the increased risk of bleeding using this agent. Therefore, an additional statement was added to indicate that this agent should only be used where there was not an increased bleeding risk.

In addition, the orthopaedic subgroup decided that due to the longer acting duration of fondaparinux and therefore the need to stop it up to 24 hours before surgery, it should not be given as the preferred thromboprophylactic agent on admission.

Use of warfarin: The orthopaedic subgroup decided that warfarin should not be recommended for this population. Warfarin was felt

to be an outdated modality, which was difficult to monitor. There were concerns with possible interactions between warfarin and other drugs and about lack of cost-effectiveness if continued after discharge.

Use of UFH: The Guideline Development Group felt that UFH should be considered as an option for patients with renal impairment.

Timing of chemical prophylaxis around surgery: The orthopaedic subgroup were mindful of the increase in bleeding risk in the period immediately after surgery. They suggested that prophylaxis with LMWH and UFH should be stopped 12 hours before surgery and recommenced once the immediate bleeding risk had reduced, 6-12 hours after the operation.

Mechanical prophylaxis: The orthopaedic subgroup noted that the use of anti-embolism stockings in patients with a fracture of the proximal femur after surgery was often painful and impractical but they felt that with care and following the recommendations relating to the use of stockings they could be used (section 6.7). The evidence demonstrates that IPCD/FID were cost-effective in this population compared with no prophylaxis and were likely to be a more practical solution than stockings in these patients.

Mechanical prophylaxis was felt to be particularly important in the period around the operation where patients were not protected by chemical prophylaxis. Likewise, if no pharmacological agents can be given for 24 hours then IPCD/FID should be provided at this time to ensure the patient has some protection from VTE events.

The orthopaedic subgroup were aware of patient compliance issues with the use of IPCD and anti-embolism stockings but agreed that they should be continued until the patient was discharged or no longer had significantly reduced mobility.

Duration of prophylaxis: The cost-effectiveness results support the provision of fondaparinux for prophylaxis outside hospital. There is no evidence for extending the duration of LMWH after hip fracture surgery and so the recommendation for LMWH up to 35 days has been extrapolated from the evidence relating to elective hip replacement.

12.7.1 Other recommendations of relevance

The specific recommendations for patients undergoing hip fracture surgery in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information, including for post discharge prophylaxis (section 32.5)

12.8 Recommendations for research

Although not identified as a top 5 research recommendation (Chapter 2.3) the orthopaedic subgroup noted that the new oral anticoagulants (such as dabigatran and rivaroxaban) have not been trialed in patients undergoing hip fracture surgery. These drugs have the potential to make extended VTE prophylaxis much easier for patients with these patients as they are oral agents as opposed to requiring self injection (as LMWH does) and as such research in these patients would be beneficial.

12.9 Summary of recommendations

- Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients undergoing hip fracture surgery.

  - Start mechanical VTE prophylaxis at admission. Choose any one of the following based on individual patient factors:

    - anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length)

    Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

  - Provided there are no contraindications, add pharmacological VTE prophylaxis. Choose any one of the following:

    - fondaparinux sodium, starting 6 hours after surgical closure, provided haemostasis has been established and there is no risk of bleeding (see Box 2),
    - LMWH, starting at admission, stopping 12 hours before surgery and restarting 6–12 hours after surgery.
    - UFH (for patients with renal failure), starting at admission, stopping 12 hours before surgery and restarting 6–12 hours after surgery.

    Continue pharmacological VTE prophylaxis for 28-35 days, according to the summary of product characteristics for the individual agent being used.

- Fondaparinux sodium is not recommended for use preoperatively for patients undergoing hip fracture surgery. If it has been used preoperatively it should be stopped 24 hours before surgery and restarted 6 hours after surgical closure, provided haemostasis has been established and there is no risk of bleeding (see Box 2).

Box 2. Bleeding Risk Factors

- Active bleeding
- Acquired bleeding disorders (such as acute liver failure)
- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR higher than 2)
- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours
- Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours
- Acute stroke
- Thrombocytopenia (platelets less than 75 x 10^9/l)
- Uncontrolled systolic hypertension (230/120 mmHg or higher)
- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease)

13 Other orthopaedic surgery

13.1 Introduction

This section has been included to allow for a comprehensive review of the evidence available as it affects orthopaedic patients, mainly, in an elective setting. The populations covered are those undergoing upper limb surgery (including shoulders, elbows and hands), lower limb surgery (excluding elective total hip and knee replacement) and arthroscopy. There is some overlap with the section on lower limb plaster casts. Spinal surgery is not considered within this chapter (see section 14) It is difficult to be clear about the baseline risk of VTE as it affects these groups because of a lack of evidence but the incidence of DVT in the groups not receiving thromboprophylaxis of the RCTs identified for knee arthroscopy ranged between 4-15% and the effect may be magnified by the large number of patients involved.

The only available studies involve arthroscopy and, clearly, there are limitations in extrapolating from these data. However, the use of a risk assessment tool and a frank discussion with each patient at the pre-operative assessment clinic as part of the informed consent process about the pros and cons of prophylaxis is highly desirable. More complex procedures, for example, shoulder or elbow arthroplasty in a patient with rheumatoid arthritis, arthroscopically assisted ACL reconstruction or open ankle arthrodesis may be associated with a greater risk.

13.1.1 Spinal surgery

Spinal surgery can be completed by orthopaedic surgeons or neurosurgeons although there is a move to the same subspecialty practice in both specialties. Studies conducted in this population have often combined cranial and spinal surgery and it is difficult to separate the two. The evidence and recommendations for spinal surgery patients is presented in chapter 14 (Cranial and Spinal Surgery).

13.2 Evidence of methods of prophylaxis

13.2.1 Summary of comparisons identified for any outcome

The only population for which there was any evidence found was for knee arthroscopy, where 4 studies were identified [94,425,443,699].

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

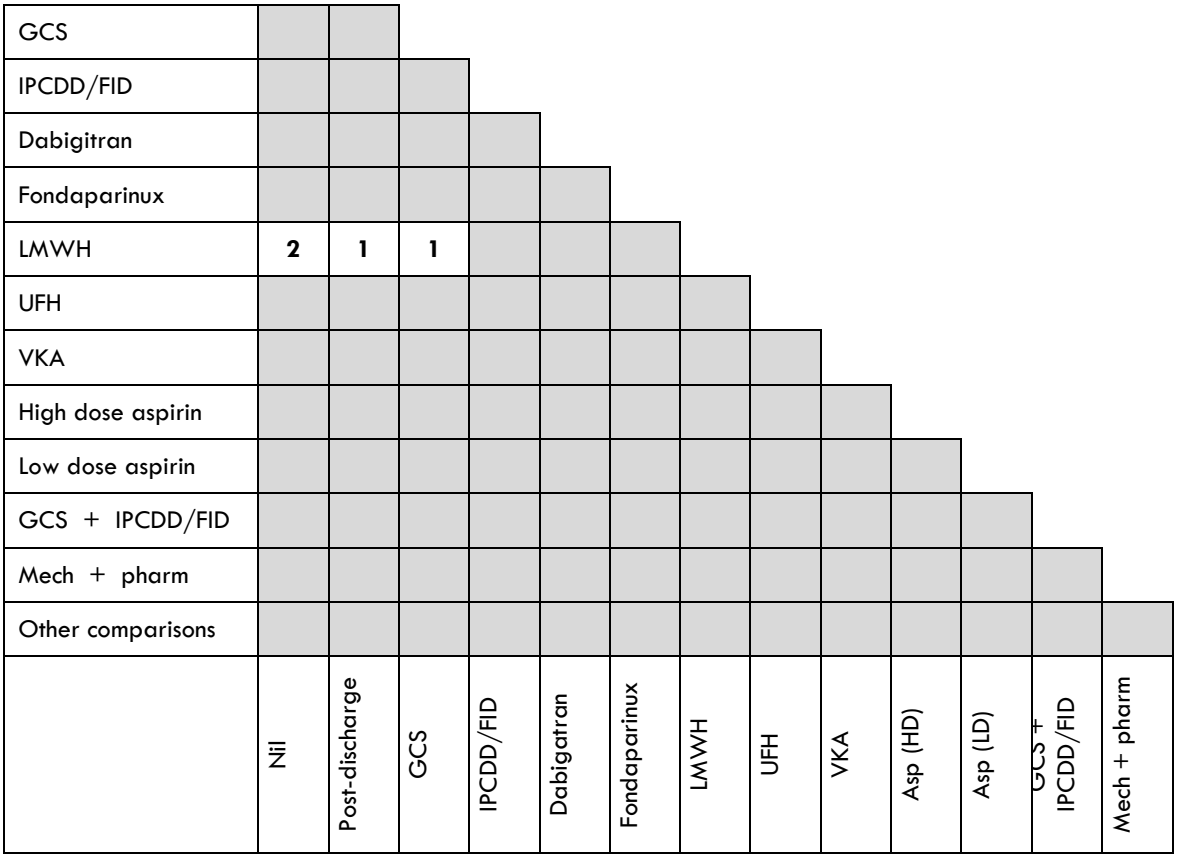


Figure 13-37: Number of studies which compared various types of prophylaxis methods.

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicates areas where no studies were identified.

GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) - low dose aspirin (≤ 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis

13.2.2 Results from pairwise comparisons

Table 13-86: DVT – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
LMWH vs nil[443,699]	2	2/183	15/186	0.014 (0.03, 0.61)	-0.08 (-0.20, 0.04)	ET: 26 FP: 13
Single proph vs single						
GCS vs LMWH [94]	1	29/660	10/657	2.89 (1.42, 5.88)	0.03 (0.01, 0.05)	ET: 37 FP: 81
Post discharge						
LMWH [425]	1	2/72	28/68	0.07 (0.02, 0.27)	-0.38 (-0.51, -0.26)	ET: 58 FP: 225

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*

Proph - prophylaxis

Table 13-87: Pulmonary embolism – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Single proph vs single						
GCS vs LMWH [94]	1	2/660	2/657	1.00 (0.14, 7.05)	0.00 (-0.01, 0.01)	ET: 37 FP: 81
Post discharge						
LMWH [425]	1	0/87	0/88	N/A	0.00 (-0.02, 0.02)	ET: 58 FP: 226

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

Table 13-88: Major bleeding – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
LMWH vs nil[443,699]	2	0/183	0/186	N/A	0.00 (-0.01, 0.01)	ET: 26 FP: 15
Single proph vs single						
GCS vs LMWH [94]	1	1/660	2/657	0.50 (0.05, 5.48)	0.00 (-0.01, 0.00)	ET: 37 FP: 83
Post discharge						
LMWH [425]	1	0/87	0/88	N/A	0.00 (-0.02, 0.02)	ET: 58 FP: 230

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

13.2.3 Additional information

13.2.3.1 All cause mortality

None of the studies reported all cause mortality. Mortality is likely to be extremely rare after knee arthroscopy. In the elective knee replacement patients, estimating a mortality rate of 0.5% a power calculation estimated that 300,000 participants in each arm were required in order to detect a statistically significant difference between interventions (Chapter 1). As the mortality rate in knee arthroscopy patients is likely to be even lower than knee replacements, an even greater number of participants would be required to detect a difference.

13.2.3.2 Additional outcomes

No RCTs or systematic reviews reported results for post thrombotic syndrome, chronic thromboembolic pulmonary hypertension, heparin induced thrombocytopenia, quality of life or length of stay as outcomes for this population.

13.3 Network meta-analysis results

No network meta-analysis was completed for this population.

13.4 Cost-effectiveness evidence

No cost effectiveness analysis was completed for this population.

13.5 Patients view

No patient views or adherence studies conducted specifically among the patient groups discussed in this chapter was identified. However, there are studies conducted in patients with hip replacement, knee replacement, lower limb plaster casts, and general surgery (Chapter 10 - 1, 21 and 9 respectively).

For patient views about specific prophylaxis agents, see section 6.6.

13.6 Summary of evidence

Table 13-4: Summary of evidence from direct evidence for DVT, symptomatic pulmonary embolism and major bleeding outcomes.

Intervention(s)	*Comparison(s)*	*Intervention favoured*		
		DVT	**PE**	**MB**
Prophylaxis vs no prophylaxis				
LMWH	No prophylaxis	**LMWH**	NR	Not sig
Single prophylaxis vs. single				
LMWH	GCS	**LMWH**	Not sig	Not sig
Post Discharge				
LMWH	No prophylaxis	**LMWH**	Not sig	Not sig
Cost Effectiveness				
There is no relevant cost-effectiveness evidence specifically for this population subgroup.				

The prophylaxis strategy which is significantly more effective in reducing DVT or PE; or resulting in significantly less major bleeding is stated in bold.
Not sig - not statistically significant difference; NR – not reported; no events – nobody in the study had the outcome. MB = Major bleeding

13.7 Recommendations and link to evidence

Recommendation	**Consider offering combined VTE prophylaxis with mechanical and pharmacological methods to patients having orthopaedic surgery (other than hip fracture, hip replacement, knee replacement) based on an assessment of risks (see section 5.9) and after discussion with the patient.** • **Start mechanical VTE prophylaxis at admission. Choose any one of the following based on individual patient factors:** – **anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)** – **foot impulse devices** – **intermittent pneumatic compression devices (thigh or knee length).** **Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.** • **Start pharmacological VTE prophylaxis 6–12 hours after surgery. Choose one of:** – **LMWH** – **UFH (for patients with renal failure).** **Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility.**
Recommendation *(From section 5.9)*	**Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:** • **surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb** • **acute surgical admission with inflammatory or intra-abdominal condition** • **expected significant reduction in mobility** • **have one or more of the risk factors shown in Box 1.**
Box 1 – VTE risk factor box	• **Active cancer or cancer treatment** • **Age over 60 years** • **Critical care admission** • **Dehydration** • **Known thrombophilias** • **Obesity (BMI over 30 kg/m^2)** • **One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory**

	pathologies, acute infectious diseases or inflammatory conditions) • **Personal history or a first degree relative with a history of VTE** • **Use of hormone replacement therapy** • **Use of oestrogen-containing contraceptive therapy** • **Varicose veins with phlebitis.** **For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).**
Relative values of different outcomes	The main outcomes considered were venous thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).
Trade off between clinical benefit and harms	The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding.
Economic considerations	No cost-effectiveness analysis was conducted for this group of patients. This is a potentially large population, and recommending prophylaxis may have significant impact on NHS costs. Patients in this population are relatively young compared to other groups, and any fatal VTE or fatal bleeding events, or long term events due to thrombosis or bleeding could result in a higher loss of quality adjusted life years than the populations where cost-effectiveness analysis has been conducted. However, the risk of pulmonary embolism is probably quite low compared with other groups, especially for patients having surgery on the upper limbs. Therefore it is unlikely that prophylaxis will be cost-effective unless patients have additional risk factors.
Quality of evidence	All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++). The evidence for this population is weak, consisting of only 4 RCTs in knee arthroscopy patients. The incidence of DVT in the studies varied and the overall incidence of PE was very low, 0.3% in the trial comparing LMWH with GCS, and there was no evidence from this population that prophylaxis reduced the risk of these events.
Other considerations	Although the orthopaedic subgroup felt that many of the patients undergoing orthopaedic surgery in the upper limb, lower limb and arthroscopy other than elective hip replacement, elective knee

replacement and hip fracture surgery would not require prophylaxis, they did acknowledge that there may be a subgroup of these patients who were at increased risk of VTE and so should be offered the opportunity for prophylaxis. The factors that identify a patient at high risk are given in the recommendation for assessing VTE risk above. The orthopaedic subgroup felt that if any of these conditions were met then prophylaxis should be considered.

Although there is only evidence for prophylaxis with LMWH in knee arthroscopy patients, the orthopaedic subgroup felt that the evidence for fondaparinux from elective hip replacement, hip fracture and knee replacement surgery could be extrapolated for this population.

Similarly mechanical methods such as anti-embolism stockings or intermittent pneumatic compression devices can be used in conjunction or as an alternative to pharmacological prophylaxis.

13.7.1 Supporting recommendations based on Guideline Development Group consensus opinion

Recommendation	**Do not routinely offer VTE prophylaxis to patients undergoing upper limb surgery. If a patient is assessed to be at increased risk of VTE (section 5.9) refer to recommendation from other orthopaedic surgery (above in section 13.7).**
Trade off between clinical benefit and harms	The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding.
Economic considerations	No cost-effectiveness analysis was conducted for this group of patients. This is a potentially large population, and recommending prophylaxis may have significant impact on NHS costs. Patients in this population are relatively young compared to other groups, and any fatal VTE or fatal bleeding events, or long term events due to thrombosis or bleeding could result in a higher loss of quality adjusted life years than the populations where cost-effectiveness analysis has been conducted. However, the risk of pulmonary embolism is probably very low especially for patients having surgery on the upper limbs compared with other groups. Therefore it is unlikely that prophylaxis will be cost-effective unless patients have additional risk factors.
Other considerations	The feedback from stakeholder consultation indicated that the initial draft of the guideline did not make it clear that many patients undergoing upper limb surgery would not need VTE prophylaxis. Stakeholders raised the issue that no studies of prophylaxis had been completed in upper limb surgery and that the studies of incidence of VTE after this type of surgery

indicated that the risk was very small.

In order to make the recommendations clearer, the orthopaedic subgroup agreed that a separate recommendation should be included to clarify this. The orthopaedic subgroup agreed that although most patients undergoing upper limb surgery would not need VTE prophylaxis all patients should still be risk assessed as recommended in section 5.9 and if there were patients who were at an increased risk VTE prophylaxis should still be considered.

13.7.2 Other recommendations of relevance

The specific recommendations for patients undergoing orthopaedic surgery in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)

13.8 Recommendations for research

Dabigatran and rivaroxaban are not licensed for this population but are oral anticoagulants that are licensed for hip and knee replacement patients. This might be an area for future research in this population, particularly where patients are identified to be at increased risk and have a lower limb plaster cast.

13.9 Summary of recommendations

- Consider offering combined VTE prophylaxis with mechanical and pharmacological methods to patients having orthopaedic surgery (other than hip fracture, hip replacement or knee replacement) based on an assessment of risks (see section 5.9) and after discussion with the patient.

    - Start mechanical VTE prophylaxis at admission. Choose any one of the following based on individual patient factors:

        - anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)
        - foot impulse devices
        - intermittent pneumatic compression devices (thigh or knee length)

        Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

    - Start pharmacological VTE prophylaxis 6–12 hours after surgery. Choose one of:

- LMWH
- UFH (for patients with renal failure).

Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:
  - surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
  - acute surgical admission with inflammatory or intra-abdominal condition
  - expected significant reduction in mobility
  - have one or more risk factors in **Box 1**.

Box 1. Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m^2)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).

- Do not routinely offer VTE prophylaxis to patients undergoing upper limb surgery. If a patient is assessed to be at increased risk of VTE (section 5.9) refer to section 13.7.

14 Cranial or Spinal Surgery (Neurological Surgery)

14.1 Introduction

This section covers inpatients undergoing cranial or spinal surgery (commonly combined and called neurosurgery). Although the discussion for cranial and spinal surgery have be separated within this chapter, the evidence has been reviewed together as many of the papers combine cranial and spinal surgery patients and do not present the results separately. Neuroendovascular interventions are also covered by this section because such patients are generally admitted to neurosurgery wards.

Evidence and recommendations specific to spinal injury (including those with spinal cord involvement) are considered within chapter 20.

14.1.1 Cranial surgery

Cranial surgery is usually completed by neurosurgeons and includes a range of operations including craniotomies for brain tumours, subarachnoid haemorrhages and aneurysms. The majority of these procedures would be less than 6 hours duration but there are some that would last longer.

14.1.2 Spinal surgery

Spinal surgery is a subspecialty of both orthopaedic surgery and neurosurgery. It includes acute spinal injury surgery and elective spinal injury. In spinal surgery the catastrophic long term neurological consequences of extradural bleeding needs to be balanced against the risk to life of VTE disease. The patient process should involve the active recording of the clinical decision rather than a passive default position of no treatment.

Baseline risk

We have estimated from the incidence of RCTs that the risk of developing DVT, and major bleeding in neurosurgery patients (cranial and spinal surgery patients combined) not receiving thromboprophylaxis is:

- DVT - 20% (95% confidence intervals: 17% to 24%)
- Major bleeding - 2% (95% confidence intervals: 0% to 5%). The major bleeding events was in one patient who had a postoperative haematoma.

Population specific factors that may increase VTE or bleeding risk

- Severe head injury or spinal injury is invariably associated with altered conscious level and/or limb paralysis. The risk of VTE is increased because early ambulation is not possible and a prolonged period of recumbency is inevitable. Usually, there is no particluar contrandication to the common methods of prophylaxis for these patients.

- An increased risk of VTE is associated with Brain (malignant or benign) tumours and cerebral haemorrhage.

- The risk of bleeding is a serious complication in patients requiring emergency neurosurgery. This is not confined to "major bleeding" which is often defined as a 2g drop in haemoglobin and/or clinically indicated transfusion. Very small volume bleeds within or compressing the brain or spinal cord can cause neurological injury which may be irreversible.

- The timing of when pharmacological prophylaxis is started is particularly important in patients with ruptured or unprotected vascular malformations or acute traumatic or untraumatic haemorrhage (because of an increased risk of bleeding).

- Many neurosurgical patients are on high doses of glucocorticoids which may alter the coagulation status of the patient.

- Some patients undergoing prolonged cranial surgery e.g meningiomas are at risk of developing disseminated intravascular coagulation.

14.2 Evidence of methods of prophylaxis

14.2.1 Summary of comparisons identified for any outcome

Sixteen randomised controlled trials which reported at least one of the three main outcomes were identified[11,90,101,164,225,415,441,495,559,607,646,647,649,680,683,701]. Some of these investigated more than two methods of prophylaxis. Of the available literature, seven studies include only cranial surgery patients [90,101,164,225,415,680,683] and two investigated spinal surgery patients only [559,701]. Three studies included mixed cranial and spinal surgery populations but did not report results separately [11,495,607], three others contained mixed populations neurological and neurosurgical patients[646,647,649] and one did not clarify the type of neurosurgery patients underwent[441]. Some of the RCTs had their data extracted from systematic reviews. Where applicable the study is cited in the evidence table for that review. Three systematic reviews included RCTs covering patients having neurosurgery[15,304,557].

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++). The evidence tables for the included studies are in Appendix D presented by order of comparison.

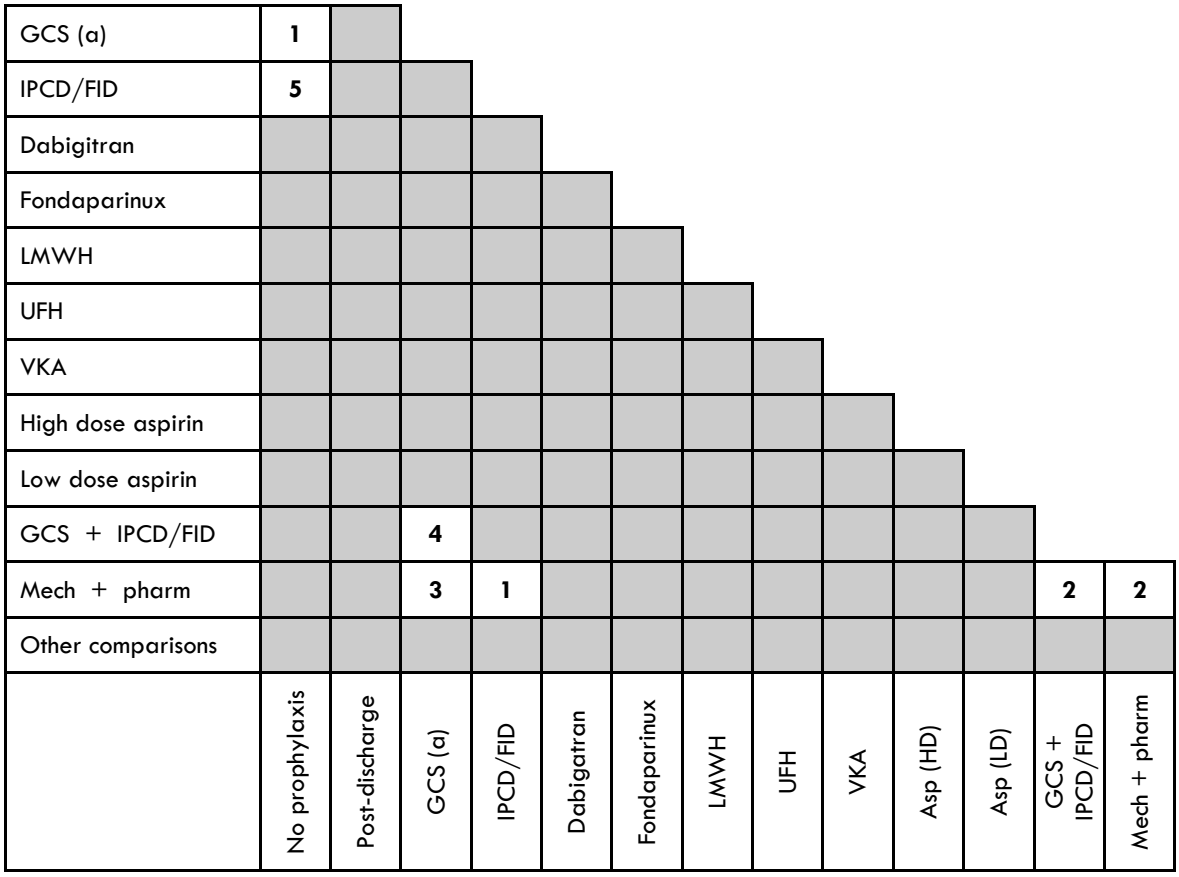


Figure 14-38: Number of studies which compared various types of prophylaxis methods.

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicates areas where no studies were identified.

GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) - low dose aspirin (≤ 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis

14.2.2 Results from pairwise comparisons

Table 14-89: DVT – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
GCS vs nil[649]	1	7/80	16/81	0.44 (0.19, 1.02)	-0.11 (-0.22, 0.00)	ET: 23 FP: 1
IPCD/FID vs nil[90,607,646,647,683]	5	13/251	52/247	0.30 (0.17, 0.53)	-0.16 (-0.22, -0.10)	ET: 24 FP: 4
LMWH vs nil[441]	1	10/64	14/58	0.65 (0.31, 1.34)	-0.09 (-0.23, 0.06)	ET: 26 FP: 13
UFH vs nil[101]	1	3/50	17/50	0.18 (0.06, 0.56)	-0.28 (-0.43, -0.13)	ET: 27 FP: 17
Double proph vs single						
IPCD + GCS vs GCS[559,649,680]	3	7/129	9/127	0.36 (0.02, 5.16) (a)	-0.02 (-0.11, 0.07)	ET: 39 FP: 117
LMWH + GCS vs GCS[11,495]	2	53/296	90/309	0.61 (0.45, 0.85)	-0.11 (-0.20, -0.03)	ET: 26 FP: 134

VKA + GCS vs GCS[559]	1	0/35	0/42	not estimable	0.00 (-0.05, 0.05)	ET: 41 FP: 155
Double proph vs double						
IPCD + GCS vs LMWH + GCS[164]	1	3/22	1/21	2.86 (0.32, 25.40)	0.09 (-0.08, 0.26)	ET: 49 FP: 202
LMWH + IPCD vs UFH + IPCD[415]	1	2/51	0/49	4.81 (0.24, 97.68)	0.04 (-0.03, 0.10)	ET: 45 FP: 177
Other strategies						
IPCD + GCS + LMWH vs GCS + LMWH[164]	1	4/23	1/21	3.65 (0.44, 30.12)	0.13 (-0.05, 0.31)	ET: 39 FP: 123
LMWH + IPCD + GCS vs IPCD + GCS [164]	1	4/23	3/22	1.28 (0.32, 5.06)	0.04 (-0.17, 0.25)	ET: 26 FP: 138
LMWH + IPCD + GCS vs UFH + IPCD + GCS[225]	1	9/75	5/75	1.80 (0.63, 5.12)	0.05 (-0.04, 0.15)	ET: 45 FP: 181

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis
(a) There was significant heterogeneity within the results (chi squared on 2 df =3.23, p=0.07, I^2 =69.1%) which appears to be atributable to one study with few patients[680].

Table 14-90: Pulmonary embolism – summary of results from RCTs

Comparison	No. of studies	Interven -tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
GCS vs nil[649]	1	0/80	0/81	not estimable	0.00 (-0.02, 0.02)	ET: 23 FP: 2
IPCD/FID vs nil[607]	1	0/47	0/48	not estimable	0.00 (-0.04, 0.04)	ET: 24 FP: 5
Double proph vs single						
IPCD + GCS vs GCS[680]	1	0/18	0/5	not estimable	0.00 (-0.23, 0.23)	ET: 39 FP: 118
LMWH + GCS vs GCS[11,495]	2	1/371	3/374	0.44 (0.06, 2.96)	-0.01 (-0.02, 0.01)	ET: 26 FP: 135
Double proph vs double						
IPCD + GCS vs LMWH + GCS[164]	1	0/22	0/21	not estimable	0.00 (-0.09, 0.09)	ET: 49 FP: 203
LMWH + IPCD vs UFH + IPCD[415]	1	0/51	0/49	not estimable	0.00 (-0.04, 0.04)	ET: 45 FP: 182
Other strategies						
IPCD + GCS + LMWH vs GCS + LMWH[164]	1	0/23	0/21	not estimable	0.00 (-0.08, 0.08)	ET: 39 FP: 124
LMWH + IPCD + GCS vs IPCD + GCS [164]	1	0/23	0/22	not estimable	0.00 (-0.08, 0.08)	ET: 26 FP: 182

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

Table 14-91: Major bleeding – summary of results from RCTs

Comparison	No. of studies	Interven -tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
LMWH vs nil[441]	1	0/67	0/63	not estimable	0.00 (-0.03, 0.03)	ET: 26 FP: 15
UFH vs nil[101]	1	2/50	1/50	2.00 (0.19, 21.36)	0.02 (-0.05, 0.09)	ET: 27 FP: 19
Double proph vs single						
LMWH + GCS vs GCS[11,495]	2	10/394	6/398	1.62 (0.55, 4.74)	0.01 (-0.01, 0.03)	ET: 26 FP: 136

VKA + GCS vs GCS[559]	1	2/35	0/42	5.97 (0.30, 120.42)	0.06 (-0.03, 0.15)	ET: 41 FP: 156
Double proph vs double						
IPCD + GCS vs LMWH + GCS[164]	1	0/22	2/21	0.19 (0.01, 3.76)	-0.10 (-0.24, 0.05)	ET: 49 FP: 204
LMWH + IPCD vs UFH + IPCD[415]	1	2/51	1/49	1.92 (0.18, 20.52)	0.02 (-0.05, 0.09)	ET: 45 FP: 179
Other strategies						
IPCD + GCS + LMWH vs GCS + LMWH[164]	1	3/23	2/21	1.37 (0.25, 7.41)	0.04 (-0.15, 0.22)	ET: 39 FP: 125
LMWH + IPCD + GCS vs IPCD + GCS [164]	1	3/23	0/22	6.71 (0.37, 122.83)	0.13 (-0.02, 0.28)	ET: 26 FP: 140
LMWH + IPCD + GCS vs UFH + IPCD + GCS[225]	1	2/75	1/75	2.00 (0.19, 21.59)	0.01 (-0.03, 0.06)	ET: 45 FP: 182

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

14.2.3 Additional information

14.2.3.1 All cause mortality

Table 14-92: Mortality – summary of results from RCTs

Comparison	No. of studies	Interven -tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
GCS vs nil[649]	1	17/80	10/81	1.72 (0.84, 3.53)	0.09 (-0.03, 0.20)	ET: 23 FP: 3
IPCD/FID vs nil[607,647]	2	9/129	8/127	1.12 (0.45, 2.75)	-0.01 (-0.06, 0.04)	ET: 24 FP: 6
LMWH vs nil[441]	1	0/67	0/63	not estimable	0.00 (-0.03, 0.03)	ET: 26 FP: 16
UFH vs nil[101]	1	0/50	0/50	not estimable	0.00 (-0.04, 0.04)	ET: 27 FP: 20
Double proph vs single						
IPCD + GCS vs GCS[649]	1	10/78	17/80	0.60 (0.29, 1.23)	-0.08 (-0.20, 0.03)	ET: 39 FP: 119
LMWH + GCS vs GCS[11,495]	2	27/394	16/398	1.53 (0.60, 3.88)	0.02 (-0.04, 0.08)	ET: 26 FP: 137
Double proph vs double						
IPCD + GCS vs LMWH + GCS[164]	1	1/22	0/21	2.87 (0.12, 66.75)	0.05 (-0.07, 0.16)	ET: 49 FP: 205
LMWH + IPCD vs UFH + IPCD[415]	1	0/51	1/49	0.31 (0.01, 7.68)	-0.02 (-0.07, 0.03)	ET: 45 FP: 180
Other strategies						
IPCD + GCS + LMWH vs GCS + LMWH[164]	1	1/23	0/21	2.75 (0.12, 64.04)	0.04 (-0.07, 0.16)	ET: 39 FP: 126
LMWH + IPCD + GCS vs IPCD + GCS [164]	1	1/23	1/22	0.96 (0.06, 14.37)	0.00 (-0.12, 0.12)	ET: 26 FP: 141
LMWH + IPCD + GCS vs UFH + IPCD + GCS[225]	1	0/75	0/75	not estimable	0.00 (-0.03, 0.03)	ET: 45 FP: 183

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

Most the studies had few deaths and a small overall sample size and showed no difference in mortality. However, two comparisons suggest prophylaxis may increase mortality.

Two studies reporting mortality compared LMWH plus GCS with GCS alone[11,495]. Overall, there is no significant difference in mortality (RR = 1.53 (0.60, 3.88) but there is a suggestion of heterogeneity (I squared =48.5%). One of the studies shows significantly more patients using LMWH plus GCS died compared to patients using GCS alone[495]. LMWH was started 18 to 24 hours postoperatively. There is no significant difference for major bleeding but, if minor bleeding is included too, the LMWH group had significantly more bleeding events overall (p=0.047). The study concludes that the deaths are not related to haemorrhage. No other reasons for the cause of mortality are explored in this study. None of the other heparin studies reported a similar mortality rate.

One study comparing GCS with no prophylaxis suggested an increase in mortality with GCS[649]. At 3 months, 17 out of 80 patients who wore GCS had died compared to 10 out of 81 of the patients not receiving prophylaxis. In a third arm 10 out of 81using IPCD plus GCS also died.

14.2.3.2 Other outcomes

No studies reported chronic thromboembolic pulmonary hypertension, post thrombotic syndrome or heparin induced thrombocytopenia in the systematic reviews.

14.2.3.3 Additional studies

One study not included in the above analysis compared IPCD plus stockings with foot pumps plus stockings[701]. This comparison was addressed in the first version of the guideline[473]. For economic model in this version of the guideline the effectiveness of IPCD devices and foot pumps were considered together. There was only one event DVT and one pulmonary embolism in the study, both occurring in the foot pumps arm. (Evidence table 30, Appendix D)

14.3 Network meta-analysis results

Network meta-analysis was not **conducted** for this population.

14.4 Cost-effectiveness evidence

No cost effectiveness analysis was completed for this population.

14.5 Patient views

No patient views papers were found specific to this population.

For patient views about specific prophylaxis agents, see section 6.6.

14.6 Summary of evidence

Intervention(s)	*Comparison(s)*	*Intervention favoured*		
		DVT	**PE**	**MB**
Prophylaxis vs no prophylaxis				
GCS	no prophylaxis	not sig	no events	-
IPCD/FID	no prophylaxis	**IPCD/FID**	no events	-
LMWH	no prophylaxis	not sig	-	no events
UFH	no prophylaxis	**UFH**	-	not sig
Single prophylaxis vs single		-	-	-
Double prophylaxis vs single				
IPCD + GCS	GCS	not sig	no events	-
LMWH + GCS	GCS	**LMWH + GCS**	not sig	not sig
VKA + GCS	GCS	no events	-	not sig
Double prophylaxis vs double				
IPCD + GCS	LMWH + GCS	not sig	no events	not sig
LMWH + GCS	UFH + GCS	not sig	no events	not sig
Other strategies				
IPCD + LMWH + GCS	LMWH + GCS	not sig	no events	not sig
LMWH + IPCD + GCS	IPCD + GCS	not sig	no events	not sig
LMWH + IPCD + GCS	UFH + IPCD + GCS	not sig	-	not sig
Cost Effectiveness				
No cost effectiveness model was completed for this population				

The prophylaxis strategy which is significantly more effective in reducing DVT or PE; or resulting in significantly less major bleeding is stated in bold.
Not sig - not statistically significant difference; '-'= not reported; no events – nobody in the study had the outcome MB = Major bleeding

Overall, there is little evidence covering prophylaxis in patients undergoing cranial surgery. Most the data available were in small studies. Giving prophylaxis does appear to reduce DVT but there are not enough data to show the level of reduction in pulmonary embolism and increase in major bleeding events (where applicable). There are no RCTs comparing single prophylaxis agents. LMWH plus GCS is better than GCS alone. There is less evidence covering prophylaxis in patients undergoing spinal surgery. Only two of the studies investigated prophylaxis in spinal surgery patients alone, neither of these compared prophylaxis to no prophylaxis.

14.7 Recommendations and link to evidence

Recommendation	**Offer VTE prophylaxis to patients undergoing cranial or spinal surgery who are assessed to be at increased risk of VTE (see section 5.9).** • **Start mechanical VTE prophylaxis from admission. Choose any one of:** – **anti-embolism stockings (thigh or knee length)** – **foot impulse devices** – **intermittent pneumatic compression devices (thigh or knee length).** **Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.** • **Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:** – **LMWH** – **UFH (for patients with renal failure)** **Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).**
Recommendation - from section 5.9	**Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:** • **surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb** • **acute surgical admission with inflammatory or intra-abdominal condition** • **expected significant reduction in mobility** • **have one or more of the risk factors shown in Box 1.**
Box 1 – VTE Risk factor box	• **Active cancer or cancer treatment** • **Age over 60 years** • **Critical care admission** • **Dehydration** • **Known thrombophilias** • **Obesity (BMI over 30 kg/m^2)** • **One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory**

	pathologies, acute infectious diseases or inflammatory conditions) • **Personal history or a first degree relative with a history of VTE** • **Use of hormone replacement therapy** • **Use of oestrogen-containing contraceptive therapy** • **Varicose veins with phlebitis.** **For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).**
Relative values of different outcomes	The outcomes considered were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome
Trade off between clinical benefit and harms	The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding. The timing of when pharmacological prophylaxis is started is particularly important in patients who have suffered a spontaneous or traumatic haemorrhage. The risk of bleeding is a serious complication in patients requiring emergency cranial or spinal surgery. In spinal surgery the catastrophic long term neurological consequences of extradural bleeding need to be balanced against the risk to life of VTE disease.
Economic considerations	No economic model was run specifically for cranial or spinal surgery patients. The economic model for general surgical patients indicated that a combination of pharmacological and mechanical prophylaxis was cost effective for this broader population as long as the risk of major bleeding is less than 1%. Given the high risk of VTE in neurosurgery patients, it is quite likely that prophylaxis is cost-effective. However, given that these patients seem to have a very high baseline risk of major bleeding and the consequences of surgical site bleeding are likely to be very serious for this group, drug prophylaxis is likely only to be cost-effective if the risk of intracranial bleeding or bleeding into the spinal column is minimised.
Quality of evidence	All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++). Seven studies investigated prophylaxis in patients undergoing cranial surgery, with an additional 7 providing information from mixed populations of cranial and spinal surgery, or other

neurological patients.

There were only 2 studies that investigated spinal surgery patients alone, a further 7 studies combined spinal surgery patients with patients undergoing cranial surgery and/or other neurology patients

Where available, most the evidence was in small studies.

Other considerations

Severe head injury and spinal injury are associated with altered conscious level and/or limb paralysis. The risk of VTE is increased because early ambulation is not possible and a prolonged period of recumbency is inevitable. There is, however, no particular contraindication to any of the methods of prophylaxis for these patients.

An increased risk of VTE is associated with Brain (malignant or benign) tumours and cerebral haemorrhage.

Many neurosurgical patients are on high doses of glucocorticoids which may alter the coagulation status of the patient.

Some patients undergoing prolonged cranial surgery e.g Meningiomas are at risk of developing disseminated intravascular coagulation.

The average duration of VTE prophylaxis for 'general surgery' patients in the trials was 7 days. This concurs with the licensing conditions for pharmacological agents for surgical patients within the BNF where the recommended duration is 5-10 days, depending on the agent used. It is known in many cases surgical patients are discharged within 5 days of their operation. The guideline development group felt that the risk of VTE may still persist beyond this time period and prophylaxis may be effective after discharge. No economic analysis was conducted for patients who were discharged before the full course of VTE prophylaxis had been given.

There are other considerations for each agent when choosing pharmacological prophylaxis. UFH is not as widely used nowadays and is mainly used for patients with renal impairment. There are also practical considerations in that it requires 3 injections per day as oppose to one injection per day for LMWH.

14.7.1 Supporting recommendations based on Guideline Development Group consensus opinion

Recommendation	**Do not offer pharmacological VTE prophylaxis to patients with ruptured cranial or spinal vascular malformations (for example, brain aneurysms) or acute traumatic or non-traumatic haemorrhage until until the lesion has been secured or the condition is stable.**
Trade off between clinical benefit and harms	The timing of when pharmacological prophylaxis is started is particularly important in patients who have suffered a spontaneous or traumatic haemorrhage. The risk of bleeding is a serious complication in patients requiring emergency cranial or spinal surgery.
Economic considerations	None
Other considerations	None

14.7.2 Other recommendations of relevance

The specific recommendations for neurosurgery patients in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)
- recommendations about patients with spinal injury (Section 20.7)
- recommendations about metastatic spinal injury from the NICE guidelines[471]

14.8 Summary of recommendations

- Offer VTE prophylaxis to patients undergoing cranial or spinal surgery who are assessed to be at increased risk of VTE (see section 5.9).
    - Start mechanical VTE prophylaxis from admission. Choose any one of:
        - anti-embolism stockings (thigh or knee length)
        - foot impulse devices
        - intermittent pneumatic compression devices (thigh or knee length)

      Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility

- Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:

  - LMWH

  - UFH (for patients with renal failure).

  Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

➢ Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:

- surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
- acute surgical admission with inflammatory or intra-abdominal condition
- expected significant reduction in mobility
- have one or more risk factors shown in **Box 1**.

Box 1. Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m^2)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).

➢ Do not offer pharmacological VTE prophylaxis to patients with ruptured cranial or spinal vascular malformations (for example, brain aneurysms) or acute traumatic or non-traumatic haemorrhage until until the lesion has been secured or the condition is stable.

15 Cardiac surgery

15.1 Introduction

This section covers patients undergoing cardiac surgery.

We have estimated, from the incidence in the RCTs (chapter 5), that the risk of developing DVT in cardiac surgery patients not receiving thromboprophylaxis:

- 14% (95% confidence intervals: 7% to 24%), although its ranking in among amongst other surgeries in our HES data would suggest that the risk could be higher.

- we do not have data from the RCTs to estimate the risk of pulmonary embolism or bleeding

Factors that may alter the risk of VTE.

- Pacing wires and implantable cardioverter-defibrillator devices may lead to an increase in upper limb deep vein thrombosis

Factors that increase the risk of bleeding or hazard associated with it

- Many patients will be receiving antiplatelet medication, heparin or warfarin and will therefore have an increased risk of bleeding.

Other special factors that would affect the choice of, and use of, specific methods of prophylaxis

- Several procedures in cardiac surgery involve the use of anticoagulation or antiplatelet therapy:

    - Full heparin anticoagulation is used during cardiopulmonary bypass which is typically one to two hours of a two to five hour surgery.

    - Surgeries performed "off pump" (surgeries performed without the use of heart lung machines) are also covered by heparin anticoagulation.

    - Most patients with coronary artery disease are given antiplatelet therapy up to shortly prior to surgery and it is recommenced soon after.

    - Many patients with valve disease have warfarin anticoagulation.

- Patients in atrial fibrillation will generally have warfarin anticoagulation.

- Many cardiac surgery patients have leg veins removed for use as grafts. This would preclude the use of both GCS and IPCD during the surgery but they could be used afterwards.

15.2 Evidence of methods of prophylaxis

15.2.1 Summary of comparisons identified for any outcome

Five randomised controlled trials which reported at least one of the three main outcomes were identified[38,41,226,345,544]. One of the RCTs[41] data were extracted from a systematic review[125].

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

	No prophylaxis	Post-discharge	GCS	IPCD/FID	Dabigatran	Fondaparinux	LMWH	UFH	VKA	Asp (HD)	Asp (LD)	GCS + IPCD/FID	Mech + pharm
GCS													
IPCD/FID													
Dabigitran													
Fondaparinux													
LMWH													
UFH	**1**						**1**						
VKA													
High dose aspirin													
Low dose aspirin													
GCS + IPCD/FID													
Mech + pharm	**1**							**1**					
Other comparisons													**1**

Figure 15-39: Number of studies which compared various types of prophylaxis methods.

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicates areas where no studies were identified.

GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) - low dose aspirin (≤ 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis

15.2.2 Results from pairwise comparisons

Table 15-93: DVT – summary of results from RCTs

Comparison	No. of studies	Interven -tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
UFH vs no prophylaxis[41]	1	3/24	8/25	0.39 (0.12, 1.30)	-0.20 (-0.42, 0.03)	ET: 27 FP: 17
UFH + IPCD vs no prophylaxis[345]	1	1/50	2/40	0.40 (0.04, 4.25)	-0.03 (-0.11, 0.05)	ET: 27 FP: 34
Single proph vs single						
LMWH vs UFH[38]	1	0/20	0/19	not estimable	0.00 (-0.09, 0.09)	ET: 32 FP: 48
Other prophylaxis strategies						
IPCD + GCS + asp vs GCS + asp[226]	1	31/164	36/166	0.87 (0.57, 1.34)	-0.03 (-0.11, 0.06)	ET: 39 FP: 127

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

Table 15-94: Pulmonary embolism – summary of results from RCTs

Comparison	No. of studies	Interven -tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Double proph vs single						-
IPCD + UFH vs UFH[544]	1	21/1355	48/1196	0.39 (0.23, 0.64)	-0.02 (-0.04, -0.01)	ET: 39 FP: 121
Other prophylaxis strategies						
IPCD + GCS + asp vs GCS + asp[226]	1	1/164	1/166	1.01 (0.06, 16.05)	0.00 (-0.02, 0.02)	ET: 39 FP: 128

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

Table 15-95: Major bleeding – summary of results from RCTs

Comparison	No. of studies	Interven -tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
UFH vs no prophylaxis[41]	1	8/24	1/25	8.33 (1.13, 61.70)	0.29 (0.09, 0.50)	ET: 27 FP: 19

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

15.2.3 Additional information

There is no additional information to add for this population.

15.3 Network meta-analysis results

Network meta-analysis was not completed for this population

15.4 Cost-effectiveness evidence

No cost effectiveness analysis was completed for this population.

15.5 Patient views

No patient views papers were found specific to this population.

For patient views about specific prophylaxis agents, see section 6.6.

15.6 Summary of evidence

Intervention(s)	*Comparison(s)*	*Intervention favoured*		
		DVT	**PE**	**MB**
Prophylaxis vs no prophylaxis				
UFH	no prophylaxis	not sig	-	not sig
UFH + IPCD	no prophylaxis	not sig	-	-
Single prophylaxis vs single				
LMWH	UFH	no events	-	-
Double prophylaxis vs single				
IPCD + UFH	UFH	-	**IPCD + UFH**	-
Other strategies				
IPCD + GCS + asp	GCS + asp	not sig	not sig	-
Cost Effectiveness				
There is no relevant cost-effectiveness evidence specifically for this population subgroup.				

The prophylaxis strategy which is significantly more effective in reducing DVT or PE; or resulting in significantly less major bleeding is stated in bold.
Not sig - not statistically significant difference; '-'= not reported; no events – nobody in the study had the outcome. MB = Major bleeding

Overall, there is little RCT evidence covering prophylaxis in patients undergoing cardiac surgery.

15.7 Recommendations and link to evidence

Recommendation	**Offer VTE prophylaxis to patients undergoing cardiac surgery who are not having other anticoagulation therapy and are assessed to be at increased risk of VTE (see section 5.9)** • **Start mechanical VTE prophylaxis at admission. Choose any one of:** – **anti-embolism stockings (thigh or knee length)** – **foot impulse devices** – **intermittent pneumatic compression devices (thigh or knee length).** **Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.** • **Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:** – **LMWH** – **UFH (for patients with renal failure).** **Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).**
Recommendation from section 5.9	**Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:** • **surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb** • **acute surgical admission with inflammatory or intra-abdominal condition** • **expected significant reduction in mobility** • **have one or more of the risk factors shown in Box 1.**
Box 1 – VTE Risk factor box	• **Active cancer or cancer treatment** • **Age over 60 years** • **Critical care admission** • **Dehydration** • **Known thrombophilias** • **Obesity (BMI over 30 kg/m^2)** • **One or more significant medical comorbidities (such**

	as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions) • **Personal history or a first degree relative with a history of VTE** • **Use of hormone replacement therapy** • **Use of oestrogen-containing contraceptive therapy** • **Varicose veins with phlebitis.** **For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).**
Relative values of different outcomes	The outcomes considered were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome
Trade off between clinical benefit and harms	The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding. Patients already receiving antiplatelet medication will have an increased risk of bleeding.
Economic considerations	There is no relevant cost-effectiveness evidence specifically for this population subgroup. However, a combination of drug and mechanical prophylaxis was found to be cost-effective for general surgery patients where the risk of major bleeding is less than 1% (Chapter 9). It seems likely that combination prophylaxis will also be cost-effective for cardiac surgery patients who are at elevated risk of VTE.
Quality of evidence	All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++). There is little RCT evidence covering cardiac surgery. Evidence was extrapolated from general surgery patients.
Other considerations	Several procedures in cardiac surgery involve the use of anticoagulation or antiplatelet therapy: Many cardiac surgery patients have leg veins removed for use as grafts. This would preclude the use of both GCS and IPCD during the surgery but they could be used after. The average duration of VTE prophylaxis for 'general surgery' patients in the trials was 7 days. This concurs with the licensing

conditions for pharmacological agents for surgical patients within the BNF where the recommended duration is 5-10 days, depending on the agent used. It is known in many cases surgical patients are discharged within 5 days of their operation. The guideline development group felt that the risk of VTE may still persist beyond this time period and prophylaxis may be effective after discharge. No economic analysis was conducted for patients who were discharged before the full course of VTE prophylaxis had been given.

There are other considerations for each agent when choosing pharmacological prophylaxis. UFH is not as widely used nowadays and is mainly used for patients with renal impairment. There are also practical considerations in that it requires 3 injections per day as oppose to one injection per day for LMWH.

15.7.1 Other recommendations of relevance

The specific recommendations for patients undergoing cardiac surgery in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)
- patients using anticoagulants or antiplatelets for reasons other than VTE prophylaxis (Chapter 1)

15.8 Summary of recommendations

- Offer VTE prophylaxis to patients undergoing cardiac surgery who are not having other anticoagulation therapy and are assessed to be at increased risk of VTE (see section 5.9)
    - Start mechanical VTE prophylaxis at admission. Choose any one of:
        - anti-embolism stockings (thigh or knee length)
        - foot impulse devices
        - intermittent pneumatic compression devices (thigh or knee length)

      Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:

  - LMWH

  - UFH (for patients with renal failure).

  Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

➢ Regard **surgical patients and patients with trauma** as being at increased risk of VTE if they meet one of the following criteria:

- surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
- acute surgical admission with inflammatory or intra-abdominal condition
- expected significant reduction in mobility
- have one or more risk factors shown in **Box 1**.

Box 1. Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m^2)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).

16 Vascular surgery

16.1 Introduction

This section covers inpatients undergoing vascular surgery. Vascular surgery encompasses two distinct patient populations: surgery for peripheral arterial disease (PAD) including carotid, aorto-iliac and limb arterial surgery; and patients with venous disease (superficial or deep venous reflux and varicose veins). A significant proportion of surgery for uncomplicated primary varicose veins is undertaken as day-case procedures.

We did not have enough data, from the incidence in the RCTs (chapter 5), to enable us to estimate the risk of developing deep vein thrombosis in vascular surgery patients not receiving thromboprophylaxis, according to our HES data, its ranking in among amongst other surgery would suggest that the risk is relatively high.

Factors that may alter the risk of VTE

- Arterial surgery patients are often elderly and immobile.
- Many arterial surgery patients will already be receiving antiplatelet therapy and some will be on warfarin.
- Systemic heparin is frequently administered during surgery for arterial disease.
- Surgery for varicose veins is mostly in women, oral contraceptive use and hormone replacement therapy are therefore more commonly associated with varicose veins surgery.

Factors that increase the risk of bleeding or hazard associated with it

- Patients using anticoagulation or antiplatelet therapy not related to surgery will have an increased risk of bleeding.

Other factors that may alter the choice of prophylaxis

- The use of intermittent compression devices is contraindicated in patients with peripheral arterial disease.
- The use of intermittent compression devices and anti-embolism / graduated compression stockings will usually be inappropriate on the operated leg for a patient undergoing lower limb arterial surgery.

- Anti-embolism / graduated compression stockings will be contraindicated for patients with lower limb arterial disease.

16.2 Evidence of methods of prophylaxis

16.2.1 Summary of comparisons identified for any outcome

Three randomised controlled trials which reported at least one of the three main outcomes were identified[181,383,615]. One of the RCTs[615] data were extracted from a systematic review[125].

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

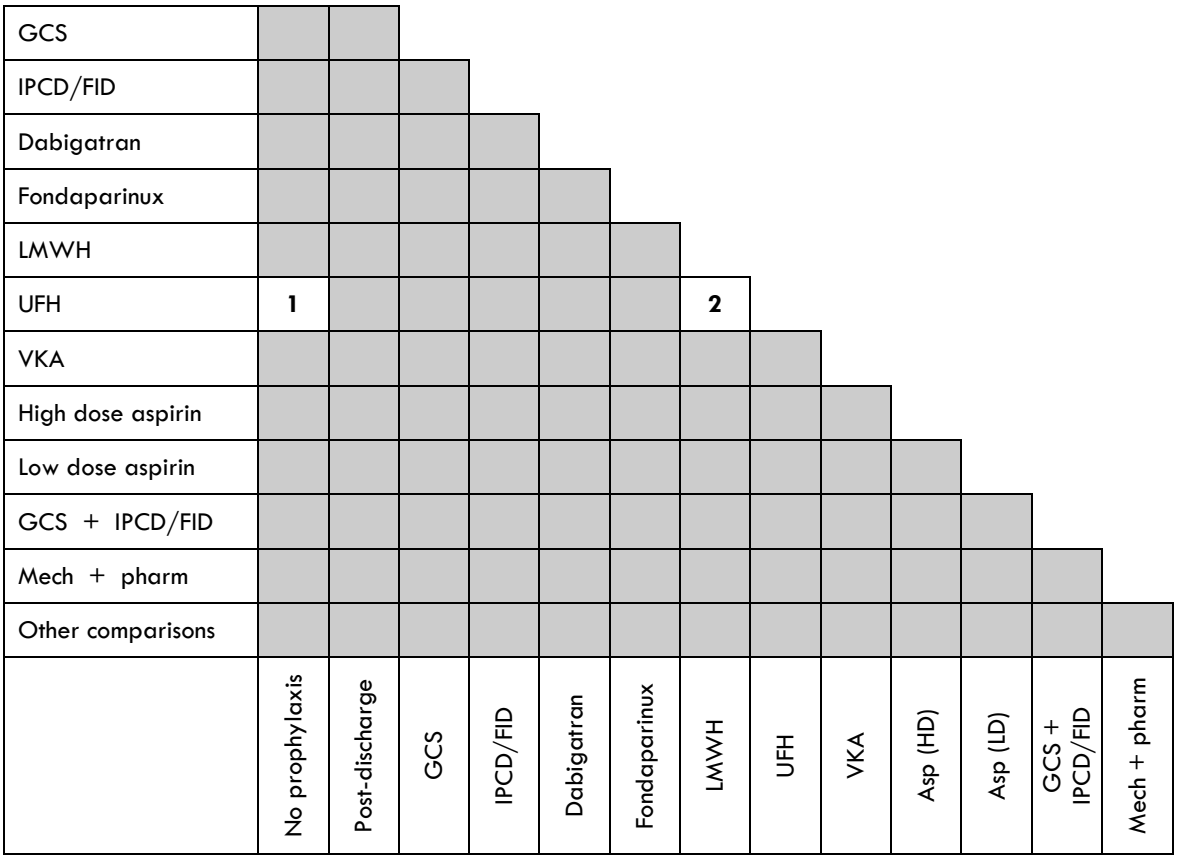


Figure 16-40: Number of studies which compared various types of prophylaxis methods.

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicates areas where no studies were identified.

GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) - low dose aspirin (≤ 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis

16.2.2 Results from pairwise comparisons

Table 16-96: DVT – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
UFH vs nil[615]	1	3/24	2/19	1.19 (0.22, 6.40)	0.02 (-0.17, 0.21)	ET: 27 FP: 17
Single proph vs single						
LMWH vs UFH[383]	1	4/41	4/34	0.83 (0.22, 3.07)	-0.02 (-0.16, 0.12)	ET: 32 FP: 48
Double proph vs double						
LMWH + introperative UFH vs UFH + introperative UFH[181]	1	10/122	4/111	2.27 (0.73, 7.05)	0.05 (-0.01, 0.11)	ET: 45 FP: 188

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

Table 16-97: Pulmonary embolism – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
UFH vs nil[615]	1	1/24	0/19	1.19 (0.22, 6.40)	0.02 (-0.17, 0.21)	ET: 27 FP: 18
Double proph vs double						
LMWH + introperative UFH vs UFH + introperative UFH[181]	1	0/122	0/111	not estimable	0.00 (0.02, 0.02)	ET: 45 FP: 189

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

Table 16-98: Major bleeding – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
UFH vs nil[615]	1	0/24	0/19	not estimable	0.00 (-0.05, 0.05)	ET: 27 FP: 19
Single proph vs single						
LMWH vs UFH[383]	1	0/41	0/34	not estimable	0.00 (-0.09, 0.09)	ET: 32 FP: 50

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

16.2.3 Additional information

There is no additional information for this population.

16.3 Network meta-analysis results

Network meta-analysis was not completed for this population

16.4 Cost-effectiveness evidence

No cost-effectiveness evidence was identified and no model produced for this population.

16.5 Patient views

No patient views papers were found specific to this population.

For patient views about specific prophylaxis agents, see section 6.6.

16.6 Summary of evidence

Intervention(s)	*Comparison(s)*	*Intervention favoured*		
		DVT	**PE**	**MB**
Prophylaxis vs no prophylaxis				
UFH	no prophylaxis	not sig	not sig	no events
Single prophylaxis vs single				
LMWH	UFH	not sig	-	no events
Double prophylaxis vs double				
LMWH + intraoperative UFH	UFH + intraoperative UFH	not sig	no events	-
Cost Effectiveness				
No cost effectiveness model was completed for this population				

The prophylaxis strategy which is significantly more effective in reducing DVT or PE; or resulting in significantly less major bleeding is stated in bold.
Not sig - not statistically significant difference; '-'= not reported; no events – nobody in the study had the outcome. MB = Major bleeding

Overall, there is little RCT evidence covering prophylaxis in patients undergoing vascular surgery.

16.7 Recommendations and link to evidence

Recommendation	**Offer VTE prophylaxis to patients undergoing vascular surgery who are not having other anticoagulant therapy and are assessed to be at increased risk of VTE (see section 2.2.1). If peripheral arterial disease is present, seek expert opinion before fitting anti-embolism stockings** • **Start mechanical VTE prophylaxis at admission. Choose any one of:** – **anti-embolism stockings (thigh or knee length)** – **foot impulse devices** – **intermittent pneumatic compression devices (thigh or knee length)** **Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.** • **Add pharmacological VTE prophylaxis for patients who have a low risk of bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:** - **LMWH** - **UFH for patients with renal failure** **Continue pharmacological VTE prophylaxis until the patients no longer has significantly reduced mobility (generally 5-7 days).**
Recommendation from section 5.9	**Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:** • **surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb** • **acute surgical admission with inflammatory or intra-abdominal condition** • **expected significant reduction in mobility** • **have one or more of the risk factors shown in Box 1.**
Box 1 – VTE Risk factor box	• **Active cancer or cancer treatment** • **Age over 60 years** • **Critical care admission**

	• **Dehydration** • **Known thrombophilias** • **Obesity (BMI over 30 kg/m²)** • **One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)** • **Personal history or a first degree relative with a history of VTE** • **Use of hormone replacement therapy** • **Use of oestrogen-containing contraceptive therapy** • **Varicose veins with phlebitis.** **For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).**
Relative values of different outcomes	The outcomes considered were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome
Trade off between clinical benefit and harms	The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding.
Economic considerations	There is no cost-effectiveness evidence for vascular surgery patients. An economic model was developed for general surgical patients. The model concluded that a combination of drug and mechanical prophylaxis was cost effective for general surgery patients where the risk of major bleeding is less than 1%. There is little trial evidence for vascular surgery patients but we believe the relative effects of prophylaxis will be similar. We consider it likely that combination prophylaxis is cost-effective for vascular patients with moderate risk of major bleeding, given their high baseline risk of VTE.
Quality of evidence	All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++). There is little RCT evidence covering vascular surgery. Evidence was extrapolated from general surgery patients.

Other considerations

Arterial surgery patients are often elderly and immobile.

Many arterial surgery patients will already be receiving antiplatelet therapy and some will be on warfarin. In addition, systemic heparin is frequently administered during surgery for arterial disease.

Surgery for varicose veins is mostly in women, oral contraceptive use and hormone replacement therapy are therefore more commonly associated with varicose veins surgery.

Patients using anticoagulation or antiplatelet therapy not related to surgery will have an increased risk of bleeding.

The use of intermittent compression devices and anti-embolism / graduated compression stockings will usually be inappropriate on the operated leg for a patient undergoing lower limb arterial surgery.

Anti-embolism / graduated compression stockings and intermittent pneumatic compression devices will be contraindicated for patients with peripheral arterial disease.

The average duration of VTE prophylaxis for 'general surgery' patients in the trials was 7 days. This concurs with the licensing conditions for pharmacological agents for surgical patients within the BNF where the recommended duration is 5-10 days, depending on the agent used. It is known in many cases surgical patients are discharged within 5 days of their operation. The guideline development group felt that the risk of VTE may still persist beyond this time period and prophylaxis may be effective after discharge. No economic analysis was conducted for patients who were discharged before the full course of VTE prophylaxis had been given.

There are other considerations for each agent when choosing pharmacological prophylaxis. UFH is not as widely used nowadays and is mainly used for patients with renal impairment. There are also practical considerations in that it requires 3 injections per day as oppose to one injection per day for LMWH.

16.7.1 Other recommendations of relevance

The specific recommendations for patients undergoing vascular surgery in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- the use of, and contraindications to, mechanical prophylaxis (Section 6.7)

- the use of pharmacological prophylaxis (Section 6.8)
- risk assessment for VTE and major bleeding (Section 5.9)
- the provision of patient information (Section 32.5)
- patients using anticoagulants or antiplatelets for reasons other than VTE prophylaxis (Chapter 1).

16.8 Summary of recommendations

➢ Offer VTE prophylaxis to patients undergoing vascular surgery who are not having other anticoagulation therapy and are assessed to be at increased risk of VTE (see section 5.9)

- Start mechanical VTE prophylaxis at admission. Choose any one of:
  - anti-embolism stockings (thigh or knee length)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length)

  Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.
- Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:
  - LMWH
  - UFH (for patients with renal failure).

  Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).

➢ Regard **surgical patients and patients with trauma** as being at increased risk of VTE if they meet one of the following criteria:

- surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
- acute surgical admission with inflammatory or intra-abdominal condition
- expected significant reduction in mobility
- have one or more risk factors shown in **Box 1**.

Box 1. Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m^2)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).

17 Day-case surgery

17.1 Introduction

This section covers patients undergoing procedures as a day-case. It will cover a wide range of procedures across many of the specialities. For the purpose of this guideline, patients are considered as day-cases their procedures meet one of the following three criteria described by the British Association of Day Surgery[84]:

- Procedure room – operation that may be performed in a suitable clean environment outside of theatres
- Day-case – "traditional day surgery"
- 23 hour stay – patients admitted and discharged within 24 hours

Special considerations for VTE

- day-case patients are likely to be more mobile and on average, younger than patients admitted for an in-patient stay.

There are no special considerations for bleeding in this group

17.2 Evidence of methods of prophylaxis

No studies were identified that investigating VTE prophylaxis in day-case surgery patients.

17.3 Network meta-analysis results

Network meta-analysis was not completed for this population

17.4 Cost-effectiveness evidence

No cost effectiveness analysis was completed for this population.

17.5 Patient views

No patient views papers were found specific to this population.

For patient views about specific prophylaxis agents, see section 6.6.

17.6 Summary of evidence

There is no RCT evidence covering prophylaxis in patients having day-case surgery.

17.7 Recommendations and link to evidence

Recommendation	**Offer VTE prophylaxis to patients undergoing day surgery who are assessed to be at increased risk of VTE (see section 5.9)** • **Start mechanical VTE prophylaxis at admission. Choose any one of:** – **anti-embolism stockings (thigh or knee length)** – **foot impulse devices** – **intermittent pneumatic compression devices (thigh or knee length)** **Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.** • **Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account patient factors and according to clinical judgement. Choose one of:** – **fondaparinux** – **LMWH** – **UFH (for patients with renal failure).** **If the patient is expected to have significantly reduced mobility after discharge, continue pharmacological VTE prophylaxis for generally 5-7 days.**
Recommendation from section 5.9	**Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:** • **surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb** • **acute surgical admission with inflammatory or intra-abdominal condition** • **expected significant reduction in mobility** • **have one or more of the risk factors shown in Box 1.**
Box 1 – VTE Risk factor box	• **Active cancer or cancer treatment** • **Age over 60 years**

	• **Critical care admission** • **Dehydration** • **Known thrombophilias** • **Obesity (BMI over 30 kg/m²)** • **One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)** • **Personal history or a first degree relative with a history of VTE** • **Use of hormone replacement therapy** • **Use of oestrogen-containing contraceptive therapy** • **Varicose veins with phlebitis.** **For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).**
Relative values of different outcomes	The outcomes considered for the review were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).
Trade off between clinical benefit and harms	The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding. These trade offs were considered to be similar to those for patients admitted to hospital for surgery. Should an individual risk factor exist then the patient would still be considered at risk of developing VTE.
Economic considerations	There is no relevant cost-effectiveness evidence specifically for this population subgroup. However, a combination of drug and mechanical prophylaxis was found to be cost-effective for general surgery patients where the risk of major bleeding is less than 1%. It seems likely that combination prophylaxis will also be cost-effective for day-case surgery patients who are at elevated risk of VTE and who have a moderate risk of major bleeding.
Quality of evidence	No evidence was identified specifically in this population.
Other considerations	The GDG discussed the use of prophylaxis in this population. Although they acknowledged that some day case patients may be younger and more mobile than patients undergoing the same type of surgery as an inpatient, this is not necessarily the case. They felt that the increase in the number of day case procedures completed may result in more complex surgery

being completed on a day case basis and that there was the potential for patients to be discharged from hospital only for them to have an extended periods of signficiantly reduced mobility at home. They agreed that the principle of risk assessment for all patients VTE was key.

The average duration of VTE prophylaxis for 'general surgery' patients in the trials was 7 days. This concurs with the licensing conditions for pharmacological agents for surgical patients within the BNF where the recommended duration is 5-10 days, depending on the agent used. The guideline development group felt that the risk of VTE may still persist beyond discharge and post-discharge prophylaxis may be effective in some cases. No economic analysis was conducted for patients who were discharged before the full course of VTE prophylaxis had been given.

There are other considerations for each agent when choosing pharmacological prophylaxis. UFH is not as widely used nowadays and is mainly used for patients with renal impairment. There are also practical considerations in that it requires 3 injections per day as oppose to one injection per day for LMWH.

17.7.1 Other recommendations of relevance

The specific recommendations for patients undergoing day-case surgery in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- The use of local anaesthesia by local infiltration with no reduction in mobility (Section 19.4)
- risk assessment for VTE and major bleeding (Section 5.9)
- the use of VTE prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)

17.8 Summary of recommendations

- Offer VTE prophylaxis to patients undergoing day surgery who are assessed to be at increased risk of VTE (see section 5.9)
    - Start mechanical VTE prophylaxis at admission. Choose any one of:
        - anti-embolism stockings (thigh or knee length)

- foot impulse devices
- intermittent pneumatic compression devices (thigh or knee length)

Continue mechanical VTE prophylaxis until the patient no longer has significantlt reduced mobility.

- Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account patient factors and according to clinical judgement. Choose one of:
  - fondaparinux
  - LMWH
  - UFH (for patients with renal failure).

  If the patient is expected to have significantly reduced mobility after discharge, continue pharmacological VTE prophylaxis for 5-7 days.

- Regard **surgical patients and patients with trauma** as being at increased risk of VTE if they meet one of the following criteria:
  - surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
  - acute surgical admission with inflammatory or intra-abdominal condition
  - expected significant reduction in mobility
  - have one or more risk factors shown in **Box 1**.

Box 1. Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m^2)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum)..

18 Other surgery

18.1 Introduction

This section covers patients undergoing surgery not mentioned elsewhere in the document (chapters 9 to 17) including plastic surgery, ear nose and throat surgery, and oral and maxillofacial surgery. It is not possible to mention all fields of surgery and all procedures but prophylaxis should be considered as for the closest comparable patient group.

The risk of VTE in this patient group may vary. Hosptial Episode Statistic data presented in section 5.3.2 for gives the following values for the symptomatic VTE, although the limitiations of this data have been discussed previously (section 5.3.2):

- Plastic surgery - 0.8%
- Breast surgery – 0.03%
- Ear, nose and throat surgery (ENT) – 0.02%
- Head and neck surgery – 0.02%
- Max facial dental surgery – 0.02%
- Eye surgery – 0.02%

Factors that might alter the risk of VTE

- These may be more mobile than other patients and therefore at less of a risk of VTE. This will depend on the type of surgery.

With the wide range of surgery types covered within this chapter it is important that the general factors that may increase the risk of bleeding, the hazard associated with it or other general factors that would affect the choice of specific methods of prophylaxis are considered for each individual surgery specialty.

18.2 Evidence of methods of prophylaxis

No studies were identified that investigated prophylaxis in these patients which is in essence why they are in this "other" group.

18.3 Network meta-analysis results

Network meta-analysis was not completed for this population

18.4 Cost-effectiveness evidence

Network meta-analysis was not **conducted** for this population.

18.5 Patient views

No patient views papers were found specific to this population.

For patient views about specific prophylaxis agents, see section 6.6.

18.6 Summary of evidence

There is no RCT evidence covering prophylaxis in patients undergoing surgery not mentioned in the other surgery chapters.

18.7 Recommendations and link to evidence

Recommendation	**Offer VTE prophylaxis to patients undergoing surgery other than that covered in chapters 9 to 17, who are assessed to be at increased risk of VTE (see section 5.9).** • **Start mechanical VTE prophylaxis at admission. Choose any one of:** – **anti-embolism stockings (thigh or knee length)** – **foot impulse devices** – **intermittent pneumatic compression devices (thigh or knee length).** **Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.** • **Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account patient factors and according to clinical judgement. Choose one of:** - **LMWH** - **UFH (for patients with renal failure).** **Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).**
Recommendation from section 5.9	**Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:** • **surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb** • **acute surgical admission with inflammatory or intra-abdominal condition** • **expected significant reduction in mobility** • **have one or more of the risk factors shown in Box 1.**
Box 1 – VTE Risk factor box	• **Active cancer or cancer treatment** • **Age over 60 years** • **Critical care admission** • **Dehydration** • **Known thrombophilias** • **Obesity (BMI over 30 kg/m^2)** • **One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or**

	inflammatory conditions) • **Personal history or a first degree relative with a history of VTE** • **Use of hormone replacement therapy** • **Use of oestrogen-containing contraceptive therapy** • **Varicose veins with phlebitis.** **For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).**
Relative values of different outcomes	The outcomes considered for the review were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).
Trade off between clinical benefit and harms	The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding.
Economic considerations	There is no relevant cost-effectiveness evidence specifically for this population subgroup. However, a combination of drug and mechanical prophylaxis was found to be cost-effective for general surgery patients where the risk of major bleeding is less than 1%. It seems likely that combination prophylaxis will also be cost-effective for other surgery patients who are at increased risk of VTE.
Quality of evidence	No evidence specific to these other groups was identified. Evidence is extrapolated from the section relating to gastrointestinal, gynaecological, urological and thoracic surgery to make recommendations.
Other considerations	The average duration of VTE prophylaxis for 'general surgery' patients in the trials was 7 days. This concurs with the licensing conditions for pharmacological agents for surgical patients within the BNF where the recommended duration is 5-10 days, depending on the agent used. It is known in many cases surgical patients are discharged within 5 days of their operation. The guideline development group felt that the risk of VTE may still persist beyond this time period and prophylaxis may be effective after discharge. No economic analysis was conducted for patients who were discharged before the full course of VTE prophylaxis had been given. There are other considerations for each agent when choosing pharmacological prophylaxis. UFH is not as widely used nowadays and is mainly used for patients with renal impairment. There are also practical considerations in that it requires 3 injections per day as oppose to one injection per day for LMWH.

18.7.1 Other recommendations of relevance

The specific recommendations for patients undergoing surgery in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)
- patients using anticoagulants or antiplatelets for reasons other than VTE prophylaxis (Chapter 1)

18.8 Summary of recommendations

- Offer VTE prophylaxis to patients undergoing surgery other than that covered in chapters 9 to 17, who are assessed to be at increased risk of VTE (see section 5.9).
    - Start mechanical VTE prophylaxis at admission. Choose any one of:
        - anti-embolism stockings (thigh or knee length)
        - foot impulse devices
        - intermittent pneumatic compression devices (thigh or knee length)

        Continue mechanical VTE prophylaxis until the patient no longer has significantlt reduced mobility
    - Add pharmacological VTE prophylaxis to patients who have a low risk of major bleeding, taking into account individual patient factors and according to clinical judgement. Choose one of:
        - LMWH
        - UFH (for patients with renal failure).

        Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility (generally 5-7 days).
- Regard **surgical patients and patients with trauma** as being at increased risk of VTE if they meet one of the following criteria:
    - surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
    - acute surgical admission with inflammatory or intra-abdominal condition
    - expected significant reduction in mobility
    - have one or more risk factors shown in **Box 1**.

Box 1. Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m^2)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).

19 Anaesthesia

19.1 Introduction

Anaesthesia is required for most operations and many investigations and other procedures. A general anaesthetic results in a patient losing consciousness. A regional anaesthetic technique involves injecting local anaesthetic into the epidural space (an epidural anaesthetic) or the subarachnoid space (a spinal anaesthetic) to achieve a sensory and/or motor block of the required area. Other drugs such as opioids may be added to the local anaesthetic agents or used as sole agents. Spinal injections are usually given as a single dose with a limited duration of action. Epidural anaesthesia may be continued for hours or days by placing additional medication through a catheter left in the epidural space. Regional techniques may be combined with sedation or a general anaesthetic. Certain procedures such as caesarean section, some urological operations or orthopaedic procedures on the lower limbs, are well suited to the use of regional techniques. Other procedures such as intracranial neurosurgery are not suitable. The use of regional anaesthesia is rare in cardiac surgery but may be used for thoracic and vascular operations.

A concern with regional anaesthesia is that when neuroaxial blockades are used, thromboprophylaxis agents will increase the risk of spinal haematoma. Therefore, the timing of the use drugs that affect haemostasis or platelet function should be carefully planned.

19.2 Clinical evidence on anaesthesia

19.2.1 Regional vs. general anaesthesia

We identified one systematic review of 11 RCTs of regional vs general anaesthesia[557] and four additional RCTs giving a total of 15 studies with 1115 participants (Evidence Table 64, Appendix D). Twelve studies were in elective orthopaedic surgery patients, two urological and one in general surgery patients. Eleven studies used an epidural regional anaesthetic and four administered a spinal anaesthetic. Eight of the 11 studies using epidural anaesthesia continued the anaesthetic into the post-operative period for pain relief (in the remaining three studies the duration of the epidural anaesthetic was either unclear or not reported). In seven studies patients were given no prophylaxis for VTE, patients wore stockings in three studies, and received a pharmacological method of prophylaxis in five studies.

Nine studies were conducted in the 1980s and six in the 1990s, with the most recent trial published in 1996. It should be noted that general anaesthetic techniques and other aspects of perioperative management have changed considerably over this period.

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

Effect on DVT: A significant risk reduction for DVT was found in patients receiving regional compared with general anaesthesia (38%) (RR=0.62, 95% CI: 0.53 to 0.73,15 studies) (Forest Plot 242, Appendix E).

Effect on pulmonary embolism: Regional anaesthesia was significantly more effective in reducing risk of pulmonary embolism than general anaesthesia, with an overall reduction of 43% (RR=0.57, 95% CI: 0.35 to 0.91) (Forest Plot 243, Appendix E).

Effect on major bleeding: Seven studies measured major bleeding events. Only one study reported an event, (RR=0.10, 95% CI: 0.01 to 1.71). The difference was not significant (Forest Plot 245, Appendix E).

19.2.2 Subgroup analysis of epidural vs spinal anaesthesia

We found no RCTs comparing spinal and epidural anaesthesia with regard to the development of post-operative VTE. A subgroup analysis of the regional vs general anaesthesia RCTs was carried out to look for a difference in the magnitude of effect based on whether spinal or epidural regional anaesthesia was used. Eleven studies used epidural and four studies used spinal regional anaesthesia.

For deep vein thrombosis, a random effects meta-analysis was used, due to the heterogeneity within the results. Subgroup analyses were not possible for proximal DVT and major bleeding as there were no studies using spinal anaesthesia that assessed these variables.

Effect on DVT: A significantly reduced risk of DVT was found with both epidural compared with general anaesthesia (RR=0.62, 95% CI: 0.51 to 0.75, 11 studies) and spinal compared with general anaesthesia (RR=0.63, 95% CI: 0.48 to 0.83, 4 studies). No significant difference in the magnitude of effect between epidural and spinal anaesthesia was found (Chi-square on 1 df = 0.03, p=0.86) (Forest Plot 246, Appendix E).

Effect on pulmonary embolism: We found a significantly reduced risk with epidural compared to general anaesthesia (RR=0.61, 95% CI: 0.38 to 0.99, 5 studies). There was a significant difference in risk of developing pulmonary embolism in a comparison of spinal vs general anaesthesia (RR=0.47, 95% CI: 0.23 to 0.96). There was no significant difference in the magnitude of effect between epidural and spinal anaesthesia Chi-square on 1 df = 0.42, p=0.52) (Forest Plot 247, Appendix E).

19.2.3 Regional and general anaesthesia vs general anaesthesia only

One study in the systematic review mentioned above[557] and one further study[145] compared the combined use of regional anaesthesia and general anaesthesia with general anaesthesia alone (Evidence Table 65, Appendix D). One study[145] was in elective hip surgery patients. All patients received vitamin K antagonists for VTE prophylaxis. Patients receiving regional anaesthesia had an epidural for the duration of surgery only. The study was small, with only 37 patients. The second study[276] was of general surgery (elective gall bladder) patients. No VTE prophylaxis was given to patients in the study. For regional anaesthesia patients, the epidural was prolonged into

the post-operative period for pain relief. The studies did not report major bleeds or pulmonary embolism. One study[145] reported the site of deep vein thrombosis. No patient had a DVT that was situated above the knee and therefore the relative risk of proximal DVT was not estimable.

Effect on DVT: No significant difference was found (RR=0.69, 95% CI: 0.26 to 1.82, two studies) (Forest Plot 248, Appendix E).

19.2.4 Risk of haematoma in anticoagulated patients receiving a regional anaesthetic

Risk of haematoma at the injection site is increased with the concomitant use of pharmacological prophylaxis agents. Removal of epidural catheter in the anticoagulated patient has also been associated with the development of spinal haematoma. The consequences of an epidural haematoma may be permanent paralysis below the level of the haematoma. The diagnosis is difficult as patients may have weakness or block because of the effects of the epidural. It would be extremely difficult to determine the true incidence as a randomised study would require very large numbers of patients due to the rarity of the event, however it has been estimated to be about 1 in 150,000 epidural blocks and 1 in 220,000 spinal anaesthetics[87].

19.3 Cost-effectiveness evidence

No cost effectiveness analysis was completed for this population.

19.4 Recommendations and link to evidence

Recommendation	**Consider regional anaesthesia for individual patients, in addition to other methods of VTE prophylaxis, as it carries a lower risk of VTE than general anaesthesia. Take into account the patients' preferences, their suitability for regional anaesthesia and any other planned method of VTE prophylaxis.**
Relative values of different outcomes	The outcomes considered were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).
Trade off between clinical benefit and harms	The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding. The timing of when pharmacological prophylaxis is started is particularly important because of the risk from bleeding.
Economic considerations	We found no evidence on the cost-effectiveness of regional anaesthesia compared with general anaesthesia in the context of VTE prophylaxis. However, there is a small body of literature that shows regional anaesthesia to be associated with faster recovery time and reduced cost for some types of surgery[447,679]. This would suggest that, when it can be performed safely, regional anaesthesia is likely to be a highly

	cost-effective form of VTE prophylaxis.
Quality of evidence	All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++). Evidence from RCTs shows that regional anaesthesia compared with general anaesthesia reduces the risk of developing postoperative VTE. There was not enough evidence to determine differences in effect for major bleeding.
Other considerations	The evidence is limited to certain surgical procedures and there are other considerations involved when selecting an anaesthetic technique. Patient preferences are also an important consideration. Regional anaesthesia alone should not be considered a suitable method of VTE prophylaxis. There are effective alternative techniques to prevent these complications and other matters to be taken into account when deciding on the most appropriate anaesthetic for a patient. In the absence of data on bleeding and the practical implications for different surgical procedures the guideline development group decided to recommend that its use be considered where practical in addition to other methods of prophylaxis. Neuroaxial blockade should be avoided in those patients with significant bleeding disorders or receiving certain drugs that affect haemostasis or platelet function. The summary of product characteristics for each agent should be consulted for the latest guidance.

19.4.1 Supporting recommendation based on Guideline Development Group consensus opinion

Recommendation	**If regional anaesthesia is used, plan the timing of pharmacological VTE prophylaxis to minimise the risk of epidural haematoma. If antiplatelet or anticoagulant agents are being used, or their use is planned, refer to the summary of product characteristics for guidance about the safety and timing of these in relation to the use of regional anaesthesia.**
Trade off between clinical benefit and harms	The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding. An additional concern is the risk of developing an epidural haematoma as a result of the regional anaesthetic technique. Consequently, the Guideline Development Group recommends

	that the timing of pharmacological prophylaxis should be carefully planned to minimise the risk of spinal haematoma if a regional anaesthetic technique is used. Patients using antiplatelets or anticoagulant agents may be at increased risk of bleeding.
Economic considerations	We found no evidence on the cost-effectiveness of the timing of regional anaesthesia. However, it seems logical that the careful consideration of timing will improve the cost-effectiveness of regional anaesthesia.
Other considerations	The type of anticoagulant used may affect the timing of insertion and removal of the catheter. Such procedures should be delayed until the anticoagulant effect of the agent is minimal. For example, this may involve removing the catheter just before the next dose of thromboprophylaxis and delaying any further thromboprophylaxis for 2 hours after epidural catheter removal. The requirements for each antiplatelet agent or anticoagulant will be different. The guideline development group recommends that clinicians refer to information within the summary of product characteristics for each agent and seek advice from experienced anaesthetists if uncertainty remains. The balance of risks and benefits should be individualised for each patient and will depend on the type of regional anaesthesia, patient risk factors (including bleeding risks), and the type and dose of anticoagulant or use of other drugs affecting haemostasis or platelet function.An additional concern is the risk of developing an epidural haematoma as a result of a regional anaesthetic technique.

Recommendation	**Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients undergoing a surgical procedure with local anaesthesia by local infiltration with no limitation of mobility.**
Trade off between clinical benefit and harms	The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding.
Economic considerations	None
Other considerations	The guideline development group decided that although a risk assessment for VTE should still be required upon admission to hospital (section 5.9), patients undergoing minor procedures under local anaesthesia without reduced mobility were likely to be at a low risk of VTE and as such routine prophylaxis was

not likely to be beneficial.

19.5 Summary of recommendations

- Consider regional anaesthesia for individual patients, in addition to other methods of VTE prophylaxis, as it carries a lower risk of VTE than general anaesthesia. Take into account the patients' preferences, their suitability for regional anaesthesia and any other planned method of VTE prophylaxis.

- If regional anaesthesia is used, plan the timing of pharmacological VTE prophylaxis to minimise the risk of epidural haematoma. If antiplatelet or anticoagulant agents are being used or their use is planned, healthcare professionals should refer to the summary of product characteristics for guidance about the safety and timing of these in relation to the use of regional anaesthesia.

- Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients undergoing a surgical procedure with local anaesthesia by local infiltration with no limitation of mobility.

20 Spinal injury

20.1 Introduction

Spinal injury and, in particular, spinal cord injury is a significant cause of morbidity and mortality with younger age groups frequently affected. Spinal injury can occur without injury to the spinal cord and when nerve injury occurs at the level below the dorsal/lumbar junction (where the injury will be to the cauda equine and not the spinal cord). Even without injury to the spinal cord or nerve injury, patients with spinal injury may be at increased risk of VTE for reasons of prolonged immobility

Most patients with spinal injury are treated conservatively but a not insignificant proportion will require spinal stabilisation. Most patients recover to a greater degree but a not insubstantial number will have a permanent neurological deficit and require assessment, at least initially, in a Regional Spinal Injury Centre.

Non-traumatic causes of spinal cord compression are covered elsewhere, for example, in the NICE Metatastatic Spinal Cord Compression guideline [471]. However, further evidence is evaluated in the Palliative care (Chapter 28) and Critical care (Chapter 29) sections of this document. The evidence for patients undergoing spinal surgery is presented in Chapter 14.

The major concern is the constantly changing balance between the initial risk of bleeding (a potential disaster within the enclosed space of the spinal column) and the subsequent increased risk of thrombotic events, particularly, with prolonged immobilisation. The small number of trials completed in this population recorded the baseline risk of DVT at between 40-50% in the absence of thromboprophylaxis. A risk assessment tool should be utilised as soon after admission as is practicable with constant clinical evaluation and re-evaluation depending on patient progress.

20.2 Evidence of methods of prophylaxis

20.2.1 Summary of comparisons identified for any outcome

Four randomised controlled trials which reported at least one of the three main outcomes were identified [233,234,442,616].

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

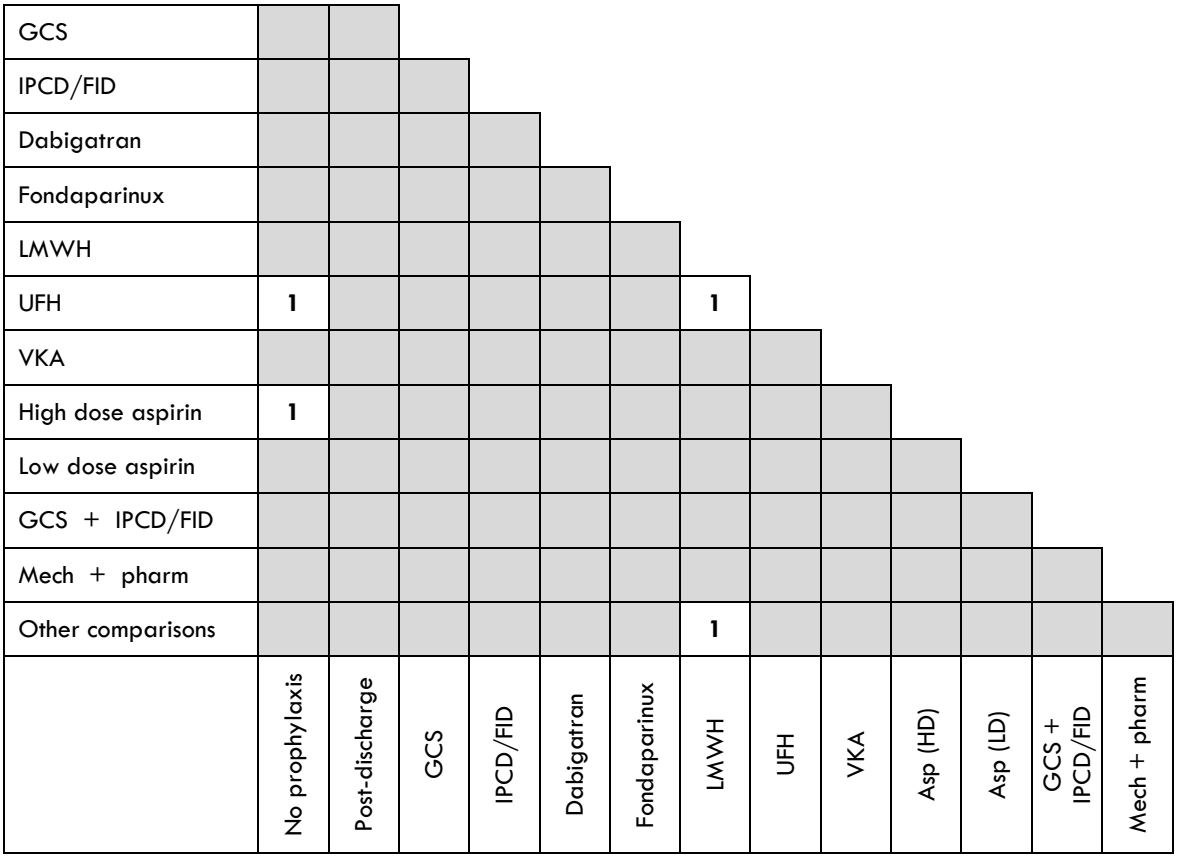


Figure 20-41: Number of studies which compared various types of prophylaxis methods.

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicates areas where no studies were identified.

GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) - low dose aspirin (≤ 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis

20.2.2 Results from pairwise comparisons

Table 20-99: DVT – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
Asp (high dose) +/- other antiplatelets vs nil [234]	1	3/13	6/15	0.58 (0.18, 1.86)	-0.17 (-0.51, 0.17)	ET: 29 FP: 28
UFH vs nil [442]	1	8/16	8/17	1.06 (0.53, 2.15)	0.03 (-0.31, 0.37)	ET: 27 FP: 17
Single proph vs single						
LMWH vs UFH [233]	1	0/20	3/21	0.15 (0.01, 2.73)	-0.14 (-0.31, 0.02)	ET: 32 FP: 48

** FP – forest plot number in appendix E; ET – evidence table number in appendix D. Proph - prophylaxis*

Table 20-100: Symptomatic pulmonary embolism – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
Asp (high dose) +/- other antiplatelets vs nil [234]	1	0/13	0/15	Not estimatable	0 (-0.13, 0.13)	ET: 29 FP: 29

** FP – forest plot number in appendix E; ET – evidence table number in appendix D. Proph - prophylaxis*

Table 20-101 : Major bleeding – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Double proph vs single						
IPCD + UFH vs LMWH [616]	1	13/246	6/230	2.03 (0.78, 5.24)	0.03 (-0.01, 0.06)	ET: 43 FP: 219

** FP – forest plot number in appendix E; ET – evidence table number in appendix D. Proph - prophylaxis*

20.2.3 Additional information

20.2.3.1 All cause mortality

Table 20-102 : All cause mortality summary from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
Asp (high dose) +/- other antiplatelets vs nil [234]	1	0/13	0/15	Not estimatable	0.00 (-0.13, 0.13)	ET: 29 FP: 31
Single proph vs single						
LMWH vs UFH [233]	1	0/20	2/21	0.21 (0.01, 4.11)	-0.10 (-0.24, 0.05)	ET: 32 FP: 51
Double proph vs single						
IPCD + UFH vs LMWH [616]	1	2/246	2/230	0.93 (0.13, 6.58)	0.00 (-0.02, 0.02)	ET: 43 FP: 220

** FP – forest plot number in appendix E; ET – evidence table number in appendix D. Proph - prophylaxis*

20.2.3.2 Additional studies

The DVT and pulmonary embolism outcomes of a study which compared the safety and efficacy of a combination of UFH plus IPCD against LMWH had been excluded from the main analysis of DVT and PE because only 107/456 (23.5%) of patients were able to be evaluated for these outcomes [616]. Major bleeding events were reported on an intention to treat basis and are presented in Table 1-3.

This study was followed with a rehabilitative phase study where patients were enrolled from week 2 for 6 additional weeks and were given UFH or LMWH prophylaxis [617]. The study was excluded as the reported patient inclusion was unclear. The study did not find any significant difference in all cause mortality, DVT, symptomatic PE and major bleeding rates.

20.2.3.3 Additional outcomes

No studies reported heparin induced thrombocytopenia, post thrombotic syndrome or chronic thromboembolic pulmonary hypertension.

20.3 Network meta-analysis results

No network meta-analysis was completed for this population

20.4 Cost-effectiveness evidence

No cost effectiveness analysis was completed for this population.

20.5 Patient views

Only two patient view or adherence to treatment studies were found in this population, and both were conducted as RCTs [106,701].

In a United States study, patients received more than 99% of the prescribed LMWH doses, for both once or twice daily regimens (Evidence Table 62, Appendix D) [106]. Most patients did not think getting the injections a "hassle" (compared to taking pills 3 times a day) or painful [106].

The other study compared FID vs IPCD among adults undergoing major thoracolumbar reconstructive spinal procedures (Evidence Table 61, Appendix D) [701]. All participants also wore thigh-length stockings and the devices were started postoperatively and worn when in bed until discharge. There was a wide range of responses in both groups ranging from extremely comfortable to extremely uncomfortable. There was no difference in visual analogue scores for comfort between the FID and the IPCD groups.

For more information patient views and adherence on specific prophylaxis methods, see section 6.6, where information from different populations are presented.

20.6 Summary of evidence

Intervention(s)	*Comparison(s)*	*Intervention favoured*		
		DVT	**PE**	**MB**
Prophylaxis vs no prophylaxis				
UFH	Nil	Not sig	-	-
Asp(HD) +/- antiplatelets	Nil	Not sig	No events	-
Single prophylaxis vs single				
UFH	LMWH	Not sig	-	-
Double prophylaxis vs single				
IPCD + UFH	LMWH	-	-	Not sig
Cost Effectiveness				
There is no relevant cost-effectiveness evidence specifically for this population subgroup.				

The prophylaxis strategy which is significantly more effective in reducing DVT or PE; or resulting in significantly less major bleeding is stated in bold.
Not sig - not statistically significant difference; '-'= not reported; no events – nobody in the study had the outcome. MB = Major bleeding

Very few RCTs had been conducted in patients with spinal injury. The studies were mostly very small, and therefore may be unable to detect any difference in the effectiveness of different strategies, even if there was one.

20.7 Recommendations and link to evidence

Recommendation	**Offer combined VTE prophylaxis with mechanical and pharmacological methods tor patients with spinal injury. Regularly reassess the patient's risks of VTE and bleeding.** • **Start mechanical VTE prophylaxis at admission or as early as clinically possible. Choose any one of:** – **anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)** – **foot impulse devices** – **intermittent pneumatic compression devices (thigh or knee length).** **Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.** • **If the benefits of reducing the risk of VTE outweigh the risks of bleeding (see Box 2) and the bleeding risk has been established as low, add pharmacological VTE prophylaxis. Choose one of:** – **LMWH** – **UFH (for patients with renal failure).** **Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility.**
Box 2. Bleeding Risk Factors	**Regard hospitalised patients as being at risk of bleeding if they have any of the following risk factors:** • **Active bleeding** • **Acquired bleeding disorders (such as acute liver failure)** • **Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with international normalised ration [INR] higher than 2)** • **Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours** • **Lumbar puncture/epidural/spinal analgesia within the previous 4 hours** • **Acute stroke** • **Thrombocytopenia (platelets < 75 x 10^9/l)** • **Uncontrolled systolic hypertension (≥ 230/120 mmHg)** • **Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease).**
Relative values of different	The main outcomes considered were venous thromboembolic

outcomes	events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).
Trade off between clinical benefit and harms	The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding.
Economic considerations	There is no relevant cost-effectiveness evidence specifically for this population subgroup. The implications for spinal injury patients developing VTE are similar to other groups of patients and the risk of VTE in this population is likely to be very high (40-47% in no prophylaxis arms of included RCTs). The results of our economic model for the general medical and surgical patients (Chapters 23 and 9) could therefore be extrapolated for this subgroup. The model result suggests that LMWH is the most cost-effective for general medical patients. This was followed by unfractionated heparin. The model for general surgical patients suggests that a combination of mechanical prophylaxis and either unfractionated heparin or LMWH are most cost - effective where the risk of major bleeding is less than 1%. It is likely that any major bleeding events have more severe consequences for this group of patients than for general medical or surgical patients from which the data have been extrapolated; especially if the bleeding occurs in the spinal cord. The importance of establishing bleeding risk before providing pharmacological prophylaxis is therefore very important.
Quality of evidence	All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++). There was very little evidence available for this group of patients. All three studies where venous thromboembolism outcomes were included had small sample sizes (mean = 34, range 28 to 41), and would not have been powered to detect significant differences in VTE events or bleeding risks. Therefore, the quality of evidence is disadvantaged from lack of precision in the results. Moreover, only two of the studies masked patients and VTE investigators to the treatment.
Other considerations	Despite a lack of evidence which is specific to this group, it had been noted that the incidence of VTE is very high (40-47% in no prophylaxis arms of included RCTs). Based on evidence in

other groups, prophylaxis should be offered, unless outweighed by the risk of bleeding. The Guideline Development Group recognised that it is difficult to determine a time point where the risk of bleeding would be significantly reduced based on the literature. This would need to be assessed individually for each patient.

There is little evidence available in terms of patients' views. The study which was found in this population found LMWH could be administered without adherence problems in the hospital setting, and most patients did not find it a painful or an inconvenience ("hassle").

20.7.1 Other recommendations of relevance

The specific recommendations for patients with spinal injury in this chapter should be read in conjunction with other relevant recommendations in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)
- recommendations about patients undergoing spinal surgery (Section 14.7)
- recommendations about patients in critical care (Section 29.7)
- recommendations about patients receiving palliative care (Section 28.7)
- recommendations about metastatic spinal injury from the NICE guidelines[471]

20.8 Recommendations for research

Although not identified as a top priority research recommendation the Guideline Development Group identified that information about prophylaxis in this group is sparse, particularly around the duration of prophylaxis and suggested that further research in this area would be helpful.

20.9 Summary of recommendations

- Offer combined VTE prophylaxis with mechanical and pharmacological methods tor patients with spinal injury. Regularly reassess the patient's risks of VTE and bleeding.
  - Start mechanical VTE prophylaxis at admission or as early as clinically possible. Choose any one of:
    - anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)
    - foot impulse device

- intermittent pneumatic compression devices (thigh or knee length)

Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.

- If the benefits of reducing the risk of VTE outweigh the risks of bleeding (see **Box 2**) and the bleeding risk has been established as low, add pharmacological VTE prophylaxis. Choose one of:
  - LMWH
  - UFH (for patients with renal failure).

  Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility.

Box 2. Bleeding Risk Factors

- Active bleeding
- Acquired bleeding disorders (such as acute liver failure)
- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with international normalised ratio [INR] higher than 2)
- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours
- Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours
- Acute stroke
- Thrombocytopenia (platelets less than 75 x 10^9/l)
- Uncontrolled systolic hypertension (230/120 mmHg or higher)
- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease)

21 Lower limb plaster casts

21.1 Introduction

The use of lower limb plaster casts in trauma and elective orthopaedic surgery affects a significant number of patients. The populations involved include trauma patients who do not require surgery, trauma patients who have had operative fixation and elective cases usually involving the knee, foot and ankle. A cast may be used for three months or more following the intervention.

Although the DVT risk (symptomatic or asymptomatic) in patients with lower limb plaster casts was reported as between 4-40% in the arms of the trials which did not receive any thromboprophylaxis, the risk of symptomatic pulmonary embolism is considerably lower (0.5%). However, the large volume of potential patients affected is a concern. In addition certain groups may be at greater risk, for example, those undergoing conservative or operative treatment on the Achilles tendon, more complex procedures with longer immobilisation, and those returning from abroad with their affected injured limb in a cast.

21.2 Evidence of methods of prophylaxis

21.2.1 Summary of comparisons identified for any outcome

Six studies were indentified in patients with lower limb plaster casts [317,356,367,374,375,377]. All these compared low molecular weight heparin (LMWH) prophylaxis against no prophylaxis.

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

In these studies, patients were given prophylaxis until the removal of plaster cast. This was 2-3 weeks in two [356,367], and 5 to 6 weeks in the other three studies [317,374,377].

One additional paper which investigated the impact of extended duration prophylaxis was found [375]. In this study, all patients received LMWH prophylaxis for 7 days after ankle surgery before being randomised to 6 weeks (or until plaster cast removal) of LMWH prophylaxis or no prophylaxis. The results of a subgroup of patients who used plaster casts is included in this section.

	No prophylaxis	Post-discharge	GCS	IPCD/FID	Dabigatran	Fondaparinux	LMWH	UFH	VKA	Asp (HD)	Asp (LD)	GCS + IPCD/FID	Mech + pharm
GCS													
IPCD/FID													
Dabigatran													
Fondaparinux													
LMWH	**5**	**1**											
UFH													
VKA													
High dose aspirin													
Low dose aspirin													
GCS + IPCD/FID													
Mech + pharm													
Other comparisons													

Figure 21-42: Number of studies which compared various types of prophylaxis methods.

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicates areas where no studies were identified.

GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) - low dose aspirin (≤ 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis

21.2.2 Results from pairwise comparisons

Table 21-103: DVT – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
LMWH vs nil [317,356,367,374,377]	5	51/633	100/ 631	0.52 (0.32, 0.87) (a)	-0.07 (-0.11, -0.03)	ET: 26 FP: 13
Post discharge						
LMWH vs nil[375]	1	21/99	33/86	0.55 (0.35, 0.88)	-0.17 (-0.30, -0.04)	ET: 58 FP: 225

** FP – forest plot number in appendix E; ET – evidence table number in appendix D. Proph - prophylaxis*

(a) There is substantial statistical heterogeneity between studies for this population (I^2 =54.5 %, χ^2 on 4 df = 8.80, p= 0.07).

Table 21-104: Symptomatic pulmonary embolism – summary of results from RCTs

Comparison	No. of studies	Interven -tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
LMWH vs nil [317,374,377]	3	0/368	2/380	0.20 (0.01, 4.22)	-0.01 (-0.02, 0.01)	ET: 26 FP: 14
Post discharge						
LMWH vs nil [375]	1	0/114	0/108	Not estimable	0.00 (-0.02, 0.02)	ET: 58 FP: 226

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

Table 21-105: Major bleeding – summary of results from RCTs

Comparison	No. of studies	Interven -tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
LMWH vs nil [356,374,377]	3	2/445	1/437	2.04 (0.19, 22.30)	0.00 (-0.01, 0.01)	ET: 26 FP: 15
Post discharge						
LMWH vs nil[375]	1	0/114	0/108	Not estimable	0.00 (-0.02, 0.02)	ET: 58 FP: 227

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

21.2.3 Additional information

Table 21-106: All cause mortality – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
LMWH vs nil [374,377]	2	0/269	0/274	Not estimable	0.00 (-0.01, 0.01)	ET: 26 FP: 16

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

21.3 Network meta-analysis results

No network meta-analysis was completed for this population.

21.4 Cost-effectiveness evidence

No cost-effectiveness analysis was completed for this population.

21.5 Patient views

One open label RCT compared subcutaneous self-injection of LMWH at the abdominal wall using disposable needles against no prophylaxis until the removal of the below knee plaster cast [317]. In this study, 12% of the 148 participants discontinued because of discomfort with self injection, approximately 60% had "no difficulties" and some patients had difficulties remembering the injections. 87% of patients in this study were male, and their average age was 49 years old.

For patient views about specific prophylaxis agents, see section 6.6.

21.6 Summary of evidence

Intervention(s)	*Comparison(s)*	*Intervention favoured*		
		DVT	**PE**	**MB**
Prophylaxis vs no prophylaxis				
LMWH	Nil	**LMWH**	Not sig	Not sig
Post discharge				
LMWH	Nil	**LMWH**	No event	No event
Cost Effectiveness				
No cost-effectiveness analysis was conducted for this group				

The prophylaxis strategy which is significantly more effective in reducing DVT or PE; or resulting in significantly less major bleeding is stated in bold.
Not sig - not statistically significant difference; no events – nobody in the study had the outcome. MB = Major bleeding

21.7 Recommendations and link to evidence

Recommendation	**Consider offering pharmacological VTE prophylaxis to patients with lower limb plaster casts after evaluating the risks (see section 5.9) and benefits based on clinical discussion with the patient. Offer *LMWH (or UFH* for patients with renal failure) until lower limb plaster cast removal.**
Recommendation from section 5.9	**Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:** • **surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb** • **acute surgical admission with inflammatory or intra-abdominal condition** • **expected significant reduction in mobility** • **have one or more of the risk factors shown in Box 1.**
Box 1 – VTE Risk factors	• **Active cancer or cancer treatment** • **Age over 60 years** • **Critical care admission** • **Dehydration** • **Known thrombophilias** • **Obesity (BMI over 30 kg/m2)** • **One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)**

	• **Personal history or a first degree relative with a history of VTE** • **Use of hormone replacement therapy** • **Use of oestrogen-containing contraceptive therapy** • **Varicose veins with phlebitis.** **For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).**
Relative values of different outcomes	The main outcomes considered were venous thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).
Trade off between clinical benefit and harms	The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding. We cannot say definitively that the benefits outweigh the harms since the mortality rate is too low to make a conclusion about all-cause mortality. The data on pulmonary embolism and major bleeding were very sparse. The only significant outcome was a 50% reduction in all DVT events with LMWH compared with no prophylaxis.
Economic considerations	No cost-effectiveness analysis was completed for this group of patients. This is a potentially large population, and recommending prophylaxis may have significant impact on NHS costs, especially as prophylaxis is continued until the cast is removed. Patients in this population are relatively young compared to other groups, and any fatal VTE or fatal bleeding events, or long term events due to thrombosis or bleeding could result in a higher loss of quality adjusted life years than the populations where cost-effectiveness analysis had been conducted. However, the risk of pulmonary embolism seems low compared with some other groups and therefore it is unlikely that prophylaxis will be cost-effective unless patients have additional risk factors.
Quality of evidence	All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++). All studies in this population compared LMWH administered until plaster cast removal against no prophylaxis or shorter term prophylaxis. The studies included specific groups of patients, and some extrapolation is required to cover plaster cast patients not included. Some of the studies which compared LMWH vs nil were

not masked.

When considering adherence data observed from RCTs, it is important to note that patients in RCTs are a selected group, and as a result of the study protocol, patients are likely to receive more intense care and support than a patient in usual practice. This may produce adherence results which are more optimistic than usual practice.

Other considerations

The orthopaedic subgroup discussed this group in detail. Although they acknowledged the reduction in DVT, they noted the very low incidence of PE in these patients. They discussed whether the patients who developed pulmonary embolism would have developed it irrespective of whether they had been given prophylaxis. Although it is by no means certain the use of a robust risk assessment tool might help to "pick out" these individuals. They decided that VTE prophylaxis should be considered and offered only after a discussion of the risks and benefits with the patient.

There is a range of procedures and injuries which require the application of lower limb plaster casts. The length of the plaster cast and the location of injury within the leg may also differ. Most patients are expected to remain mobile (although not weight bearing on the affected limb), while others may remain immobile, generally. These are the factors which may put patients at different levels of risks. Among the RCTs reviewed, risk of DVT in the arm which did not receive prophylaxis ranged from 4.3% in a study among patients with injuries not requiring surgery[356] to 40.4% in a study where all patients had Achilles tendon rupture and received surgery [374].

The practicality and adherence of self-administering subcutaneous LMWH injection and other mechanical prophylaxis methods was also considered. Although the result from a RCT showed that most people could self-administer LMWH without problems, there are still some patients who were not comfortable with it, and who reported problems remembering the injection.

Dabigatran and rivaroxaban are new oral anticoagulants which are licensed for use after hip and knee replacement. They are not licensed in this population. The orthopaedic subgroup felt that as no evidence had been gained in this population it was not appropriate to recommend them for lower limb plaster cast patients, although more research into these agents may make them suitable for use in this population in the future. Fondaparinux has not been evaluated in this group of patients and is therefore not recommended.

21.7.1 Other recommendations of relevance

The specific recommendations for patients with lower limb plaster casts in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)

21.8 Recommendations for research

21.8.1 Thromoprophylaxis for patients with lower limb plaster casts

The GDG recommended the following research question:

- What is the clinical and cost effectiveness of pharmacological prophylaxis for reducing the risk of VTE in patients with lower limb plaster casts?

Why this is important

A number of randomised controlled trials have been published reporting the use of VTE prophylaxis in patients with lower limb plaster casts. However, within these trials there has been a range of patients including patients with soft tissue injuries and no operation, those with operated and unoperated fractures and patients having elective procedures. The incidence of VTE in the published trials that did not use VTE prophylaxis ranges from 4%–40%. The implications of providing pharmacological prophylaxis for all patients with lower limb plaster casts are potentially considerable with respect to cost. Trials stratifying patients by reason for plaster cast would be useful to determine which patients should be recommended for prophylaxis.

Recommended design: RCT

(More details in Appendix F).

21.9 Summary of recommendations

- Consider offering pharmacological VTE prophylaxis to patients with lower limb plaster casts after evaluating the risks (see section 5.9) and benefits based on clinical discussion with the patient. Offer LMWH (or UFH for patients with renal failure) until lower limb plaster cast removal.

- Regard **surgical patients and patients with trauma** as being at increased risk of VTE if they meet one of the following criteria:
  - surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb **or**
  - acute surgical admission with inflammatory or intra-abdominal condition **or**
  - expected significant reduction in mobility **or**
  - have one or more risk factors in **Box 1.**

Box 1. Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m^2)
- One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory diseases)
- Personal history or a first degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis.

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).

22 Major trauma

22.1 Introduction

The majority of patients suffering significant trauma require assessment and management by the orthopaedic service. There may be associated injury to the head, chest or abdomen, in those with multiple trauma, most frequently in road traffic collisions. However, major pelvic and spinal injury and multiple long bone fractures in isolation constitute significant orthopaedic trauma. A proportion will require management in a critical care setting, in either an Intensive Care or High Dependency Unit, for which additional guidance can be found in Chapter 29.

There is no evidence for the use of pharmacological or mechanical VTE prophylaxis for patients with minor injuries such as simple fractures requiring an upper limb plaster cast who are mobile and have no other risk factors for VTE. However, further guidance for patients with these types of injuries and significant reduction in mobility or an increased risk for VTE (Section 5.9) can be found in the guidance for general medcial patients (Chapter 23). Guidance for patients undergoing upper limb surgery can be found in the section for 'other orthopaedic surgery' (Chapter 13).

For major trauma patients, the main concern is the constantly changing balance between the initial risk of bleeding and the subsequent increased risk of thrombotic events. Trauma patients have been identified to be at increased risk of venous thromboembolism as although none of the RCTs identified had a "no prophylaxis" arm, the incidence of DVT even when thromboprophylaxis was provided was reported as up to 37%.

The safe management of these patients should include a risk assessment tool for VTE with continuous clinical monitoring of the potential initial bleeding risk and the subsequent increased thrombotic tendency.

22.2 Evidence of methods of prophylaxis

A total of 5 studies were identified [124,218,222,354,620]. Two of these studies compared low molecular weight heparin (LMWH) against mechanical methods (e.g. anti-embolism stockings, intermittent pneumatic compression devices or foot impulse devices)[222,354]. Another study compared LMWH immediate initiation against initiation after using 'pulsatile foot pumps' only for the first 5 days [620].

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

22.2.1 Summary of comparisons identified for any outcome

	No prophylaxis	Post-discharge	GCS	IPCD/FID	Dabigatran	Fondaparinux	LMWH	UFH	VKA	Asp (HD)	Asp (LD)	GCS + IPCD/FID	Mech + pharm
GCS													
IPCD/FID													
Dabigatran													
Fondaparinux													
LMWH													
UFH						**2**							
VKA													
High dose aspirin													
Low dose aspirin													
GCS + IPCD/FID													
Mech + pharm													
Other comparisons							**3**						

Figure 22-43: Number of studies which compared various types of prophylaxis methods.
Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicates areas where no studies were identified.
GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) - low dose aspirin (≤ 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis

Table 22-107 : Types of injury in included study

Study	Comparison	Population
Cohn et al, 1999[124]	LMWH vs UFH	"moderately injured" – mixed population
Knudson et al, 1996[354]	IPCD+GCS or FID vs LMWH	Mixed trauma population – ISS >10: 53% – Fractures: Lower extremity :16.9% – Head injury (GCS ≤ 8): 7%
Ginzburg et al, 2003[222]	IPCD or FID vs LMWH	ISS ≥9 – Injuries: Chest: 37.3%; head: 22.9% – Fractures: Leg or pelvis: 35.1%
Geerts et al, 1996[218]	LMWH vs UFH	ISS ≥9, 67.5% motor vehicle accident – Spinal cord injury: 8.6% – Fractures: Pelvic/femur :38.1%; tibial :17.8%

Study	Comparison	Population
Stannard et al, 2006[620]	FID + delayed LMWH	Severe blunt skeletal trauma, AIS ≥ 3, with single or multiple long bone fracture – 52% of patients had injury at the acetabulum – The following is the % of a certain type of injury out of total injuries reported: 25% hip, 16 % pelvis, 20% long bones

22.2.2 Results from pairwise comparisons

Table 22-108 : DVT – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Single proph vs single						
LMWH vs UFH [124,218]	2	40/163	62/168	0.69 (0.50, 0.95)	-0.09 (-0.18, -0.01)	ET: 32 FP: 48
IPCD/FID vs LMWH [222]	1	6/224	1/218	5.84 (0.71, 48.10)	0.02 (0.00, 0.05)	ET: 37 FP: 87
Other prophylaxis strategies						
(IPCD + GCS) or FID vs LMWH [354]	1	2/82	1/120	2.93 (0.27, 31.75)	0.02 (-0.02, 0.05)	ET: 37 FP: 101
FID + delayed LMWH vs LMWH [620]	1	9/103	13/97	0.65 (0.29, 1.46)	-0.05 (-0.13, 0.04)	ET: 52 FP: 211

** FP – forest plot number in appendix E; ET – evidence table number in appendix D. Proph - prophylaxis*

Table 22-109 : Symptomatic pulmonary embolism – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Single proph vs single						
LMWH vs UFH [124,218]	2	1/182	0/187	3.16 (0.13, 76.91)	0.01 (-0.01, 0.02)	ET: 32 FP: 49
IPCD/FID vs LMWH [222]	1	1/224	1/218	0.97 (0.06, 15.46)	0.00 (-0.01, 0.01)	ET: 37 FP: 88
Other prophylaxis strategies						
(IPCD + GCS) or FID vs LMWH [354]	1	0/82	0/120	Not estimatable	0.00 (-0.02, 0.02)	ET: 37 FP: 102
FID + delayed LMWH vs LMWH [620]	1	0/103	2/97	0.19 (0.01, 3.88)	-0.02 (-0.05, 0.01)	ET: 52 FP: 212

** FP – forest plot number in appendix E; ET – evidence table number in appendix D. Proph - prophylaxis*

Table 22-110: Major bleeding – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Single proph vs single						
LMWH vs UFH [218]	1	5/171	1/173	5.06 (0.60, 42.85)	0.02 (0.00, 0.05)	ET: 32 FP: 50
IPCD/FID vs LMWH [222]	1	4/224	4/218	0.97 (0.25, 3.84)	0.00 (-0.03, 0.02)	ET: 37 FP: 89
Other prophylaxis strategies						
(IPCD + GCS) or FID vs LMWH [354]	1	0/82	0/120	Not estimatable	0.00 (-0.02, 0.02)	ET: 37

** FP – forest plot number in appendix E; ET – evidence table number in appendix D. Proph - prophylaxis*

22.2.3 Additional information

Table 22-111: All cause mortality – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Single proph vs single						
LMWH vs UFH [218]	1	2/171	0/173	5.06 (0.24, 104.59)	0.01 (-0.01, 0.03)	ET: 32 FP: 51
IPCD/FID vs LMWH [222]	1	0/224	0/218	Not estimatable	0.00 (-0.01, 0.01)	ET: 37 FP:
Other prophylaxis strategies						
(IPCD + GCS) *or* FID vs LMWH [354]	1	0/82	0/120	Not estimatable	0.00 (-0.02, 0.02)	ET: 37

** FP – forest plot number in appendix E; ET – evidence table number in appendix D. Proph - prophylaxis*

22.3 Network meta-analysis results

No network meta-analysis was completed for this population.

22.4 Cost-effectiveness evidence

An original cost-effectiveness analysis was not completed for this population. One study was identified in the published literature [413]. This study was based on one of the randomised trials included in our review Geerts et al, 1996[218] (Table 22-107). This found that LMWH was dominated by UFH (that is patients receiving UFH had longer life expectancy and incurred less cost) due to increased bleeding from LMWH. However, they did not include the impact of prophylaxis on post-thrombotic syndrome or chronic thromboemblic pulmonary hypertension and therefore they will have under-estimated the health gain and over-estimated the cost associated with LMWH. Furthermore, the results of this study are only partially applicable to this guideline trauma population as costs were assessed from a Canadian (rather than as UK NHS perspective) and quality adjusted life years (QALYs) were not estimated.

22.5 Patient views

One of the RCTs reported adherence to recommended duration of FID use [620]. In this study, patients were advised to use FID for at least 12 hours per day. Most patients were compliant and the mean duration of use was 13.3 hours (range of 1 to 23 hours per day). A few patients did not wear the pump for the recommended period, especially when patients began to walk.

No other patient view or adherence studies conducted in major trauma patients were identified. For patient views about specific prophylaxis agents, see section 6.6.

22.6 Summary of evidence

Table 22-112: Summary of evidence from direct results for DVT, pulmonary embolism and major bleeding outcomes.

Intervention(s)	*Comparison(s)*	*Intervention favoured*		
		DVT	**PE**	**MB**
LMWH	UFH	**LMWH**	Not sig	Not sig
IPCD or FID	LMWH	Not sig	Not sig	Not sig
Other strategies				
FID + delayed LMWH	LMWH	Not sig	Not sig	-
IPCD + GCS or FID	LMWH	Not sig	Not sig	Not sig
Cost effectiveness Results				
No cost-effectiveness analysis was conducted in this population				
One economic study was identified which suggested UFH was cost effective for major trauma patients but is subject to a number of limitation as described in section 1.4				

The prophylaxis strategy which is significantly more effective in reducing DVT or PE; or resulting in significantly less major bleeding is stated in bold.
Not sig - not statistically significant difference; '-'= not reported, no events – nobody in the study had the outcome. MB = Major bleeding

22.7 Recommendations and link to evidence

Recommendation	**Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients with major trauma. Regularly reassess the patient's risks of VTE and bleeding.** • **Start mechanical VTE prophylaxis at admission or as early as clinically possible. Choose any one of:** – **anti-embolism stockings (thigh or knee length), used with caution(see section 6.7)** – **foot impulse devices** – **intermittent pneumatic compression devices (thigh or knee length)** **Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.** • **If the benefits of reducing the risk of VTE outweigh the risks of bleeding (see *Box 2*) and when the bleeding risk has been established as low, add pharmacological VTE prophylaxis. Choose one of:** – **LMWH** – **UFH (for patients with renal failure).** **Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility.**
Recommendation–from section 5.9	**Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:** • **surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb** • **acute surgical admission with inflammatory or intra-abdominal condition** • **expected significant reduction in mobility** • **have one or more of the risk factors shown in Box 1.**
Box 1 –Risk Factors for VTE	• **Active cancer or cancer treatment** • **Age over 60 years** • **Critical care admission** • **Dehydration** • **Known thrombophilias** • **Obesity (BMI over 30 kg/m^2)** • **One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory**

	conditions) • **Personal history or a first degree relative with a history of VTE** • **Use of hormone replacement therapy** • **Use of oestrogen-containing contraceptive therapy** • **Varicose veins with phlebitis.** **For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).**
Recommendation–from section 5.9	**Assess all patients for risk of bleeding before offering pharmacological VTE prophylaxis*. Do not offer pharmacological VTE prophylaxis to patients with any of the risk factors for bleeding shown in Box 2, unless the risk of VTE outweighs the risk of bleeding.** ****Consult the summary of product characteristics for the pharmacological VTE prophylaxis being used or planned for further details.***
Box 2-Risk Factors for bleeding	• **Active bleeding** • **Acquired bleeding disorders (such as acute liver failure)** • **Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with international normalised ratio [INR] higher than 2)** • **Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours** • **Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours** • **Acute stroke** • **Thrombocytopenia (platelets less than 75 x 109/l)** • **Uncontrolled systolic hypertension (230/120 mmHg or higher)** • **Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease)**
Relative values of different outcomes	The main outcomes considered were venous thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).
Trade off between clinical benefit and harms	The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding. In this group, patients are at an increased risk of both VTE and bleeding.

Economic considerations

Although no cost-effectiveness model was developed for this population, the implications for trauma patients developing VTE are similar to other groups of patients, and the risk of developing VTE in this group is likely to be high. The cost-effectiveness of thrombrophylaxis is robust in many medical and surgical patients. However, this is a group where the risk of major bleeding (and fatal bleeding is potentially high). It is assumed that providing mechanical prophylaxis for major trauma patients is cost-effective and that pharmacological prophylaxis is cost-effective as long as the risk of bleeding has subsided.

Quality of evidence

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

The generalisability of evidence from studies to individual patients should be considered. The RCTs included moderate to severe trauma patients with a variety of injuries, with the more severe patients usually managed in specialised trauma centres. There is a range of risks for VTE and bleeding, depending on the type, location and severity of the injuries.

The orthopaedic subgroup noted that orthopaedic trauma methods have changed over the last decade and so some of the evidence published may not represent the methods and techniques currently used. This may have had an impact on the incidence of DVT in these studies. No statistical heterogeneity was found in the results.

Other considerations

When fractures are stabilised, bleeding risk generally decreases, but this might be accompanied by increasing thrombosis risk. It is difficult to determine the time point where the risk of thromboembolism exceeds the risk of bleeding in an individual patient based on the literature. This would require each individual to be assessed and monitored closely.

Although there are no studies with a nil prophylaxis arm it was noted that the incidence of VTE is very high in this group (risk of DVT was up to 37% even when VTE prophylaxis was used). Based on evidence in other groups, prophylaxis should be offered, unless outweighed by the risk of bleeding.

The orthopaedic subgroup felt that in some situations where a trauma patient is at increased risk of VTE but pharmacological prophylaxis is contraindicated due to bleeding risks and mechanical prophylaxis is contraindicated due to lower limb injury, the use of temporary inferior vena caval filters could be considered (Chapter 8).

There is little evidence available in terms of patients' views.

22.7.1 Other recommendations of relevance

The specific recommendations for patients with major trauma in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)
- patients being managed in a critical care setting (Section 29.7)

22.8 Summary of recommendations

- Offer combined VTE prophylaxis with mechanical and pharmacological methods to patients with major trauma. Regularly reassess the patient's risks of VTE and bleeding:
  - Start mechanical VTE prophylaxis at admission or as early as clinically possible. Choose any one of:
    - anti-embolism stockings (thigh or knee length), used with caution (see section 6.7)
    - foot impulse devices
    - intermittent pneumatic compression devices (thigh or knee length)

    Continue mechanical VTE prophylaxis until the patient no longer has significantly reduced mobility.
  - If the benefits of reducing the risk of VTE outweigh the risks of bleeding (see **Box 2**) and when the bleeding risk has been established as low, add pharmacological VTE prophylaxis. Choose one of:
    - LMWH
    - UFH (for patients with renal failure).

    Continue pharmacological VTE prophylaxis until the patient no longer has significantly reduced mobility.
- Regard **surgical patients and patients with trauma** as being at increased risk of VTE if they meet one of the following criteria:
  - surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb **or**
  - acute surgical admission with inflammatory or intra-abdominal condition **or**
  - expected significant reduction in mobility **or**
  - have one or more risk factors shown in **Box 1.**

Box 1 Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m^2)
- One or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
- Personal history or first-degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and 6 weeks post partum)

- Assess all patients for risk of bleeding before offering pharmacological VTE prophylaxis*. Do not offer pharmacological VTE prophylaxis to patients with any of the risk factors for bleeding shown in BOX 2, unless the risk of VTE outweighs the risk of bleeding.

* *Prescribers shouldconsult the summary of product characteristics for the pharmacological VTE prophylaxis being used or planned for further details.*

Box 2 Risk factors for bleeding

- Active bleeding
- Acquired bleeding disorders (such as acute liver failure)
- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with international normalised ratio[INR] higher than 2)
- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours
- Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours
- Acute stroke
- Thrombocytopenia (platelets less than 75 x 109/l)
- Uncontrolled systolic hypertension (230/120 mmHg or higher)
- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease)

23 General medical patients

23.1 Introduction

Although VTE is most often associated with surgery, 70-80% of hospital-acquired fatal pulmonary embolisms (PEs) occur in medical patients[192]. Apart from being an older cohort, 40% of medical patients have more than one risk factor for VTE, including previous VTE, cancer, stroke, heart failure, chronic obstructive airways disease, sepsis and bed rest. The baseline risk of VTE is estimated to be around 15% for those who are acutely unwell in medical beds[217], with risks rising to about 50-60% having been reported after severe stroke[335].

The risk of bleeding is different from surgical patients as medical patients by definition do not have the same open wounds however they are at similar risks of gastrointestinal haemorrhage. The use of thromboprophylaxis in medical patients provides an opportunity to greatly reduce the morbidity due to VTE, however the uptake of thromboprophylaxis in medical patients is poor and some studies report that the majority of patients are left unprotected[107,123].

23.2 Evidence of methods of prophylaxis

Eleven (11) randomised controlled trials which reported at least one of the three main outcomes (DVT, PE and major bleeding) were identified [45,121,141,191,256,257,350,387,390,395,579].

Another two studies did not report DVT, PE or major bleeding but reported all cause mortality and other outcomes[212,418].

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

23.2.1 Summary of comparisons identified for any main outcomes

	No prophylaxis	Post-discharge	GCS	IPCD/FID	Dabigatran	Fondaparinux	LMWH	UFH	VKA	Asp (HD)	Asp (LD)	GCS + IPCD/FID	Mech + pharm
GCS													
IPCD/													
Dabigatran													
Fondaparinux	**1**												
LMWH	**6**												
UFH	**1**						**5**						
VKA													
High dose aspirin													
Low dose aspirin													
GCS + IPCD/FID													
Mech + pharm													
Other comparisons													

Figure 23-44: Number of studies which compared various types of prophylaxis methods.

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicates areas where no studies were identified.

GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) - low dose aspirin (≤ 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis

23.2.2 Results from pairwise comparisons

Table 23-113: DVT – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
LMWH vs Nil[141,191,579]	3	29/488	63/479	0.46 (0.31, 0.70)	-0.06 (-0.10, -0.03)	ET: 26 FP: 13
Fondaparinux vs Nil[121]	1	18/321	29/323	0.62 (0.35, 1.10)	-0.03 (-0.07, 0.01)	ET: 25 FP: 9
Single proph vs single						
LMWH vs UFH[45,256,387]	3	11/738	15/742	0.79 (0.36, 1.73)	-0.01 (-0.02, 0.00)	ET: 32 FP: 48

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*

Proph - prophylaxis

Table 23-114: Symptomatic pulmonary embolism – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
LMWH vs nil[390,395,579]	3	8/2027	13/1986	0.61 (0.25,1.50)	0.00 (-0.01, 0.00)	ET: 26 FP: 14
Fondaparinux vs Nil[121]	1	4/425	11/414	0.35 (0.11, 1.10)	-0.02 (-0.04, 0.00)	ET: 25 FP: 10
Single proph vs single						
LMWH vs UFH[45,257,350,387]	4	4/1698	7/1651	0.72 (0.16, 3.25)	0.00 (-0.01, 0.00)	ET: 32 FP: 49

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

Table 23-115: Major bleeding – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
LMWH vs nil[191,390,395,579]	4	29/2367	18/2355	1.61 (0.79, 3.26)	0.00 (-0.01, 0.02)	ET: 26 FP: 15
Fondaparinux vs Nil[121]	1	1/425	1/414	0.97 (0.06, 15.52)	0.00 (-0.01, 0.01)	ET: 25 FP: 11
Single proph vs single						
LMWH vs UFH[45,256,257,350,387]	5	9/1924	15/1901	0.64 (0.27,1.49)	0.00 (-0.01, 0.00)	ET: 32 FP: 50

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

23.2.3 Additional information

23.2.3.1 All cause mortality

Table 23-116: All cause mortality summary from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables*
Proph vs no proph						
UFH vs nil[212]	1	304/5776	333/5917	0.94; (0.80, 1.09)	0.00 (-0.01, 0.00)	ET: 27 FP: 20
LMWH vs nil[141,191,390,395,418,577]	6	171/3819	179/3825	0.97 (0.79, 1.18)	0.00 (0.00, 0.00)	ET: 26 FP: 16
Fondaparinux vs Nil[121]	1	14/425	25/414	0.55 (0.29, 1.03)	-0.03 (-0.06, 0.00)	ET: 25 FP: 12
Single proph vs single						
LMWH vs UFH[45,256,257,350,387]	5	49/1924	42/1901	1.12 (0.54, 2.35)	0.00 (-0.02, 0.02)	ET: 32 FP: 51

** FP – forest plot number in appendix E; ET – evidence table number in appendix D.*
Proph - prophylaxis

23.2.3.2 Composite venous thromboembolism outcomes

Composite venous thromboembolism was reported as the primary outcome in five studies [45,121,350,395,579]. The results obtained using composite VTE outcomes were consistent with

the PE and DVT data reported separately and did not change the conclusions of the study.

23.2.3.3 Other outcomes

No studies reported chronic thromboembolic pulmonary hypertension or post thrombotic syndrome. One study reported on the incidence of heparin induced thrombocytopenia[45] but found no significant difference between the group receiving LMWH and the group receiving UFH (1/233 and 0/216 respectively).

23.3 Network meta-analysis results

23.3.1 Introduction

A network meta-analysis was completed for DVT, symptomatic pulmonary embolism and major bleeding. Details on the network meta-analysis methods can be found in section 3.10.

23.3.2 Results

DVT results

There were 7 studies included in the network meta-analysis for DVT [45,121,141,191,256,387,579].

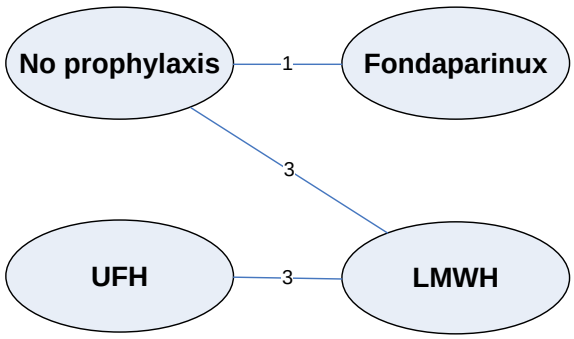


Figure 23-45: Network diagram for DVT. Numbers indicate the number of studies which contributed results for each comparison

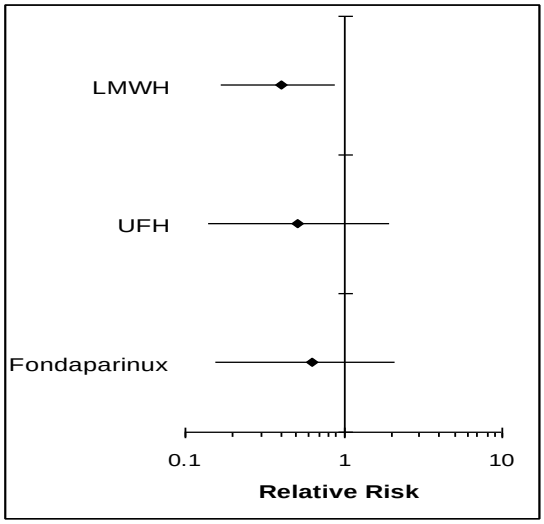


Figure 23-46: DVT – network meta-analysis results of interventions compared to no prophylaxis

Table 23-117: DVT – network meta-analysis results

Intervention (compared with no prophylaxis)	Relative Risk (95% credible intervals)
LMWH	0.40 (0.17, 0.89)
UFH	0.52 (0.14, 1.96)
Fondaparinux	0.63 (0.16, 2.10)

Credible intervals are the Bayesian equivalent of confidence intervals.
The residual deviance was 12.7, which is quite close to the number of data points of 14, suggesting that the model fits the data well.

Symptomatic PE results

There were 8 studies included in the network meta-analysis for symptomatic PE [45,121,257,350,387,390,394,579].

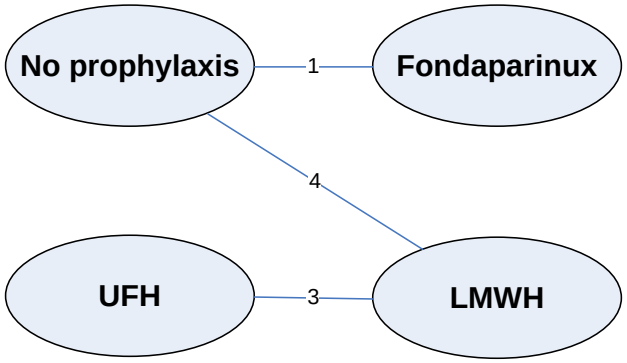


Figure 23-47: Network diagram for symptomatic pulmonary embolism. Numbers indicate the number of studies which contributed results for each comparison

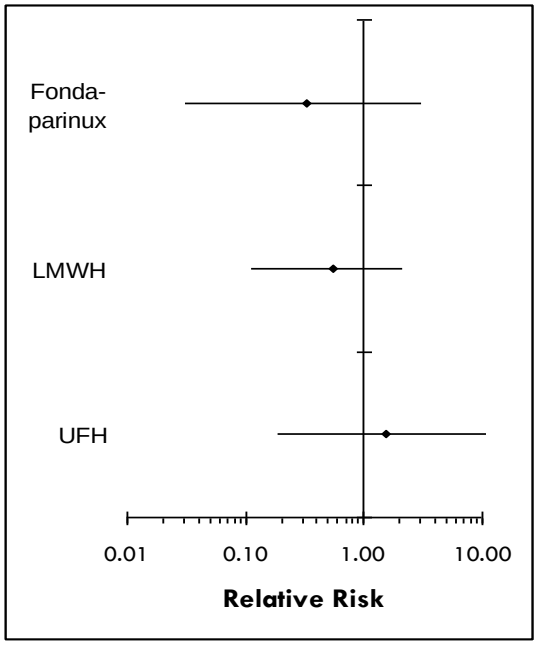


Figure 23-48: Symptomatic pulmonary embolism – network meta-analysis results of interventions compared to no prophylaxis

Table 23-118: Symptomatic pulmonary embolism – network meta-analysis results

Intervention (compared with no prophylaxis)	Relative Risk (95% credible intervals)
Fondaparinux	0.33 (0.03, 3.08)
LMWH	0.56 (0.11, 2.13)
UFH	1.55 (0.19, 13.80)

Credible intervals are the Bayesian equivalent of confidence intervals.
The residual deviance was16.3, which is quite close to the number of data points of 16, suggesting that the model fits the data well

Major bleeding results

A network meta-analysis for major bleeding was conducted using studies across hip fracture surgery, hip replacement surgery, knee replacement surgery, general medical patients and general surgical patients.

One hundred and twenty eight (128) studies were included in the analysis of which:

- 10 studies were in **medical patients**[45,121,191,256,257,350,387,390,394,579],
- 48 studies were in **general surgery patients**[10,14,29,40,50,52,72,75,76,92,113,199,210,227,230,238,262,266,267,269,280,283,321,324,329,358,366,385,439,496,499,503,504,516,517,530,552,553,570,575,588,589,633,639,641,645,657,667,703,711,713],
- 28 studies were in **elective hip replacement patients**[126,129,151,153,174,188,195,201,202,243,260,293,299,377,380,400,409,421,465,527,573,574,635,650,651,659,684],
- 9 studies were in patients undergoing **hip fracture surgery** [175,178,204,248,463,533,609,704,715]
- 15 studies were in **elective knee replacement patients** [36,66,130,186,201,202,274,388,389,399,436,476,479].
- 7 studies were in **mixed orthopaedic surgery patients**[69,200,242,250,292,459,531]
- 11 studies were in **mixed surgery patients** [54,166,270,271,340-344,396,416,486,568,569,575,585,655].

Seven of these studies included three comparison arms[153,299,380,504,533,633,655].

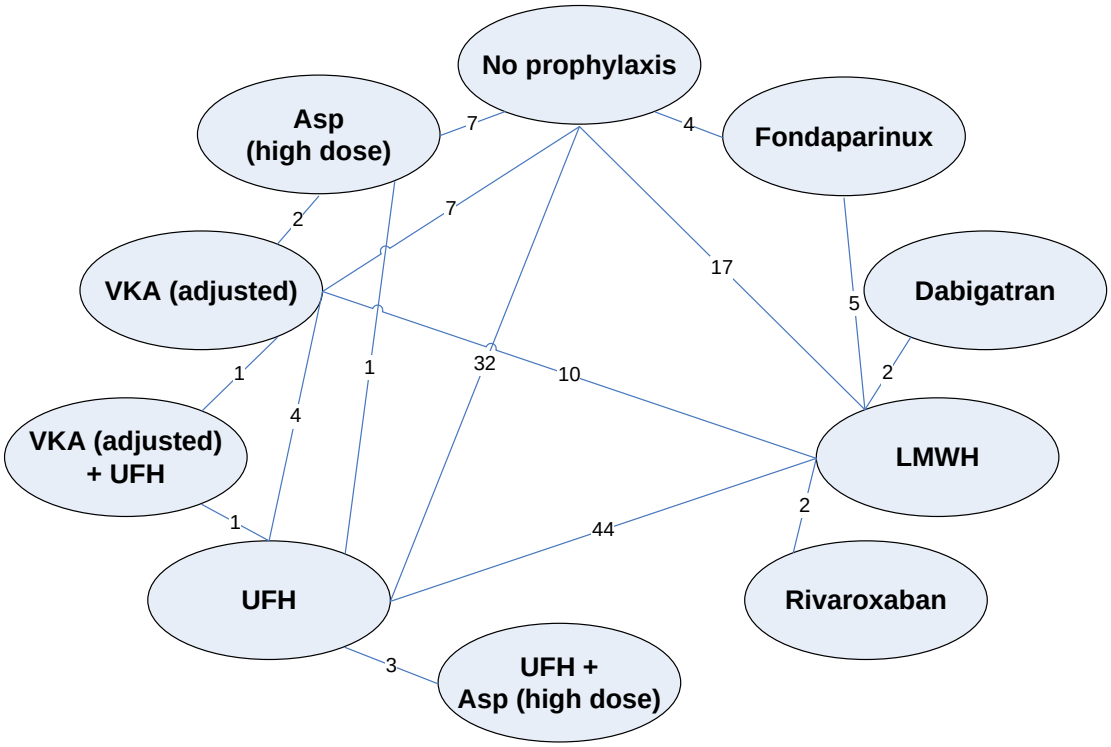


Figure 23-49: Network diagram for major bleeding. Numbers indicate the number of studies which contributed results for each comparison

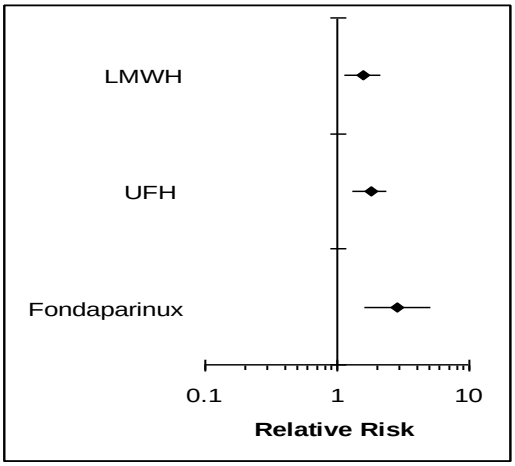


Figure 23-50: Major bleeding – network meta-analysis results of interventions compared to no prophylaxis (pooled across all population subgroups)*

Table 23-119: Major bleeding – network meta-analysis results (pooled across all population subgroups) *

Intervention (compared with no prophylaxis)	Relative Risk (95% credible intervals)
LMWH	1.57 (1.16, 2.16)
UFH	1.79 (1.34, 2.43)
Fondaparinux	2.85 (1.62, 5.22)

Credible intervals are the Bayesian equivalent of confidence intervals.
The residual deviance was 291.5, which is quite close to the number of data points of 263, suggesting that the model fits the data well.

* Only the results for interventions included in the network meta-analysis for DVT were shown included in Figure 23-50 and

Table 23-119.

All cause mortality

Twelve studies were included in the analysis of all cause mortality[45,121,141,191,212,256,257,387,390,394,418,579].

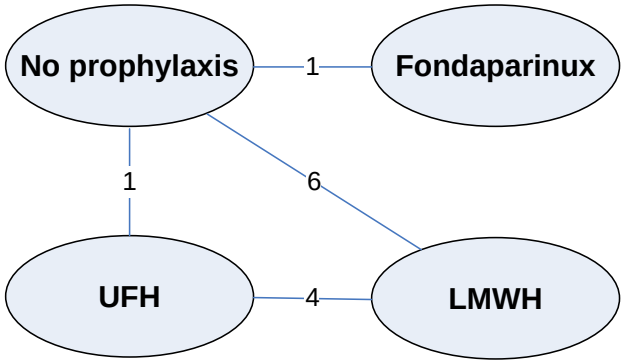


Figure 23-51: Network diagram for all cause mortality. Numbers indicate the number of studies which contributed results for each comparison

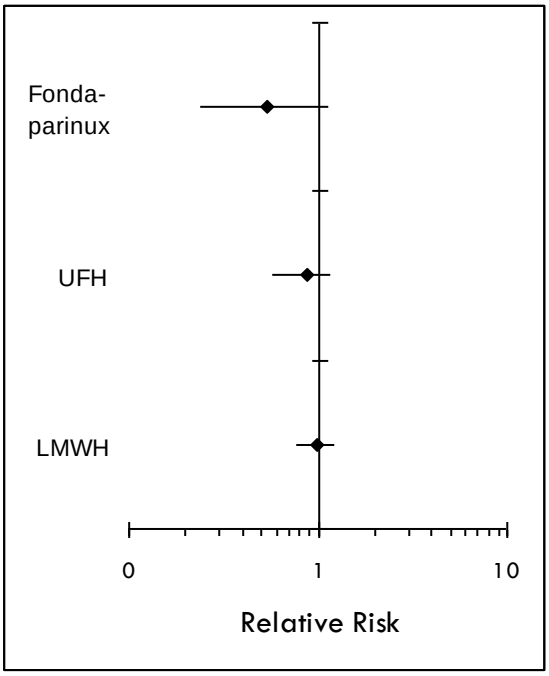


Figure 23-52: All cause mortality – network meta-analysis results of interventions compared to no prophylaxis

Table 23-120: All cause mortality– network meta-analysis results

Intervention (compared with no prophylaxis)	Relative Risk (95% credible intervals)
Fondaparinux	0.54 (0.24, 1.14)
UFH	0.87 (0.58, 1.16)
LMWH	0.99 (0.78, 1.24)

Credible intervals are the Bayesian equivalent of confidence intervals.
The residual deviance was 22.5, which is quite close to the number of data points of 24, suggesting that the model fits the data well.

23.4 Cost-effectiveness evidence

23.4.1 Introduction

General assumptions and methods for model are described in chapter 4.

Data used for the cost-effectiveness analysis which were specific to medical patients can be found in Table 23-121 and Table 23-122.

Table 23-121: Baseline risk and other population specific parameters used in the economic model for general medical patients

Baseline Characteristics	*Source*	*Value*
Mean age (years)	Systematic review of RCTs (a) (weighted mean)	74
% Male	Systematic review of RCTs (a)	47%
Standardised Mortality Ratio (b)	Mortality rate = 15.3% [277](c)	357% (1 year)
Mean duration of prophylaxis	Systematic review of RCTs (a)	10 days
Proportion of DVTs that are symptomatic (Ratio of symptomatic DVTs to all DVTs)	Systematic review of RCTs (a)	6.2% (40/644)
Major Bleed Fatality Rate (d)	Systematic review of RCTs (a)	14.3% (8/56)
PE Fatality Rate (e)	Systematic review of RCTs (a)	44.7% (17/38)
DVT risk	No prophylaxis/placebo arms of RCTs from systematic review (a)	13.4%
Symptomatic PE risk		0.9%
Major bleeding risk		0.4%

(a) *This refers to the systematic review of RCTs for the current guideline*
(b) *Ratio of the death rate in the surgical group compared with the death rate in the general population, adjusting for age and sex*
(c) *Rate calculated from the mortality rate for general medical patients at 1 year (Herrman Lingen (2001) [277]) divided by death rate in the general population matched for age and gender. (Office of National statistics (2005)[500].*
(d) *Fatal major bleeds divided by all major bleeds*
(e) *Fatal PEs divided by all symptomatic PE*

Table 23-122: Weights used for events in the base case analysis

Event	Cost (£)	QALYs lost	Net loss (£) (a)
DVT Asymptomatic	0	0.0000	0
DVT Symptomatic	576	0.0035	645
Post-thrombotic syndrome	5,818	0.1492	8,803
Chronic pulmonary hypertension	69,123	3.9706	148,536
Pulmonary embolism - fatal	0	7.3079	146,157
Pulmonary embolism - symptomatic	2,521	0.0041	2,603
Major bleeding - No long-term sequalae	722	0.0267	1,255
Major bleeding - Stroke	23,691	5.2444	128,579
Major bleeding - fatal	0	7.3079	146,157
Heparin-induced thrombocytopaenia (sensitivity analysis only)	2,512	1.0891	24,294

(a) Net loss is the sum of the resource cost plus the QALY loss:
Net loss=cost+ (20,000 x QALYs lost)

23.4.2 Results: standard duration prophylaxis

23.4.2.1 Base case results

Event rates by strategy can be found in Appendix G.

Table 23-123: Base case results – deterministic and probabilistic results

Intervention (ordered by mean probabilistic INB)	*Deterministic INB*	*Probabilistic INB*	
	Mean	*Mean*	*% of simulations where strategy was most cost effective*
LMWH	329	328	72.3%
UFH	118	116	17.7%
Nil	0	0	1.7%
Fondaparinux	-61	-58	8.3%

INB = Incremental Net Benefit. The strategy with the highest probabilistic mean INB is the most cost effective overall

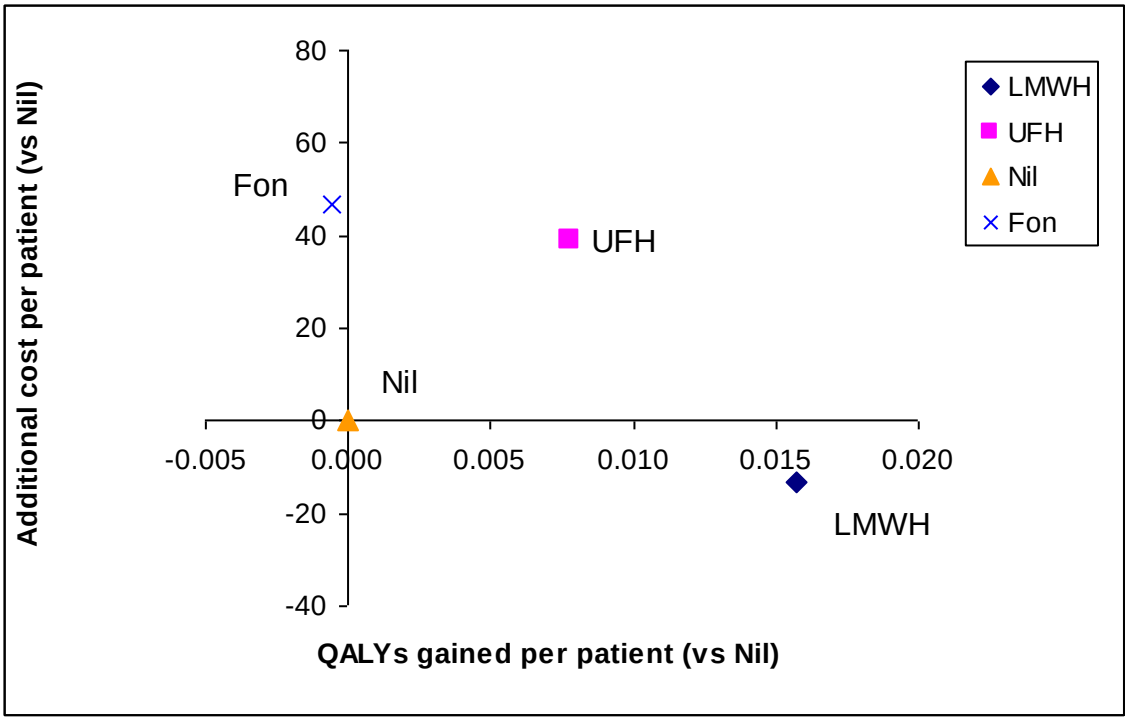


Figure 23-53: Base case results of the cost effectiveness analysis for medical patients (probabilistic analysis)

Fon = fondaparinux; UFH = Unfractionated Heparin, LMWH = Low molecular weight heparin

23.4.2.2 Deterministic sensitivity analysis

Table 23-124: Deterministic sensitivity analysis results

Factors changed within the Model	*Most Cost Effective Strategy*
Base case	LMWH
Base case (probabilistic)	LMWH
Chronic Thromboembolic Pulmonary Hypertension and Post Thrombotic Syndrome	
0% Chronic Thromboembolic Pulmonary Hypertension	LMWH
0.5% Chronic Thromboembolic Pulmonary Hypertension	LMWH
1% Chronic Thromboembolic Pulmonary Hypertension	LMWH
0% Chronic Thromboembolic Pulmonary Hypertension and 0% Post Thrombotic Syndrome	LMWH
High Post Thrombotic Syndrome rate (e.g. 30% after symptomatic DVT and 21% after asymptomatic DVT)	LMWH
Low Post Thrombotic Syndrome (e.g. 15% after symptomatic DVT and 8% after asymptomatic DVT)	LMWH
Low cost for Post Thrombotic Syndrome	LMWH
High cost for Post Thrombotic Syndrome	LMWH
High cost for Chronic Thromboembolic Pulmonary Hypertension	LMWH
Other Sensitivity Analyses	
Include Heparin Induced Thrombocytopenia (LMWH=0.8%, UFH=0.8%)	LMWH
Reduced incidence of Heparin Induced Thrombocytopenia (LMWH=0.2%, UFH=2.6%)	LMWH
Using PE relative risk for symptomatic PE and not DVT relative risk	LMWH
Using population specific major bleeding relative risks	LMWH
Discounted LMWH cost = £1	LMWH
Fatality after PE = 10%	LMWH
Fatality after Major Bleeding = 5%	LMWH
Increased NICE threshold (£30,000/ QALY)	LMWH

Table 23-125: Deterministic results, by baseline risk of pulmonary embolism and major bleeding

		Major bleeding risk												
		0%	0.5%	1%	1.5%	2%	2.5%	3%	3.5%	4%	4.5%	5%	5.5%	6%
PE risk	0%	LMWH	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
	0.5%	LMWH	LMWH	LMWH	LMWH	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
	1%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	Nil	Nil	Nil	Nil	Nil	Nil	Nil
	1.5%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	Nil	Nil	Nil	Nil
	2%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	Nil	Nil
	2.5%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
	3%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
	3.5%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
	4%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
	4.5%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
	5%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
	5.5%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH
	6%	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH	LMWH

We considered in a threshold sensitivity analysis what would happen if patients discharged early received their prophylaxis at home. We found that even if every patient required district nurse visits to deliver their prophylaxis, LMWH was still cost-effective.

23.4.3 Conclusion of cost-effectiveness analysis

The cost effective analysis for general medical patients indicates that LMWH is the most effective and most cost effective strategy followed by unfractionated heparin. Fondaparinux was less effective than no prophylaxis in the base case, due to the increase in major bleeding.

LMWH remained the most cost effective in all of the deterministic sensitivity analyses completed.

23.5 Patient views

There is a lack of patient views evidence from medically ill patients about thromboprophylaxis. Therefore, patient views of thromboprophylaxis in this group could only be inferred from other populations. A recent qualitative study conducted in the United Kingdom among cancer patients receiving palliative care showed acceptability of thromboprophylaxis. This study found that patients were aware of the purpose of subcutaneous LMWH thromboprophylaxis. They balanced the potential benefit of venous thromboembolism reduction against potential side effects (bruising was quoted) and found it acceptable [492].

For patient views about specific prophylaxis agents, see section 6.6 Patient views.

23.6 Summary of evidence

Table 23-126: Summary of evidence from network meta-analysis results for DVT, symptomatic pulmonary embolism and major bleeding outcomes.

Intervention(s)	*Comparison(s)*	*Intervention favoured*		
		DVT	**PE**	**MB**
Prophylaxis vs no prophylaxis				
UFH	No prophylaxis	Not sig	Not sig	Not sig
LMWH	No prophylaxis	**LMWH**	Not sig	Not sig
Fondaparinux	No prophylaxis	Not sig	Not sig	Not sig
Cost-effectiveness				
In the base case cost effectiveness analysis using probabilistic analysis, LMWH is the most cost-effective strategy, followed by unfractionated heparin.				
LMWH remained the most cost effective in all of the deterministic sensitivity analyses.				

The prophylaxis strategy which is significantly more effective in reducing DVT or PE; or resulting in significantly less major bleeding is stated in bold.
Not sig - not statistically significant difference; no events – nobody in the study had the outcome. MB = Major bleeding

23.7 Recommendations and link to evidence

Recommendation	**Offer pharmacological VTE prophylaxis to general medical patients assessed to be at increased risk of VTE. Choose any one of:** • **fondaparinux sodium** • **LMWH*** • **UFH (for patients with renal failure).** **Start pharmacological prophylaxis as soon as possible after risk assessment has been completed. Continue until the patient is no longer at increased risk of VTE.** ****At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for of label use should be obtained and documented.***
Recommendation –from section 5.9	**Regard medical patients as being at increased risk of VTE if they:** • **have had or are expected to have significantly reduced mobility for 3 days or more, or** • **are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors shown in Box 1.**

Box 1 – Risk Factors for VTE	• **Active cancer or cancer treatment** • **Age over 60 years** • **Critical care admission** • **Dehydration** • **Known thrombophilias** • **Obesity (BMI over 30 kg/m²)** • **One or more significant medical comorbidities (for example: heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)** • **Personal history or a first degree relative with a history of VTE** • **Use of hormone replacement therapy** • **Use of oestrogen-containing contraceptive therapy** • **Varicose veins with phlebitis.** **For women who are pregnant for have given birth within the previous 6 weeks please refer to recommendations in Chapter 30 (Pregnancy and up to 6 weeks post partum)**
Relative values of different outcomes	The outcomes included in the economic model were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome). Each of these events had a cost and loss of quality adjusted life year associated with it, the details of which are provided in the methods of cost effectiveness chapter (chapter 4).
Trade off between clinical benefit and harms	The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of major bleeding in the economic model. Our decision model indicated that the QALYs lost due to major bleeding were outweighed by the QALYs gained from drug prophylaxis.
Economic considerations	An original cost-effectiveness analysis was conducted for medical patients. The cost effectiveness analysis for general medical patients indicates that LMWH is the most effective and most cost effective strategy followed by unfractionated heparin. Lower risk patients are often not included in trials. It was felt by the Guideline Development Group that for those medical

patients who are soon mobile and do not have predisposing risk factors, the risk of VTE was too low for prophylaxis to be cost-effective.

Quality of evidence

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

Only LMWH was demonstrated to be statistically significant in reducing the risk of DVT compared to no prophylaxis among general medical patients. The efficacy of UFH and fondaparinux were not statistically significant. It is unclear whether the sample sizes were powered to demonstrate a difference. However, there was a trend that these prophylactic methods reduce the risk of DVT and PE compared to no prophylaxis. Their efficacy could be also be inferred from studies conducted in surgical patients.

Directness of evidence obtained was a concern due to the strict inclusion criteria used in many of the clinical trials. There are only a small number of trials identified in medical patients and generally the inclusion criteria was narrow, including only patients with acute medical illness with a hospital stay of at least 3 days and often with severely limited mobility. Many studies excluded patients with an increased risk of bleeding.

Other considerations

Alternative thromboprophylaxis options were listed so that individual patient factors could be taken into account when selecting an appropriate prophylaxis agent. For example, some patients may have concerns about using a product of animal origin. If this is a concern, a synthetic product such as fondaparinux may be appropriate.

Although UFH is seldom used, it will be a useful alternative for patients with renal failure.

There is a lack of information about patient views on the acceptability or preference of thromboprophylaxis agents in this population. It is also unclear how thromboprophylaxis strategies impact on patient's quality of life. A qualitative study which had been conducted in UK among palliative care patients showed that patients found LMWH acceptable and a component of care.

Despite the recognition of specific risk factors it is impossible to predict exactly within a group at risk, which individual will have a VTE. Therefore in the view of the Guideline Development Group, the standard approach should be to administer thromboprophylaxis to all those at increased risk.

Recommendation	**Consider offering mechanical VTE prophylaxis to medical patients in whom pharmacological prophylaxis is contraindicated. Choose any one of:** • **anti-embolism stockings (thigh or knee length)** • **foot impulse devices** • **intermittent pneumatic compression devices (thigh or knee length)**
Relative values of different outcomes	The Guideline Development Group considered that it was a priority to reduce the risk of death from PE and to prevent long term morbidity from DVT such as post thrombotic syndrome. The main consideration for this recommendation is ensuring some measure of thromboprophylaxis is provided for patients at increased risk of VTE but who are also at an increased of bleeding.
Trade off between clinical benefit and harms	For mechanical methods (IPCD, FID and anti-embolism stockings) it is unclear whether the benefits outweigh the risks in general medical patients because RCT evidence in this group is lacking. For anti-embolism stockings, there is even greater uncertainty about the benefit vs risk trade off than IPCDs and FIDs. Although shown to be effective in surgical patients (Chapter 9), it was shown to be ineffective in stroke patients and associated with cutaneous adverse reactions (Chapter 24). Although evidence from stroke patients cannot be directly applied to medical patients, neither can it be ignored. The benefits are more likely to outweigh the harms in patients that aren't receiving other forms of prophylaxis.
Economic considerations	Mechanical methods of prophylaxis were not considered in the economic model because there were no suitable trials in medical patients. Such methods are highly cost-effective for general surgery patients when compared with no prophylaxis and are not associated with increased bleeding (Chapter 9). However anti-embolism stockings have been shown to be ineffective and harmful in stroke patients (Chapter 24). We think it possible that they would be cost-effective in medical patients who are at elevated risk of VTE (in the absence of drug prophylaxis).

Quality of evidence

No studies which investigated anti-embolism stockings, intermittent pneumatic compression devices or foot impulse devices in general medical patients were found.

Randomised controlled trials in surgical populations showed that these methods are effective at reducing venous thromboembolism without an associated increase in bleeding.

The following are the evidence available in non-surgical patients:

Foot impulse devices and intermittent pneumatic pump devices:

- Stroke patients: a very small RCT with total of 26 patient, and two RCTs in patients who also used GCS all showed no significant difference.

Anti-embolism stockings:

- Acute coronary syndrome: One RCT (n=160) showed no significant difference in DVT risk reduction.
- Stroke: Two RCTs were found and both showed no significant difference in effectiveness. One of these, a large multi-centred RCT with 2518 participants, showed increased risks of cutaneous adverse events.

Other considerations

Because there was uncertainty about the trade off between risk and benefits in these methods, the GDG deliberated at great length whether a recommendation should be made about mechanical prophylaxis in medical patients.

However, the GDG considered that the absence of any recommendations for medical patients at increased risk of VTE but contraindicated to pharmacological prophylaxis may result in variations of practice and may result in some high risk patients going without thromboprophylaxis. Therefore, a decision was made to make a cautious recommendation that clinicians should consider one of the three forms of mechanical prophylaxis (including anti-embolism stockings) in medical patients contraindicated to pharmacological prophylaxis. The decision was not unanimous but it was the majority decision of the GDG.

The GDG were unanimous that this is an area where research is needed.

23.7.1 Other recommendations of relevance

The specific recommendations for general medical admissions in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)

- the provision of patient information (Section 32.5)

23.8 Recommendations for research

23.8.1 Pharmacological and mechanical prophylaxis in a broader population of medical patients:

The Guideline Development Group recommended the following research question:

- What is the clinical and cost effectiveness of pharmacological prophylaxis, mechanical prophylaxis and combined pharmacological and mechanical prophylaxis for reducing the risk of VTE in medical patients?

Why this is important

Only a small number of trials with medical patients were identified and generally the inclusion criteria were narrow, for example, patients with an acute medical illness, with a hospital stay of more than 5 days, and often with severely limited mobility. Further research into less severely ill patient groups would be beneficial.

The evidence concerning mechanical prophylaxis in medical patients is sparse. There have been a few small trials of patients with coronary syndrome but the only large, randomised controlled trial was of patients with stroke. This trial showed that routine care plus thigh-length anti-embolism stockings did not confer significantly more protection against VTE than routine care alone and was associated with significantly more harm. All of these trials included large proportions of patients who were taking aspirin, which may have influenced the results.

New trial(s) should investigate the benefits of reducing the risk of VTE balanced against the risk of bleeding. The trial(s) should compare pharmacological prophylaxis alone, mechanical prophylaxis alone, and combined mechanical and pharmacological prophylaxis. The benefit of extended-duration prophylaxis in medical patient groups may also be investigated.

Recommended design: RCT

Further details are provided in Appendix F

23.9 Summary of recommendations

- Offer pharmacological VTE prophylaxis to general medical patients assessed to be at increased risk of VTE (see Section 5.9). Choose any one of:
  - fondaparinux sodium
  - LMWH*
  - UFH (for patients with renal failure)

  Start pharmacological prophylaxis as soon as possible after risk assessment has been completed. Continue until the patient is no longer at increased risk of VTE.

  ** At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off label use should be obtained and documented.*

- Regard medical patients as being at increased risk of VTE if they:
  - have had or are expected to have significantly reduced mobility for 3 days or more ***or***
  - are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors shown in **Box1**.

Box 1 Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m^2)
- One or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
- Personal history or first-degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum).

- Consider offering mechanical VTE prophylaxis to medical patients in whom pharmacological prophylaxis is contraindicated. Choose any one of:
  - anti-embolism stockings (thigh or knee length)
  - foot impulse devices
  - intermittent pneumatic compression devices (thigh or knee length)

24 Stroke patients

24.1 Introduction

Recent stroke has been associated with an increased developing venous thromboembolism (VTE) [217]. Reasons for this increased risk of VTE is thought to be due to the alteration in blood flow as a results of the weakness in the affected limb, possibly leading to vessel wall injury, and a resulting hypercoagulable state related to changes in the blood after stroke[236]. A wide range of VTE incidence has been reported for stroke patients with estimates of between 15-60%[18,120]. Diagnosing DVT after stroke may be difficult as symptoms may be similar to those related to the stroke such as leg swelling[236]. One study[149] reviewed stroke patients 6 months after onset and found that patients who developed a DVT after stroke had a statistically significant poorer outcome, using a modified Rankin score, compared to those who did not develop DVT.

Stroke is divided into two main types; ischaemic stroke caused by blood clots preventing blood flow to the brain and haemorrhagic stroke caused by bleeding into/of the brain. Both types of stroke are associated with an increased risk of VTE[236]. NICE published guidelines in 2008 for the diagnosis and acute management of stroke and transient ischaemic attacks[477].

24.2 Evidence of methods of prophylaxis

24.2.1 Summary of comparisons identified for any outcome

Seventeen (17) studies were identified that considered the interventions under consideration for stroke patients [35,157,158,165,167,240,278,369,434,435,466,509,520,538,540,581,598]. Of these, 2 studies were three arm trials [509,520]. Only studies using prophylactic-doses were included.

Only three of these studies included haemorrhagic stoke patients [158,434,435] all other patients were ischaemic stroke patients.

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

Although it is likely that many patients within a large RCT of thigh length anti-embolism stockings vs no stockings s[158] were treated with aspirin, the authors have not provided this information in the paper published for the study. For this reason the results of the

study have been reported as 'GCS vs. no prophylaxis' rather than 'GCS + aspirin vs. aspirin'.

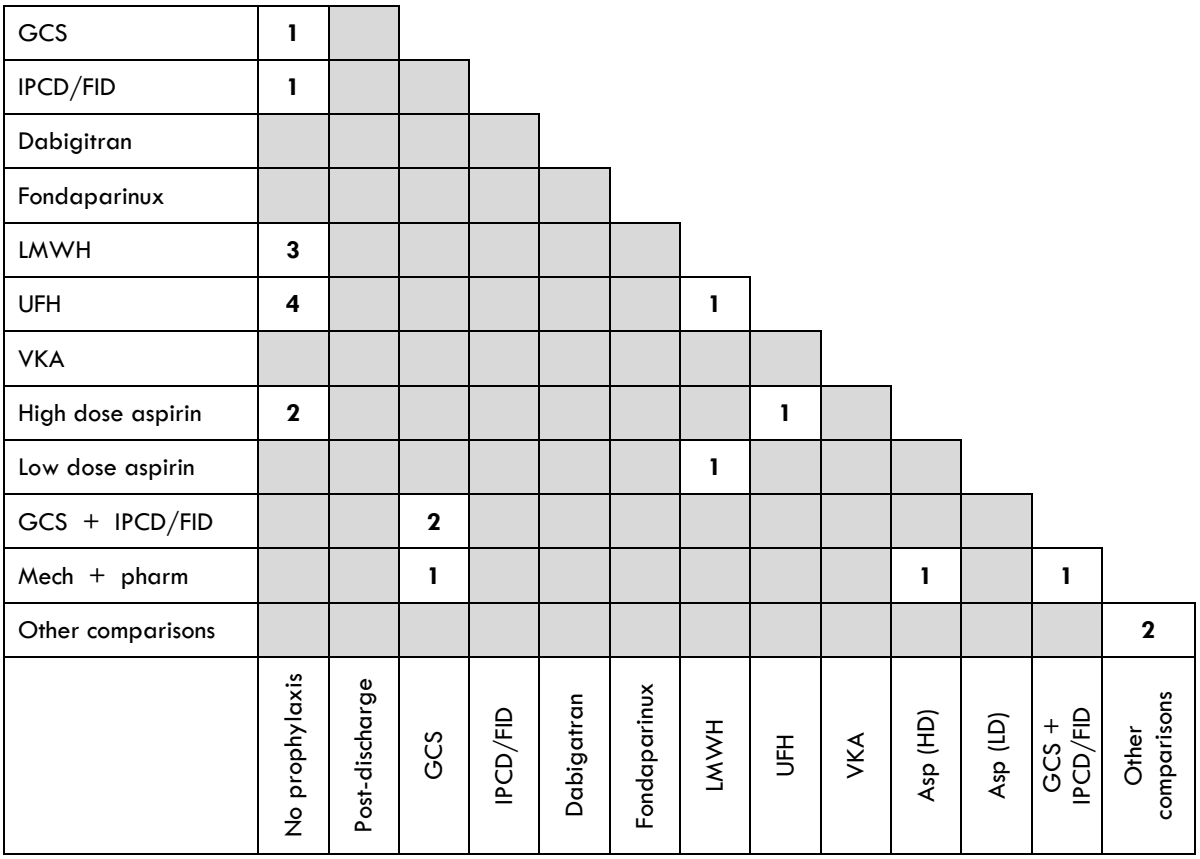


Figure 24-54: Number of studies which compared various types of prophylaxis methods.

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicates areas where no studies were identified.

GCS – anti-embolism /graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) - low dose aspirin (≤ 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis

24.2.2 Results from pairwise comparisons

Table 24-127: DVT – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
GCS vs nil [158]	1	205/1256	224/1262	0.92 (0.77,1.09)	-0.01 (-0.04,0.02)	ET: 23 FP: 1
IPCD/FID vs nil [538]	1	6/13	6/13	1.00 (0.44, 2.29)	0.00 (-0.38, 0.38)	ET: 24 FP: 4
LMWH vs nil [240,540,581]	3	23/89	36/110	0.74 (0.40, 1.35)	-0.08 (-0.25, 0.08)	ET: 26 FP: 13
UFH vs nil [167,434,435,520]	4	41/238	146/243	0.31 (0.23, 0.41)	-0.35 (-0.61, -0.09)	ET: 27 FP: 17
Asp (high dose) vs nil [157,520]	2	9/54	21/54	0.43 (0.22, 0.85)	-0.22 (-0.38. -0.06)	ET: 29 FP: 28

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Pharm vs pharm						
LMWH vs UFH [278]	1	14/76	24/72	0.55 (0.31, 0.98)	-0.15 (-0.29, -0.01)	ET: 32 FP: 48
Asp (high dose) vs UFH [520]	1	6/35	7/40	0.98 (0.36, 2.64)	0.00 (-0.18, 0.17)	ET: 36 FP: 64
Double proph vs single						
GCS + aspirin vs aspirin [466]	1	7/65	7/32	0.49 (0.19, 1.28)	-0.11 (-0.25, 0.05)	ET: 38 FP: 114
IPCD/FID + GCS vs GCS [369,509]	2	11/181	17/184	0.65 (a) (0.15, 2.81)	-0.04 (-0.17, 0.09)	ET: 39 FP: 117
UFH + GCS vs GCS [509]	1	5/120	6/115	0.80 (0.25, 2.54)	-0.01 (-0.06, 0.04)	ET: 27 FP: 142
Other strategies						
LMWH + Asp vs UFH + Asp [165,598]	1	67/666	118/669	0.57 (0.43, 0.75)	-0.08 (-0.11, -0.04)	ET: 45 FP: 184
IPCD/FID + GCS vs UFH + GCS [509]	1	8/117	5/120	1.64 (0.55, 4.87)	0.03 (-0.03, 0.08)	ET: 50 FP: 200

** FP – forest plot number in appendix E; ET – evidence table number in appendix D. Proph - prophylaxis*

a) *There is substantial statistical heterogeneity between studies for this population (I^2=70.3%, χ^2 on1 df = 3.37, p= 0.07)*

Table 24-128: Pulmonary embolism – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
GCS vs nil [158]	1	13/1256	20/1262	0.65 (0.33,1.31)	-0.01 (-0.01,0.00)	ET: 23 FP: 2
Asp (high dose) vs nil [520]	1	1/40	0/40	3.00 (0.13,71.51)	0.03 (-0.04. 0.09)	ET: 29 FP: 29
Pharm vs pharm						
LMWH vs UFH [278]	1	2/106	4/106	0.50 (0.09, 2.67)	-0.02 (-0.06, 0.03)	ET: 32 FP: 49
LMWH vs Asp (low dose) [35]	1	4/507	4/491	0.97 (0.24, 3.85)	0.00 (-0.01, 0.01)	ET: 36 FP: 52
Double proph vs single						
GCS + aspirin vs aspirin [466]	1	0/65	0/32	Not estimable	0.00 (-0.05, 0.05)	ET: 38 FP: 115
IPCD/FID + GCS vs GCS [369]	1	0/64	0/69	Not estimable	0.00 (-0.03, 0.03)	ET: 39 FP: 118
Other strategies						
LMWH + Asp vs UFH + Asp [165,598]	2	1/938	7/942	0.21 (0.04, 1.21)	-0.01 (-0.01, 0.00)	ET: 45 FP: 185

** FP – forest plot number in appendix E; ET – evidence table number in appendix D. Proph - prophylaxis*

Table 24-129: Major bleeding – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
LMWH vs nil [540,581]	2	8/74	4/77	2.21(a) (0.69, 7.00)	0.06 (-0.08, 0.20)	ET: 26 FP: 15
UFH vs nil [167]	1	0/35	0/30	Not Estimable	0.00 (-0.06, 0.06)	ET: 27 FP: 19
Pharm vs pharm						
LMWH vs UFH [278]	1	1/106	0/106	3.00 (0.12,72.82)	0.01 (-0.02, 0.04)	ET: 32 FP: 50
Other strategies						
LMWH + Asp vs UFH + Asp [165,598]	2	14/1149	11/ 1145	1.18 (a) (0.41, 3.41)	0.00 (-0.01, 0.01)	ET: 45 FP: 186

** FP – forest plot number in appendix E; ET – evidence table number in appendix DProph - prophylaxis*

a) There is some evidence of statistical heterogeneity (I^2=36.3%, χ^2 on 1df = 1.57, p = 0.21)

24.2.3 Additional information

24.2.3.1 All cause mortality

Table 24-5: All cause mortality – summary of results from RCTs

Comparison	No. of studies	Intervent-ion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables*
Proph vs no proph						
GCS vs nil [158]	1	122/ 1256	110/ 1262	1.11 (0.87, 1.42)	0.01 (-0.01, 0.03)	ET: 23 FP: 3
LMWH vs nil [240,540,581]	3	15/102	5/111	2.75 (1.11, 6.83)	0.08 (0.01, 0.14)	ET: 26 FP: 16
UFH vs nil [167,434,435,520]	4	44/235	64/247	0.83 (0.44, 1.55)	-0.04 (-0.14, 0.06)	ET: 27 FP: 20
Asp (high dose) vs nil [520]	2	7/40	5/40	1.40 (0.48, 4.04)	0.05 (-0.11, 0.21)	ET: 29 FP: 31
Pharm vs pharm						
LMWH vs UFH [278]	1	9/106	8/106	1.13 (0.45, 2.80)	0.01 (-0.06, 0.08)	ET: 32 FP: 51
Asp (high dose) vs UFH [520]	1	7/40	10/40	0.70 (0.30, 1.66)	-0.08 (-0.25, 0.10)	ET: 36 FP: 67
Double proph vs single						
GCS + aspirin vs aspirin [466]	1	9/65	4/32	1.11 (0.37, 3.32)	0.01 (-0.13, 0.16)	ET: 38 FP:116
IPCD/FID + GCS vs GCS [369,509]	2	15/191	24/192	0.65 (0.37, 1.14)	-0.05 (-0.41, 0.30)	ET: 39 FP: 119
UFH + GCS vs GCS [509]	1	0/120	0/115	Not Estimable	0.00 (-0.02, 0.02)	ET: 27 FP: 145
Other strategies						
LMWH + Asp vs UFH + Asp [165,598]	2	69/1149	60/1145	1.15 (0.82, 1.61)	0.01 (-0.01, 0.03)	ET: 45 FP: 187
IPCD/FID + GCS vs UFH + GCS [509]	1	0/114	0/120	Not Estimable	0.00 (-0.02, 0.02)	ET: 50 FP: 201

** FP – forest plot number in appendix E; ET – evidence table number in appendix D. Proph - prophylaxis*

24.2.3.2 Additional outcomes

None of the included studies reported chronic thromboembolic pulmonary hypertension, heparin induced thrombocytopenia or post thrombotic syndrome as outcomes.

One study[158] reported cutaneous adverse events related to the use of GCS, ie skin breaks, ulcers, blisters or skin necrosis. The event rate in the GCS arm was 64/1256 vs 16/1262 in the control arm without GCS (RR 4.02, 95% CI 2.31 to 6.91, p<0.001). Lower limb ischaemia or amputation was 7/1249 in the GCS arm and 2/1262 in the control arm (RR 3.54 95% CI 0.74 to 16.99, P=0.108).

24.3 Network meta-analysis results

No network meta-analysis was completed for this population.

24.4 Cost-effectiveness evidence

No cost effectiveness analysis was completed for this population.

24.5 Patient views

No studies investigating the experience of prophylaxis in stroke patients were found. Section 6.6 contains more information on patient views on specific prophylaxis agents.

24.6 Summary of evidence

Intervention(s)	*Comparison(s)*	*Intervention favoured*		
		DVT	**PE**	**MB**
Prophylaxis vs no prophylaxis				
IPCD/FID	No prophylaxis	Not sig	-	-
GCS	No prophylaxis	Not sig	Not sig	-
Aspirin (high dose)	No prophylaxis	**Asp (HD)**	Not sig	-
UFH	No prophylaxis	**UFH**	-	No events
LMWH	No prophylaxis	Not sig	-	Not sig
Single prophylaxis vs single				
LMWH	UFH	**LMWH**	Not sig	Not sig
Aspirin (High dose)	UFH	Not sig	Not sig	Not sig
Double prophylaxis vs single				
GCS + aspirin	aspirin	Not sig	No events	
IPCD/FID + GCS	GCS	Not sig	No events	-
UFH + GCS	GCS	Not sig	-	-
Other Strategies				
LMWH + Asp	UFH + Asp	**LMWH + Asp**	Not sig	Not sig
IPCD/FID + GCS	UFH + GCS	Not sig	-	-
Cost Effectiveness				
No cost effectiveness model was completed for this population				

The prophylaxis strategy which is significantly more effective in reducing DVT or PE; or resulting in significantly less major bleeding is stated in bold. Not sig - not statistically significant difference; '-'= not reported; no events – nobody in the study had the outcome. MB = Major bleeding

24.7 Recommendations and link to evidence

Recommendation	**Do not offer anti-embolism stockings for VTE prophylaxis to patients who are admitted for stroke.**
Relative values of different outcomes	The outcomes identified as important by the Guideline Development Group were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).
Trade off between clinical benefit and harms	Unlike pharmacological prophylaxis, mechanical methods do not increase the risk of bleeding. However, anti-embolism stockings have been shown to be ineffective in reducing the risk of VTE in stroke patients and were associated with an increased risk of cutaneous adverse reactions.
Economic considerations	No economic model was run specifically for stroke patients. Anti-embolism stockings were found to be ineffective in reducing VTE in stroke patients and had cutaneous side effects; this is therefore not a cost-effective intervention for this population.
Quality of evidence	All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++). One large multicentred RCT with more than 2500 patients compared anti-embolism stockings against usual care in stroke patients. This study has some minor limitations (Evidence table 23, Appendix D) but the GDG agreed that the generality of the results could be applied to the stroke population.
Other considerations	One study showed that anti-embolism stockings are ineffective in reducing the risk of VTE in stroke patients, but are associated with an increased risk of cutaneous adverse events. This contradicts previous beliefs based on the extrapolation of efficacy observed in surgical patients that GCS may be effective at reducing VTE and challenged the notion that mechanical prophylaxis methods are harmless. In the study, the number of patients who were using aspirin during the study was not reported but is expected to be high as currently aspirin is the standard treatment for most patients with ischaemic stroke. The GDG had considered whether this could have reduced the observed efficacy of stockings, but concluded that the results of the study were still applicable as the current NICE guidelines recommend initial treatment with aspirin for isachemic stroke[477].

	No patient views evidence was found specifically for this population
Recommendation	**Consider offering prophylactic-dose LMWH* (or UFH for patients with renal failure) if:** • **a diagnosis of haemorrhagic stroke has been excluded, *and*** • **the risk of bleeding (haemorrhagic transformation of stroke or bleeding into another site) is assessed to be low, *and*** • **the patient has one or more of:** – **major restriction of mobility** – **previous history of VTE** – **dehydration** – **comorbidities (such as malignant disease).** **Continue until the acute event is over and the patient's condition is stable.** * ***At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off label use should be obtained and documented.***
Relative values of different outcomes	The outcomes identified as important by the Guideline Development Group were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome). The risk of bleeding was felt to be important in this population as ischaemic stroke patients have a risk of haemorrhagic transformation.
Trade off between clinical benefit and harms	Patients are likely to be relatively immobile after stroke and therefore are predisposed to an increased risk of VTE. However, the Guideline Development Group felt that this should be balanced against the risk of bleeding, including haemorrhagic transformation which can have very serious consequences. In addition, the risk of bleeding on admission may not be known and so caution should be applied before prescribing pharmacological thromboprophylaxis agents.
Economic considerations	No economic model was run specifically for stroke patients. The economic model for general medical patients indicated that pharmacological prophylaxis was cost effective for this broader population. Given the high risk of VTE in stroke patients, it is possible that prophylaxis is cost-effective. However, given that

	the consequences of bleeding are likely to be very serious for this group, drug prophylaxis is likely only to be cost-effective if the risk of intracranial bleeding is minimised. Therefore the guideline development group recommended only considering pharmacological prophylaxis to a subset of stroke patients who have been established as at increased risk for VTE and only those in whom the bleeding risks have been established as low.
Quality of evidence	All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++). Seven of the 17 studies (41.2%) were published prior to 2000. The treatment of stroke has changed over the last 10 years. There were only two studies which compared heparin prophylaxis in addition to aspirin treatment and so the remaining studies may not be directly applicable to the current stroke population.
Other considerations	The current NICE Stroke guidelines recommend initial treatment with aspirin for ischaemic stroke[477], which should not be discontinued in order to provide thromboprophylaxis. The three conditions identified within the recommendation (major restriction of mobility, previous history of VTE, and dehydration or medical comorbidity) are based on the stroke guideline. Adding prophylactic-dose anticoagulant agents to aspirin is likely to increase bleeding and so it is important that the bleeding risk is established as low before thromboprophylaxis is commenced. The Department of Health has published the National Stroke strategy.

Recommendation	**Until the patient can have pharmacological VTE prophylaxis, consider offering a foot impulse or intermittent pneumatic compression device.**
Relative values of different outcomes	The outcomes identified as important to the Guideline Development Group (GDG) were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome). The risk of bleeding was of particular importance to stroke patients, with significance adverse impact on patients' morbidity and mortality.
Trade off between clinical benefit and harms	Patients with haemorrhagic stroke have already experienced bleeding into a critical location (brain) while patients with ischaemic stroke are also at risk of haemorrhagic transformation. The GDG agreed that bleeding was a more immediate risk for this population than the risk of developing

VTE and measures should be taken to prevent increasing this risk. Pharmacological prophylaxis is likely to increase additional bleeding risk and may lead to long term morbidity in this population. Foot impulse or intermittent pneumatic compression devices do not increase the risk of bleeding but may cause damage to the skin. In the absence of evidence of benefit or harm for this group which is at a high risk of VTE, foot impulse or intermittent pneumatic compression devices may offer some protection without the risk of bleeding.

Economic considerations

No economic model was run specifically for stroke patients. There were no studies investigating the effectiveness of mechanical prophylaxis usingfoot impulse or IPC devices for stroke or other medical patients but mechanical prophylaxis has been shown to be cost-effective for general surgical patients compared with no prophylaxis (Chapter 9). Although there is insufficient trial evidence in stroke patients, we believe that these patients are likely to have the same biological mechanisms of clotting that may be alleviated by the active pumping actions generated by foot impulese and IPC devices. The Guideline Development Group believed that foot impulse and IPC devices are likely to be cost-effective for patients with haemorrhagic stroke, where pharmacological prophylaxis is contraindicated since the risk of VTE in this group is relatively high.

Quality of evidence

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

Randomised controlled trials in surgical populations showed that these methods are effective at reducing venous thromboembolism without an associated increase in bleeding

One small study (n=26) investigated the use of IPC devices compared with no prophylaxis in stroke patients. There was no statistically significant difference in DVT events. Two RCTs in patients who also used GCS also showed no significant difference.

Other considerations

No patient views evidence was found specifically for this population

The stakeholder comments during the consultation reflected the concern that a large proportion of stroke patients who are at high risk of VTE and contraindicated to pharmacological prophylaxis may be left without any protection since anti-embolisms stockings are no longer recommended for patients admitted for stroke and foot impulse or IPC devices are not being mentioned in the guideline. The GDG had considered these important concerns carefully against the evidence available and also noted that there is a large, ongoing RCT among stroke patients to evaluate the effectiveness of IPC

devices.

In the absence of evidence (either of effectiveness or of harm), the GDG did not want to exclude the possibility that these devices have a different mechanism of action from anti-embolism stockings in VTE prevention. Therefore, the (lack of) effectiveness of anti-embolism stockings in stroke patients should not preclude the use of foot impulse and IPC devices in patients who are contraindicated to pharmacological prophylaxis. However, clinicians will have to carefully consider the risk vs benefits in each patient. Factors which should be considered include the risk of VTE and the exclusion of acute DVT (mechanical devices are contraindicated in acute DVT and there is a high risk of DVT in stroke patients)

There was a clear consensus with regard to this decision.

24.7.1 Other recommendations of relevance

The specific recommendations for patients with stroke in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)
- patients using anticoagulants or antiplatelets for reasons other than VTE prophylaxis (Chapter 1)

24.8 Recommendations for research

The GDG recommended the following research question:

- What is the overall risk/benefit of low molecular weight heparin and/or fondaparinux sodium in respect of both stroke outcome and the development of VTE for patients with acute stroke?

Why this is important

Patients with either ischaemic or haemorrhagic stroke have a risk of both VTE and bleeding into the brain. 'Stroke: diagnosis and management of acute stroke and transient attack [TIA]' (NICE clinical guideline 68, published July 2008) recommends the use of aspirin for treatment of ischaemic stroke but does not recommend anticoagulants. There is recent evidence to suggest that prophylactic-doses of anticoagulants in addition to aspirin reduce the risk of VTE in patients with ischaemic stroke but there are no data showing an effect of these anticoagulants on the stroke itself. Do they increase the risk of haemorrhagic transformation and so increase neurological damage? This research should

include patients with haemorrhagic or ischaemic strokes to identify which patients would benefit from additional pharmacological prophylaxis.

Recommended design: RCT

Further details are provided in Appendix F

24.9 Summary of recommendations

- Do not offer anti-embolism stockings for VTE prophylaxis to patients who are admitted for stroke.

- Consider offering prophylactic-dose LMWH* (or UFH for patients with renal failure) if:

  - a diagnosis of haemorrhagic stroke has been excluded, **and**

  - the risk of bleeding (haemorrhagic transformation of stroke or bleeding into another site) is assessed to be low, **and**

  - the patient has one or more of:
    - major restriction of mobility
    - previous history of VTE
    - dehydration
    - comorbidities (such as malignant disease).

  Continue until the acute event is over and the patient's condition is stable.

  **At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off label use should be obtained and documented.*

- Until the patient can have pharmacological VTE prophylaxis, consider offering a foot impulse or intermittent pneumatic compression device.

25 Acute coronary syndromes

25.1 Introduction

All patients admitted with acute coronary syndrome (ACS) consisting of a history of chest pain, and raised cardiac enzymes or altered electrocardiogram should have a VTE assessment performed on admission (section 5.9). The risk of DVT in patients with ACS is estimated from the nil prophylaxis arms of trials to be 21% (95% confidence intervals 17% to 25%).

Patients diagnosed with ACS are treated with anti-thrombotics. These treatments primarily consist of aspirin, clopidogrel and heparin. The duration of each therapy varies, with aspirin often being life-long, clopidogrel in the order of 12 months and heparin for a period of three to five days post event. Patients who receive full dose anti-coagulation with either intravenous unfractionated heparin (UFH) or low molecular weight heparin (LMWH) do not require further VTE prophylaxis whilst receiving full anticoagulation. Once full dose anti-coagulation is stopped the protection it provides diminishes allowing an increased risk of VTE. A repeat VTE risk assessment is required. VTE prophylaxis should be given if the assessment indicates unless the patient has significant bleeding risk.

For patients who are admitted and do not require treatment with full-dose anticoagulation, a VTE assessment is required. Studies indicate that neither aspirin nor clopidogrel when given alone provides adequate VTE protection and patients remain at risk of VTE. Patients should receive additional pharmacological prophylaxis unless the patient has a significant bleeding risk.

None of the studies identified in this chapter investigated the anti-thrombotic effect of clopidogrel and aspirin combinations. Several studies investigate the long term use of clopidogrel (which was not within the scope of this guideline) and have concluded that these combinations were relatively ineffective at reducing venous thromboembolic endpoints [61,95,118].

25.2 Evidence of methods of prophylaxis

25.2.1 Summary of comparisons identified for any outcome

Seven RCTs were identified which investigated VTE prophylaxis in patients with acute coronary syndrome [42,70,209,251,338,522,672]. Most of the evidence was conducted in patients after myocardial infarction.

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

	No prophylaxis	Post-discharge	GCS	IPCD/FID	Dabigatran	Fondaparinux	LMWH	UFH	VKA	Asp (HD)	Asp (LD)	GCS + IPCD/FID	Mech + pharm
GCS													
IPCD/FID													
Dabigitran													
Fondaparinux													
LMWH													
UFH	**5**												
VKA													
High dose aspirin	**1**												
Low dose aspirin													
GCS + IPCD/FID													
Mech + pharm										**1**			
Other comparisons													

Figure 25-55: Number of studies which compared various types of prophylaxis methods.

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicates areas where no studies were identified.

GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) - low dose aspirin (≤ 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis

25.2.2 Results from pairwise comparisons

Table 25-130: DVT – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
High Dose Aspirin vs nil [70]	1	2/25	1/14	1.12 (0.11,11.28)	0.01 (-0.16, 0.18)	ET: 29 FP: 28
UFH vs nil [42,209,251,522,672]	5	16/213	51/215	0.33 (0.16, 0.69)	-0.17 (-0.23, -0.10)	ET: 27 FP: 17
Double proph vs single						
GCS + Asp LD vs Asp LD [338]	1	0/80	8/80	0.06 (0.00, 1.00)	-0.10 (-0.17,-0.03)	ET: 38 FP: 114

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*

Proph - prophylaxis

Table 25-131: Pulmonary embolism – summary of results from RCTs

Comparison	No. of studies	Interven -tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
High dose aspirin vs nil [70]	1	0/25	1/14	0.19 (0.01, 4.43)	-0.07 (-0.23, 0.09)	ET: 29 FP: 29
UFH vs nil [42,251]	2	1/76	3/74	0.46 (0.06, 3.49)	-0.03 (-0.09, 0.03)	ET: 27 FP: 18

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

Table 25-132: Major bleeding – summary of results from RCTs

Comparison	No. of studies	Interven -tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
High dose aspirin vs nil [70]	1	0/25	0/14	Not Estimable	0.00 (-0.11, 0.11)	ET: 29 FP: 30

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

25.2.3 Additional information

25.2.3.1 All cause mortality

Only two studies reported all cause mortality as an outcome [70,672].

Comparison	No. of studies	Interven -tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
High dose aspirin vs nil [70]	1	1/25	1/14	0.56 (0.04, 8.28)	-0.03 (-0.19, 0.12)	ET: 29 FP: 31
UFH vs nil [672]	1	6/63	5/64	1.22 (0.39, 3.79)	0.02 (-0.08, 0.11)	ET: 27 FP: 20

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

25.2.3.2 Other outcomes

No studies reported heparin induced thrombocytopenia, post-thrombotic syndrome or chronic thromboembolic pulmonary hypertension as outcomes.

25.3 Network meta-analysis results

No network meta-analysis was completed for this population.

25.4 Cost-effectiveness evidence

We did not prioritise this population for original cost-effectiveness analysis and no relevant cost-effectiveness studies were found in the literature.

25.5 Patient views

No patient view papers were found for this population. Section 6.6 contains more information on patient views about specific prophylaxis agents.

25.6 Summary of evidence

Table 25-133: Summary of evidence from direct evidence for DVT, symptomatic pulmonary embolism and major bleeding outcomes.

Intervention(s)	*Comparison(s)*	*Intervention favoured*		
		DVT	**PE**	**MB**
Prophylaxis vs no prophylaxis				
Aspirin (high dose)	no prophylaxis	Not Sig	Not Sig	Not Sig
UFH	no prophylaxis	**UFH**	Not Sig	-
Double prophylaxis vs single				
Asp (LD) + GCS	Asp (LD)	**Asp (LD) + GCS**	-	-
Cost Effectiveness				
There is no relevant cost-effectiveness evidence specifically for this group.				

The prophylaxis strategy which is significantly more effective in reducing DVT or PE; or resulting in significantly less major bleeding is stated in bold.
Not sig - not statistically significant difference; '-'= not reported; no events – nobody in the study had the outcome. MB = Major bleeding

25.7 Recommendations and link to evidence

Recommendation	**Do not offer additional pharmacological or mechanical prophylaxis for VTE to patients who are having full anticoagulant therapy (for example, fondaparinux sodium, LMWH or UFH).**
Relative values of different outcomes	The outcomes identified as important by the Guideline Development Group were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).
Trade off between clinical benefit and harms	The risk of developing venous thromboembolism was weighed against the increased risk in bleeding caused by

pharmacological prophylaxis.

Economic considerations

There is no relevant cost-effectiveness evidence specifically for this group. However, we have built an economic model for the general medical patients and we believe that the baseline risk of VTE in the acute coronary syndrome subgroup will at least be similar to that in the general medical group. The result of the model suggests that LMWH and UFH are cost-effective strategies in general medical patients, with the former being more cost-effective than the latter. For patients with acute coronary syndromes there are further benefits from anti-coagulants in addition to their usual thromboprophylactic properties and therefore these drugs are likely to be even more cost-effective than for other population subgroups.

Quality of evidence

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

The quality of evidence for this section is low. All of the studies included within this section were conducted over 15 years ago. The Guideline Development Group noted that since this time, the treatment of ACS conditions had changed and there were concerns that the included studies did not reflect the current situation.

Additionally the population of patients included in this study may not be representative of all those patients with acute coronary syndromes. Most of the studies were conducted after myocardial infarction.

Other considerations

The current treatment for acute coronary syndrome usually involves anticoagulant treatment. In this situation where anticoagulants are provided for treatment, no additional prophylaxis is required for reducing the risk of VTE.

Recommendation	**Consider offering additional mechanical or pharmacological VTE prophylaxis to patients who are having antiplatelet agents to treat other conditions and who are assessed to be at increased risk of VTE (see section 5.9). Take into account the risk of bleeding (see *Box 2*) and of comorbidities such as arterial thrombosis.** ▪ **If the risk of VTE outweighs the risk of bleeding, consider offering pharmacological VTE prophylaxis according to the reason for admission** ▪ **If the risk of bleeding outweighs the risk of VTE, offer mechanical VTE prophylaxis**
Recommendation–from section 5.9	**Regard medical patients as being at increased risk of VTE if they:** • **have had or are expected to have significantly reduced mobility for 3 days or more, or** • **are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors shown in Box 1.**
Box 1 –Risk Factors for VTE	• **Active cancer or cancer treatment** • **Age over 60 years** • **Critical care admission** • **Dehydration** • **Known thrombophilias** • **Obesity (BMI over 30 kg/m^2)** • **One or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)** • **Personal history or first-degree relative with a history of VTE** • **Use of hormone replacement therapy** • **Use of oestrogen-containing contraceptive therapy** • **Varicose veins with phlebitis** **For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum)**
Recommendation–from	**Assess all patients for risk of bleeding before offering**

section 5.9	**pharmacological VTE prophylaxis*. Do not offer pharmacological VTE prophylaxis to patients with any of the risk factors for bleeding shown in Box 2, unless the risk of VTE outweighs the risk of bleeding.** ***Consult the summary of product characteristics for the pharmacological VTE prophylaxis being used or planned for further details.***
Box 2-Bleeding Risk Factors	• **Active bleeding** • **Acquired bleeding disorders (such as acute liver failure)** • **Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR higher than 2)** • **Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours** • **Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours** • **Acute stroke** • **Thrombocytopenia (platelets less than 75 x 109/l)** • **Uncontrolled systolic hypertension (230/120 mmHg or higher)** • **Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease)**
Trade off between clinical benefit and harms	The outcomes identified as important by the Guideline Development Group were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome). Patients who are using anticoagulants and/or antiplatelets for treatment of their condition may still be at risk of VTE. The risks associated with DVT need to be traded against the risk of bleeding. In addition, some antiplatelet treatment is provided to reduce the risk of arterial side thrombosis. The risks associated with stopping these treatments should be carefully considered.
Economic considerations	No cost effectiveness model was completed for this population. The health gain and cost savings of preventing VTE events should be balanced against the morbidity and costs associated

	with providing pharmacological prophylaxis including treatment of prophylaxis related adverse events such as major bleeding.
Other considerations	The decisions about whether to add additional pharmacological prophylaxis should be based on a risk assessment of the individual patient taking into account their risk of patients. Such decisions should be made by healthcare professionals and should be documented in the patient's notes.

25.7.1 Other recommendations of relevance

The specific recommendations for patients with acute coronary syndromes in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)
- patients using anticoagulants or antiplatelets for reasons other than VTE prophylaxis (Chapter 1)

25.8 Summary of recommendations

- Do not offer additional pharmacological or mechanical prophylaxis for VTE to patients who are having full anticoagulant therapy (for example, fondaparinux sodium, LMWH or UFH).
- Consider offering additional mechanical or pharmacological VTE prophylaxis to patients who are having antiplatelet agents to treat other conditions and who are assessed to be at increased risk of VTE (see section 5.9). Take into account the risk of bleeding (see **Box 2**) and of comorbidities such as arterial thrombosis.
  - If the risk of VTE outweighs the risk of bleeding, consider offering pharmacological VTE prophylaxis according to the reason for admission
  - If the risk of bleeding outweighs the risk of VTE, offer mechanical VTE prophylaxis.
- Regard medical patients as being at increased risk of VTE if they:
  - have had or are expected to have significantly reduced mobility for 3 days or more **or**
  - are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors in **Box 1**.

Box 1 – Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m^2)
- One or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
- Personal history or first-degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and 6 weeks post partum)

Box 2 Risk factors for bleeding

- Active bleeding
- Acquired bleeding disorders (such as acute liver failure)
- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR higher than 2)
- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours
- Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours
- Acute stroke
- Thrombocytopenia (platelets less than 75 x 109/l)
- Uncontrolled systolic hypertension (230/120 mmHg or higher)
- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease)

26 Cancer

26.1 Introduction

Active cancer is an additional risk factor for VTE and the prothrombotic tendency varies with tumour type[556]. Furthermore, many surgical procedures are carried out as part of curative or palliative cancer treatment.

Whilst the increased bleeding risk of cancer patients receiving full anticoagulation is well recognised when compared to non cancer patients, there has been no evidence identified suggesting this is the case with primary thromboprophylaxis. However the studies reviewed excluded those at highest risk of bleeding. Based on the clinical evidence standard contraindications to VTE prophylaxis should apply to this group.

This chapter deals with two populations:

- cancer patients admitted to hospital with an acute illness which may or may not be due to their cancer diagnosis
- cancer patients admitted to hospital for oncological treatment.

For patients with cancer who are undergoing surgery, refer to guidance provided for the specific types of surgery in chapters 9 to 18.

26.2 Evidence of methods of prophylaxis

26.2.1 Summary of comparisons identified for any outcome

A number of studies reported on the use of VTE prophylaxis in general medical patients, and most of these trials [45,121,141,191,350,387,390,395,418,579] included some cancer patients within their population, although the proportion of patients included varied. The full review of these studies is detailed in chapter 23 and details on the proportion of cancer patients included can be found in the evidence tables (Appendix D).

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

Although a number of studies have been completed which investigate the potential anti-cancer properties of anticoagulants, only studies reporting VTE outcomes were included in this review. Only one study was identified which met these criteria which compared

adjusted low dose warfarin (target INR 1.3-1.9) against no prophylaxis in women with metastatic breast carcinoma [398]. The average duration of prophylaxis in this study was 180 days.

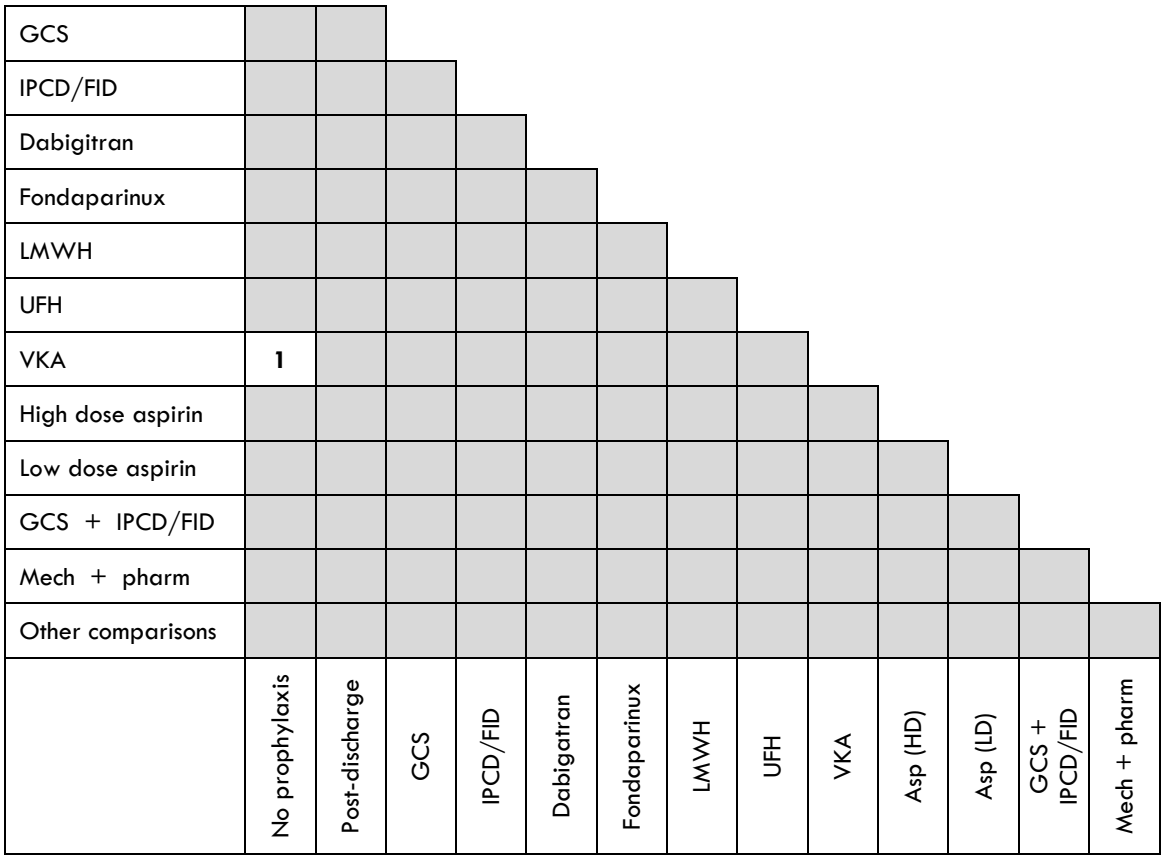


Figure 26-56: Number of studies which compared various types of prophylaxis methods.

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicates areas where no studies were identified.

GCS – anti-embolism / graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) - low dose aspirin (< 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis

26.2.2 Results from pairwise comparisons

Table 26-134: Symptomatic pulmonary embolism – summary of results from RCTs

Comparison	No. of studies	Interven -tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
VKA vs nil [398]	1	1/152	1/159	1.05 (0.07, 16.58)	0.00 (-0.02, 0.02)	ET: 28

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*

Proph - prophylaxis

Table 26-135: Major bleeding – summary of results from RCTs

Comparison	No. of studies	Interven -tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
VKA vs nil [398]	1	1/152	2/159	0.52 (0.05, 5.71)	-0.01 (-0.03, 0.02)	ET: 28 FP: 26

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

26.2.3 Additional information

26.2.3.1 All cause mortality

Table 26-136: All cause mortality – summary of results from RCTs

Comparison	No. of studies	Interven -tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
VKA vs nil [398]	1	87/152	99/159	0.92 (0.77, 1.10)	-0.05 (-0.16, 0.06)	ET: 28 FP: 27

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

26.2.3.2 Other outcomes

No studies reported chronic thromboembolic pulmonary hypertension or post-thrombotic syndrome.

26.3 Network meta-analysis results

Network meta-analysis was not completed for this population.

26.4 Cost-effectiveness evidence

No cost-effectiveness model was created for this population.

26.5 Patient views

One study qualitative study was conducted among 28 cancer patients receiving palliative care in the UK[492]. This study recruited patients who received LMWH for at least 5 days, and recruitment stopped when theme saturation was achieved. The study found that patients were aware of the purpose of subcutaneous LMWH thromboprophylaxis, and they understood that death could be a consequence of VTE. The potential benefit of reducing the risk of VTE was balanced against potential side effects (bruising was quoted) and patients found it acceptable to receive the LMWH injections[492] (Evidence table 62, Appendix D).

Patient views about specific prophylaxis agents are within section 6.6.

26.6 Summary of evidence

Table 26-137: Summary of evidence from network meta-analysis results for DVT, symptomatic pulmonary embolism and major bleeding outcomes.

Intervention(s)	*Comparison(s)*	*Intervention favoured*		
		DVT	**Symp PE**	**MB**
Prophylaxis vs no prophylaxis				
VKA	nil	-	Not sig	Not sig
Cost-effectiveness				
No cost-effectiveness model was completed for this population				

The prophylaxis strategy which is significantly more effective in reducing DVT or symptomatic PE; or resulting in significantly less major bleeding is stated in bold. Not sig = not a statistically significant difference'-'= not reported. MB = Major bleeding

26.7 Recommendations and link to evidence

Recommendation	**Offer pharmacological VTE prophylaxis to patients with cancer who are assessed to be at increased risk of VTE (see Section 5.9). Choose any one of:** • **fondaparinux sodium** • **LMWH*** • **UFH (for patients with renal failure).** **Start pharmacological prophylaxis as soon as possible after risk assessment has been completed. Continue until the patient is no longer at increased risk of VTE.** ***At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off-label use should be obtained and documented.***
Recommendation –from section 5.9	**Regard medical patients as being at increased risk of VTE if they:** • **have had or are expected to have significantly reduced mobility for 3 days or more, or** • **are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors in Box 1.**
Box 1 –Risk Factors for VTE	• **Active cancer or cancer treatment** • **Age over 60 years** • **Critical care admission** • **Dehydration** • **Known thrombophilias** • **Obesity (BMI over 30 kg/m^2)**

	• **One or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)** • **Personal history or first-degree relative with a history of VTE** • **Use of hormone replacement therapy** • **Use of oestrogen-containing contraceptive therapy** • **Varicose veins with phlebitis** • **For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum)**
Relative values of different outcomes	The outcomes identified as important by the Guideline Development Group were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome). The Guideline Development Group noted that although the reduction of risk of fatal events was the most important outcome, when the evidence was reviewed for general medical patients there was not enough evidence to conclude that prophylaxis reduced all cause mortality. In the absence of this evidence the Guideline Development Group identified symptomatic VTE and bleeding events as the most important outcomes.
Trade off between clinical benefit and harms	The benefit of reducing VTE events is balanced with the potential harms of bleeding due to anticoagulation.
Economic considerations	An economic model was developed for general medical patients. The model concluded that LMWH and UFH were the most cost-effective strategies in general medical patients. However, the cost-effectiveness of drug prophylaxis in cancer patients is harder to assess because although these patients have increased risk of VTE they might also have an increased risk of bleeding. Furthermore, the QALYs gained might be less for cancer patients if their life expectancy is low even in the absence of a VTE.
Quality of evidence	All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++). The quality of the evidence specific to cancer patients was low.

	Although 92% (12/13) RCTs of prophylaxis in general medical patients included some patients with cancer, there was only one study which provided results specifically for this population [579]. This showed that LMWH reduced VTE events by approximately 50% compared with no prophylaxis, although this was not statistically significant, probably due to the small numbers of patients included (72 cancer patients). The quality of the studies for general medical patients has been discussed elsewhere (chapter 23).
Other considerations	None
Recommendation	**Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients with cancer having oncological treatment who are ambulant.**
Relative values of different outcomes	The outcomes identified as important by the Guideline Development Group were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome). The Guideline Development Group agreed that reducing the risk of symptomatic VTE balanced against the risk of major bleeding were the most important outcomes.
Trade off between clinical benefit and harms	The benefit of reducing VTE events is balanced with the potential harms of bleeding due to anticoagulation.
Economic considerations	There was no economic model developed for this population. The GDG considered that, as with other patient groups, if these patients are ambulant the risk of VTE is not large enough to justify the adverse events and costs of prophylaxis.
Quality of evidence	All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++). There was only one study investigating prophylaxis for the reducing the risk of VTE in patients undergoing treatment for cancer [398]. This was a small study (n=315) of people undergoing treatment for breast cancer and so these data may not be applicable to other populations. Likewise, this was an ambulant population with prophylaxis provided over 180 days. Additionally, this study was published more than 10 years ago and since then treatment methods have changed.
Other considerations	If these patients have central venous catheters, more guidance for this population can be found in Chapter 27.

26.7.1 Other recommendations of relevance

The specific recommendations for patients with cancer in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- mechanical alternatives for patients contraindicated to pharmacological VTE prophylaxis (Section 23.7)
- the provision of patient information (Section 32.5)
- patients using anticoagulants or antiplatelets for reasons other than VTE prophylaxis (Chapter 1)
- patients with central venous catheters (Section 27.7)

26.8 Recommendations for research

The current evidence for thromboprophylaxis in hospitalised cancer patients is based on studies in general medical patients that had included cancer patients. Therefore a study to identify best practice within the cancer population alone should be conducted.

Recognition that some cancers are more thrombogenic than others, supports a view that this should be done in specific cancer groups. Such cancer groups worthy of consideration include myeloma, pancreatic, lung, ovarian and primary brain.

New oral anticoagulant agents such as dabigatran and rivaroxaban should be evaluated in the general cancer population.

26.9 Summary of recommendations

- Offer pharmacological VTE prophylaxis to patients with cancer who are assessed to be at increased risk of VTE (see Section 5.9). Choose one of the following:
  - fondaparinux sodium
  - LMWH*
  - UFH (for patients with renal failure).

  Start pharmacological prophylaxis as soon as possible after risk assessment has been completed. Continue until the patient is no longer at increased risk of VTE.

  * At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. *Informed consent for off-label use should be obtained and documented.*

- Regard medical patients as being at increased risk of VTE if they:
  - have had or are expected to have significantly reduced mobility for 3 days or more, **or**

- are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors shown in **Box 1.**

Box 1 - Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m^2)
- One or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
- Personal history or first-degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and 6 weeks post partum)

➢ Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients with cancer having oncological treatment who are ambulant.

27 Patients with central venous catheters

27.1 Introduction

Central venous catheters (CVCs) are commonly used in a wide variety of patients for indications such as monitoring of haemodynamics, administration of parenteral nutrition, blood products, chemotherapy, and infusion fluids. One important complication of the use of CVCs is catheter-related thrombosis (CRT), the majority of which are asymptomatic. These are of uncertain clinical significance[148], but CRT has been reported in adult patients with cancer to cause morbidities including pulmonary embolism and postphlebitic syndrome[64,460].

The incidence of CRT in adult patients with cancer has been described in a number of clinical observational and interventional studies; however it is impossible to define the incidence of thrombotic events precisely, given the variation in a range of relevant factors that make an inter-study comparison difficult. These include differences in study design and the observed patient population, variation in the method of catheter type and insertion, inconsistent description of the thrombotic event e.g. difficultly in separating mural thrombosis from catheter occlusion by catheter sleeve, significant differences in patient follow up and the sensitivity and specificity of the radiological methods used to confirm the diagnosis[662].

An average of approximately 40% of all patients with CVCs are reported to develop venographically demonstrable thrombi[535]. There is, however, a wide variation in the published incidence of symptomatic CRT in adult cancer patients, from 0.3-28.3%[706]. If the study endpoint is venography-detected venous thromboembolism (VTE), the thrombosis rate rises to 27-66%, most of which are asymptomatic[662]. More recent studies, however, have shown a marked decline in incidence of CRT which is likely to be due to improvements in catheter technology, placement and aftercare[706].

The risk of thrombosis and the risk of bleeding differ among different patient populations. Firstly, the underlying disease can affect the risk of thrombosis as in cancer. The risk is further increased when patients receive treatment such as surgery or chemotherapy[351]. The nature of the substances administered again increases the risk. Chemotherapy may directly damage vascular endothelium[419] and the hyperosmolality of parenteral nutrition may also change the vessel wall[180]. The type and location of the catheter is important[662] but there is a paucity of properly powered trials with adequate follow up on risk factors. In adult patients with cancer, patient history of VTE and previous catheter insertions, inadequate position of CVC tip, left-sided CVC insertion and chest radiotherapy have been identified as significant risk factors for CRT[391,535,664]. Many other risk factors have been postulated but not proven.

Chemotherapy may lower the number of circulating platelets which may induce bleeding. The dose of the anticoagulant may increase major bleeding[706].

27.2 Evidence of methods of VTE prophylaxis

As the outcomes used in other chapters are not appropriate for patient with central venous catheters the Guideline Development Group defined the important outcomes as:

- symptomatic and/or asymptomatic catheter related thrombosis
- major bleeding
- all cause mortality

Pulmonary Embolism and post-thrombotic syndrome are not presented as they are poorly reported in thromboprophylaxis trials for this population.

12 randomised controlled trials which reported at least one of the following outcomes; all cause mortality, catheter related thrombosis or major bleeding [4,59,83,136,265,331,417,449,457,489,663,706].

No methodologically strong studies have been performed in patients receiving parenteral nutrition, in renal patients or in the intensive care setting. Thromboprophylaxis in cancer patients with CVCs has been studied most widely and therefore forms the basis of the evidence of thromboprophylaxis in patients with central venous catheters. No generalisations should be made from this specific population.

27.2.1 Summary of comparisons identified for any main outcomes

	No prophylaxis	Post-discharge	GCS	IPCD/FID	Dabigatran	Fondaparinux	LMWH	UFH	VKA	Asp (HD)	Asp (LD)	GCS + IPCD/FID	Mech + pharm
GCS													
IPCD/FID													
Dabigatran													
Fondaparinux													
LMWH	**4**												
UFH	**3**												
VKA	**4**						**1**						
High dose aspirin													
Low dose aspirin													
GCS + IPCD/FID													
Mech + pharm													
Other comparisons													

Figure 27-57: Number of studies which compared various types of VTE prophylaxis methods.

Numbers in boxes indicate the number of RCTs for each comparison. Boxes shaded grey indicates areas where no studies were identified.

GCS – anti-embolism /graduated compression stockings; IPCD/FID – intermittent pneumatic compression devices or foot impulse devices; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Asp (HD) – high dose aspirin (>300mg), Asp (LD) - low dose aspirin (≤ 300mg); mech – mechanical prophylaxis (i.e. anti-embolism / graduated compression stockings, intermittent pneumatic compression devices or foot impulse devices); pharm – pharmacological prophylaxis

27.2.2 Results from pairwise comparisons

Table 27-138: All (symptomatic and asymptomatic) catheter related thrombosis – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
LMWH vs Nil[331,457,489,663]	4	50/506	51/359	0.81(a) (0.41, 1.59)	-0.06 (-0.18, 0.06)	ET: 68 FP: 235
UFH vs nil[4,83,417]	3	9/108	25/106	0.41 (0.18, 0.94)	-0.14 (-0.27, 0.00)	ET: 68 FP: 235
VKA vs Nil[59]	1	4/42	15/40	0.25 (0.09, 0.70)	-0.28 (-0.45, 0.11)	ET: 68 FP: 235

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*

Proph - prophylaxis

(a) There is substantial statistical heterogeneity between studies for this population (I^2 =55.9%, χ^2 on 2 df = 6.80, p=0.08).

Table 27-139: Clinically relevant (symptomatic) catheter related thrombosis– summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
LMWH vs Nil[331,489,663]	3	12/490	12/346	0.68 (0.29, 1.57)	-0.01 (-0.04, 0.01)	ET: 68 FP: 236
VKA vs Nil[59,136,265,706]	4	36/637	40/626	0.89 (0.57, 1.39)	0.00 (-0.03, 0.03)	ET: 68 FP: 236
Single proph vs single						
Fixed VKA vs Adjusted dose VKA[706]	1	34/471	13/473	2.63 (1.40, 4.91)	0.04 (0.02, 0.07)	ET: 68 FP: 241

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

Table 27-140: Major bleeding – summary of results from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
UFH vs nil[4]	1	2/65	2/63	0.97 (0.14, 6.67)	0.00 (-0.06, 0.06)	ET: 68 FP: 237
VKA vs nil[136,706]	2	7/538	4/529	1.13 (a) (0.02, 52.56)	0.00 (-0.01, 0.01)	ET: 68 FP: 237
LMWH vs nil[331,457,489,663]	4	2/557	1/408	0.97 (0.12, 7.68)	0.00 (-0.04, 0.04)	ET: 68 FP: 237
Single proph vs single						
VKA vs LMWH[449]	1	2/24	1/21	1.75 (0.17, 17.95)	0.04 (-0.11, 0.18)	ET: 68 FP: 239
Fixed dose VKA vs Adjusted dose VKA[706]	1	7/471	16/473	0.44 (0.18, 1.06)	-0.02 (-0.04, 0.00)	ET: 68 FP: 242

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis
(a) There is substantial statistical heterogeneity between studies for this population (I^2 =78.0%, χ^2 on 1 df =4.54, p=0.03).

27.2.3 Additional information

27.2.3.1 All cause mortality

Table 27-141: All cause mortality summary from RCTs

Comparison	No. of studies	Interven-tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
LMWH vs nil[331,457,663]	3	18/493	23/349	0.70 (0.38, 1.30)	-0.02 (-0.08, 0.05)	ET: 68 FP: 238
VKA vs Nil[59,136,265]	3	34/235	35/229	0.95 (0.62, 1.46)	0.00 (-0.04, 0.04)	ET: 68 FP: 238
Single proph vs single						
VKA vs LMWH[449]	1	4/30	6/29	0.64	-0.07	ET: 68

				(0.20, 2.05)	(-0.26, 0.12)	FP: 240

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

27.2.3.2 Other outcomes

Four studies additionally reported non-catheter related thrombosis [136,449,663,706].

- Couban et al.[136] reported non-significant difference between fixed dose warfarin and no VTE prophylaxis in reducing symptomatic non-CVC associated DVT or PE (RR 0.96 [95%CI: 0.20, 4.67]).

- Mismetti et al.[449] compared LMWH with warfarin and reported non-significant changes in asymptomatic or symptomatic upper extremity thrombosis or symptomatic DVT of lower limbs. (RR=0.58 [95% CI: 0.19, 1.79])

- Verso et al[663] reported no significant difference in asymptomatic or sympotomatic upper limb DVT between LMWH and placebo (RR=0.79 [95% CI: 0.47, 1.31]). Fatal pulmonary embolism was recorded but no events were reported in either arm.

- Young et al[706] reported non-significant differences between warfarin (fixed dose 1mg daily (79%) and dose adjusted warfarin to maintain the INR between 1.5 and 2.0 (21%)) and no warfarin in catheter-related plus non-catheter related thrombotic events (RR=0.78 [95% CI: 0.50, 1.24])

- Young et al[706] reported on a combined endpoint of CRT and major bleeding and demonstrated no significant difference between warfarin vs no warfarin (as above) (RR= 1.23 [95% CI: 0.83, 1.52]) and fixed dose vs. dose adjusted warfarin (RR=0.84 [95% CI: 0.74, 2.04]).

No studies reported chronic thromboembolic pulmonary hypertension or post thrombotic syndrome. Three studies recorded heparin induced thrombocytopenia as an outcome, but there were no events in any study[4,449,489].

27.3 Network meta-analysis results

No network meta-analysis was completed for this population.

27.4 Cost-effectiveness evidence

We did not prioritise this population subgroup for original cost-effectiveness analysis and no relevant cost-effectiveness studies were found in the literature.

27.5 Patient views

No studies on patient views for patients with central venous catheters were identified.

Patient views about specific VTE prophylaxis agents are within section 6.6.

27.6 Summary of evidence

Table 27-142: Summary of evidence from direct evidence results for catheter related thrombosis, symptomatic catheter related thrombosis and major bleeding.

Intervention(s)	*Comparison(s)*	*Intervention favoured*		
		CRT	**Clinical CRT**	**MB**
Prophylaxis vs no prophylaxis				
UFH	nil	**UFH**	-	Not sig
LMWH	nil	Not sig	Not sig	Not sig
VKA	nil	**VKA**	Not sig	Not sig
Single Prophylaxis vs single				
LMWH	VKA	-	-	Not sig
Fixed VKA	Adjusted VKA	-	Not sig	Not sig
Cost Effectiveness There is no relevant cost-effectiveness evidence specifically for this population subgroup.				

CRT = Catheter related thrombosis (asymptomatic and symptomatic events); Clinical CRT = clinically relevant catheter related thrombosis; MB= major bleeding.
The prophylaxis strategy which is significantly more effective in reducing CRT or Clinical CRT; or resulting in significantly less major bleeding is stated in bold. Not sig = not statistically significant difference. '-'= not reported. MB = Major bleeding

27.7 Recommendations and link to evidence

Recommendation	**Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients with central venous catheters who are ambulant.**
Recommendation	**Consider offering pharmacological VTE prophylaxis with LMWH * (or UFH for patients with renal failure) to patients with central venous catheters who are at increased risk of VTE (See Section 5.9).** * ***At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent should be obtained and documented.***
Recommendation –from section 5.9	**Regard medical patients as being at increased risk of VTE if they:** • **have had or are expected to have significantly reduced mobility for 3 days or more, or** • **are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors in Box1.**
Box 1 –Risk Factors for VTE	• **Active cancer or cancer treatment** • **Age over 60 years** • **Critical care admission** • **Dehydration** • **Known thrombophilias** • **Obesity (BMI over 30 kg/m^2)** • **One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)** • **Personal history or a first degree relative with a history of VTE** • **Use of hormone replacement therapy** • **Use of oestrogen-containing contraceptive therapy** • **Varicose veins with phlebitis.** **For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum)**
Relative values of different	The Guideline Development Group identified all cause

outcomes

mortality and both symptomatic catheter related and non-catheter related thrombosis as the most important outcomes for this population. The guideline development group also agreed that asymptomatic catheter related events could be used as a surrogate for symptomatic events in this population.

Trade off between clinical benefit and harms

The Guideline Development Group felt that the balance between the benefits of reducing thrombotic events needed to be balanced against the harms of increased bleeding.

Economic considerations

There is no relevant cost-effectiveness evidence specifically for this population subgroup. There is no clinical evidence that these patients are at higher risk of symptomatic VTE than other medical patients who do not have central venous catheters. This suggests that they should be treated as for other medical patients.

Quality of evidence

The overall quality of the evidence was poor. The studies included a wide range of populations including cancer patients and non-cancer patients (e.g parenteral nutrition patients) surgical patients. Some members indicated that the patients who have catheters inserted currently are different to those patients included in the trials as they are less sick and therefore at a lower risk of thrombosis.

The Guideline Development Group noted that the trials used a number of different definitions and measurement methods for detecting events which made it difficult to compare the results of the individual studies.

The guideline development group were aware that some of the studies were old, particularly some of the studies comparing UFH and warfarin with no VTE prophylaxis. There were concerns that since the publication of these studies, factors such as the catheter material, method of insertion and mobility of patients had changed. Additionally the sample size of many comparisons were small, even when the studies were combined meaning that a statistical difference was unlikely to be detected even if there was one.

The above factors may be apparent in the range of incidence rates in the no prophylaxis arms in the studies which range from 9 – 62%.

Other considerations

The guideline development group agreed that although there is some evidence that VTE prophylaxis is effective at reducing all catheter related thrombosis without significant increase in major bleeding, patients should not be routinely offered VTE prophylaxis. This was based on the low quality of the evidence available (old trials)
The guideline development group agreed that if patients with catheters had reduced mobility for 3 days or additional risk

factors they should be offered VTE prophylaxis as per general medical patients.

Warfarin was not recommended for this population as in the most recent trial published there was no evidence of efficacy. In addition warfarin is difficult to monitor and the Guideline Development Group were concerned about the possible interactions between warfarin and other drugs.

As the use of a CVC is a risk factor for VTE the GDG noted that other non invasive administration routes of therapy should be considered as an alternative route to central venous catheters where possible if the efficacy is the same and after discussion with the patient. For example, oral chemotherapy should be used instead of intravenous chemotherapy via CVCs.

27.7.1 Other recommendations of relevance

The specific recommendations for patients with central venous catheters in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- mechanical alternatives for patients contraindicated to pharmacological VTE prophylaxis (Section 23.7)
- the provision of patient information (Section 32.5)
- patients with cancer (Section 26.7)

27.8 Recommendations for research

Although none of the top 5 research recommendation was identified in this population, it was felt appropriate to suggest large international trials with the new oral anticoagulants (such as dabigatran and rivaroxaban) in patients with central venous catheters.

27.9 Summary of recommendations

- Do not routinely offer pharmacological or mechanical VTE prohylaxis to patients with central venous catheters who are ambulant.
- Consider offering pharmacological VTE prophylaxis with LMWH * or UFH (for patients with renal failure) to patients with central venous catheters who are at increased risk of VTE (See Section 5.9)

**At the time of publication (January 2010) some types of LMWH do not have UK marketing authorization for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent should be obtained and documented.*

- Regard medical patients as being at increased risk of VTE if they:
  - have had or are expected to have significantly reduced mobility for 3 days or more **or**
  - are expected to have ongoing reduced mobility relative to their normal state **and** have one or more of the risk factors shown in **Box 1**.

Box 1 Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m^2)
- One or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
- Personal history or first-degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and 6 weeks post partum)

28 Palliative care

28.1 Introduction

The need for provision of palliative care has been recognised across all incurable malignant and non malignant disease services. In addition, advances in therapeutic interventions have resulted in the palliative care population living longer despite incurable disease.

For the purposes of these guidelines a distinction needs to be made between a *terminal* patient; that is when a patient appears to be approaching death or has been admitted for end of life care and a *palliative* patient which encompasses any patient with incurable disease at any point of their disease journey. Palliative care patients may therefore encompass a spectrum of patients all with incurable illness, yet with a breadth of performance status, symptomatology and life expectancy. The majority of palliative care patients are admitted through the acute hospital take and the appropriateness of thromboprophylaxis should be made on an individual basis. In view of the heterogeneity of the palliative population, it could be argued that a blanket policy to withhold thromboprophylaxis in the palliative setting would be as ethically challenging as one which advocates thromboprophylaxis for all. Further discussion on the role of thromboprophylaxis in palliative care can be found in Noble et al[490].

There is very little evidence specifically in the palliative care population and recommendations are based on extrapolation from the general medical population. However, one study[311] suggests a 50% prevalence of asymptomatic DVT in hospice patients with cancer, although the symptom burden of VTE is unclear since dysnoea and leg oedema are common in this population due to other pathology.

28.2 Evidence of methods of prophylaxis

One study[681] was found which investigated low molecular weight heparin (LMWH) vs no prophylaxis in palliative care patients. This study was stopped early after failing to recruit eligible patients in a reasonable time. At the time of stopping 20 patients had been recruited. The study was underpowered to detect difference in the any of the outcomes recorded and the results have not been recorded here.

28.3 Network meta-analysis results

Network meta-analysis was not completed for this population.

28.4 Cost-effectiveness evidence

No cost effectiveness model was completed for this population.

28.5 Patient views

A recent qualitative study conducted in the United Kingdom among cancer patients receiving palliative care showed acceptability of thromboprophylaxis. This study found that patients were aware of the purpose of subcutaneous LMWH thromboprophylaxis. They balanced the potential benefit of venous thromboembolism reduction against potential side effects (bruising was quoted) and found it acceptable[492]. It also highlighted an awareness amongst patients of some of the risks of VTE and a desire to be involved in the decision making process.

For patient views about specific prophylaxis agents, see section 6.6.

28.6 Summary of evidence

Evidence statements
There is no clinical effectiveness evidence for this population
There is no cost effectiveness evidence for this population

28.7 Recommendations and link to evidence

Recommendation	**Consider offering pharmacological VTE prophylaxis to patients in palliative care who have potentially reversible acute pathology. Take into account potential risks and benefits and the views of patients and their families and/or carers. Choose any one of:** - **fondaparinux sodium** - **LMWH*** - **UFH (for patients with renal failure).** **** At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off-label use should be obtained and documented.***
Recommendation	**Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients admitted for terminal care or those commenced on an end-of-life care pathway.**
Recommendation	**Review decisions about VTE prophylaxis for patients in palliative care daily, taking into account the views of patients, their families and/or carers and the multidisciplinary team.**
Relative values of different outcomes	The Guideline Development Group noted that VTE prophylaxis in palliative care patients is for symptom prevention rather than with the sole purpose of trying to prolong life. Long term

	sequelae of VTE such as post thrombotic syndrome and chronic thromboembolic pulmonary hypertension are less important in the palliative care population. It is recognised that patients on an end of life care pathway (e.g. Liverpool Care Pathway; details of pathway available from: www.mcpcil.org.uk/liverpool_care_pathway), will be prescribed appropriate symptom control medicines to manage VTE related symptomatology in the last hours of life.
Trade off between clinical benefit and harms	The benefit of reducing VTE events was balanced with the potential harms of bleeding and qualitative aspects of receiving thromboprophylaxis.
Economic considerations	No economic model was completed for this population. There is evidence in medical patients that LMWH is clinically and cost effective at reducing the risk of VTE. However, the cost-effectiveness of drug prophylaxis in palliative care patients is harder to assess because although these patients might have an increased risk of symptomatic VTE, they might also have an increased risk of bleeding. Furthermore, the quality- adjusted life years (QALYs) gained might be less for palliative care patients if for example their life expectancy is low even in the absence of a VTE. Finally, if extended prophylaxis is required then the cost-effectiveness may diminish further when the costs of home visits are taken in to consideration.
Quality of evidence	There is no directly applicable evidence for the effectiveness of prophylaxis in the palliative care population. There is high quality evidence of effectiveness of LMWH across other medical and surgical populations.
Other considerations	**Patient views:** One qualitative study investigated attitudes towards prophylaxis in people within a specialist palliative care unit setting. This study indicated that LMWH was well tolerated in this population. **When to stop prophylaxis:** Given the lack of directly applicable evidence in palliative patients it is difficult to provide precise rules for when to stop prophylaxis. The Guideline Development Group agreed it was important to review the provision of thromboprophylaxis at regular intervals and suggested 48 hrs as an appropriate time point. However, there was insufficient evidence to recommend prolonged prophylaxis once the patient was discharged.

28.7.1 Other recommendations of relevance

The specific recommendations for patients receiving palliative care in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- mechanical alternatives for patients contraindicated to pharmacological VTE prophylaxis (Section 23.7)
- the provision of patient information (Section 32.5)
- patients with cancer (Section 26.7)

28.8 Recommendations for research

Currently no sufficiently powered thromboprophylaxis studies have been completed in the palliative care population. Whilst extrapolations from the general medical studies support appropriate use of LMWH in palliative care, it has been suggested that these are not a sufficiently representative population. Furthermore, the outcome measures used for these studies are considered less appropriate in an advanced disease population in whom quality of life is as important, if not more important, than VTE related clinical outcome[491].

There is a need to identify the symptomatic burden of VTE in the palliative care population with emphasis on the impact of VTE on quality of life. In addition, patient relevant outcome measures specific to this population need to be established in order to evaluate the role of thromboprophylaxis. The new oral anticoagulants such as dabigatran and rivaroxaban would be appropriate agents to study in the advanced disease setting

28.9 Summary of recommendations

- Consider offering pharmacological VTE prophylaxis to patients in palliative care who have potentially reversible acute pathology. Take into account potential risks and benefits and the views of patients and their families and/or carers. Choose any one of:
  - fondaparinux sodium
  - LMWH*
  - UFH (for patients with renal failure).

  * *At the time of publication (January 2010) some types of LMWH do not have UK marketing authorisation for VTE prophylaxis in medical patients. Prescribers should consult the summary of product characteristics for the individual LMWH. Informed consent for off-label use should be obtained and documented.*

- Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients admitted for terminal care or those commenced on an end-of-life care pathway.

- Review decisions about VTE prophylaxis for patients in palliative care daily, taking into account the views of patients, their families and/or carers and the multidisciplinary team.

29 Critical care

29.1 Introduction

Patients admitted to a critical care facility (who are generally in need of level 2 or level 3 care) can be separated into some distinct groups by their disease process:

1. patients with any acute illness that has resulted in one or more organ systems failing and have a need for interventions to support organ function

2. patients who need a higher level of observation and intervention that can not safely be provided elsewhere

3. patients who have had complex or prolonged surgical procedures and hence require a duration of recovery with a higher level of observation and monitoring than can be provided elsewhere in order to rapidly detect and mange any deterioration

4. patients who are dying and there is ongoing consideration of organ donation.

The data available to support decision making in such critically ill patients were scarce and suffers from wide variations in the nature of such units around the world, the heterogeneous population served and the very high all cause mortality seen. Each group has its own unique risk factors for VTE and risks of bleeding or other complications.

The unifying feature is that during times of severe physiological upset, the inflammatory response is at a maximal and the patient is almost always immobile and likely to have a number of intravascular catheter devices. This puts the patient at a much higher risk of developing venous thrombi. The same patient may however also be at an increased risk of bleeding, either due to a coagulopathy as a consequence of their disease or interventions; or be at risk of bleeding into a surgical field with disastrous consequences such as in spinal surgery or neurosurgery.

Also, the medications and equipment used in critical care may increase the risk of bleeding further. As examples; patients who require renal replacement support usually also require co-administration of heparin to stop thrombus formation in the external circuit; coagulopathy is a recognised complication of some treatments for sepsis and of large volume blood transfusions.

The critically ill patients will have a number of such risk factors which may change in nature, number and significance many times throughout their stay. Also, many invasive procedures may be carried out during such an admission (central lines, lumbar punctures,

chest drains etc) and so relative risks of bleeding as a consequence will also change many times.

Patients admitted to critical care units have an increased risk of developing venous thromboembolic disease and steps must be taken to recognise and manage such risks at a very early stage. However, the relative risk of significant bleeding is also high and so it is incumbent on staff to evaluate these risks very frequently and consider the best form of VTE prophylaxis on an individual patient basis.

29.2 Evidence of methods of prophylaxis

29.2.1 Summary of comparisons identified for any outcome

One study conducted specifically in intensive care patients was found[191]. This study was conducted among chronic obstructive pulmonary disease (COPD) patients with acute respiratory decompensation requiring mechanical ventilation in multiple medical intensive care centres. This study compared the effectiveness of LMWH against placebo. This study is included in the general medical patients section (Section 23) and the results are shown below.

29.2.2 Results from pairwise comparisons

Table 29-143: DVT – summary of results from RCTs

Comparison	No. of studies	Interven -tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
LMWH vs nil [191]	1	13/84	24/85	0.55 (0.30, 1.00)	-0.13 (-0.25, 0.00)	ET: 26 FP: 13

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

Symptomatic Pulmonary Embolism

No study reported symptomatic pulmonary embolism as an outcome.

Table 29-144: Major bleeding – summary of results from RCTs

Comparison	No. of studies	Interven -tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
LMWH vs nil[191]	1	6/108	3/113	2.09 (0.54, 8.16)	0.03 (-0.02, 0.08)	ET: 26 FP: 15

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph – prophylaxis

29.2.3 Additional information

29.2.3.1 All cause mortality

Table 29-145: All cause mortality – summary of results from RCTs

Comparison	No. of studies	Interven -tion	Control	Relative risk	Absolute effect	Forest plots & Evidence tables *
Proph vs no proph						
LMWH vs nil[191]	1	8/108	8/113	1.05 (0.41, 2.69)	0.00 (-0.07, 0.07)	ET: 26 FP: 16

** FP – forest plot number in appendix E; ET – evidence table number in appendix D*
Proph - prophylaxis

29.2.3.2 Additional studies

One additional study was identified which was designed to evaluate whether heparin interfered with the efficacy of activated protein C (drotrecogin alfa) in patients with severe sepsis[397]. Patients were randomised to receive low molecular weight heparin (LMWH) or unfractionated heparin (UFH) (evaluated as a combined heparin group) or no prophylaxis during their treatment period with activated protein C (usually 96 hours) and revert back to their usual prophylaxis strategy after the activated protein C administration had stopped. In this study, there were no statistically significant difference between the groups in all cause mortality (28 days follow up), major bleeding, or a composite outcomes of venous thrombotic events (Evidence Table 26, Appendix D)

29.3 Network meta-analysis results

No network meta-analysis was completed for this population.

29.4 Cost-effectiveness evidence

We did not prioritise this population subgroup for original cost-effectiveness analysis and no relevant cost-effectiveness studies were found in the literature.

29.5 Patient views

No patient view papers conducted specifically in this population were identified.

For patient views about specific prophylaxis agents, see section 6.6.

29.6 Summary of evidence

Intervention(s)	*Comparison(s)*	*Intervention favoured*		
		DVT	**PE**	**MB**
Prophylaxis vs no prophylaxis				
LMWH	Nil	**LMWH**	-	Not sig
Cost Effectiveness Analysis				
There is no relevant cost-effectiveness evidence specifically for this population subgroup.				

The prophylaxis strategy which is significantly more effective in reducing DVT or PE; or resulting in significantly less major bleeding is stated in bold. Not sig = not statistically significant difference. '-'= not reported. MB = Major bleeding

The only study found in this population showed a significant reduction in DVT events with LMWH compared with no prophylaxis but was not significant for major bleeding.

29.7 Recommendations and link to evidence

Recommendation	**Assess all patients on admission to the critical care unit for their risks of VTE and bleeding (see section 5.9). Reassess patients' risks of VTE and bleeding daily and more frequently if their clinical condition is changing rapidly.** ***Note: Relevant recommendations from section 5.9 are reproduced in section 29.8, below***
Recommendation	**Offer VTE prophylaxis to patients admitted to the critical care unit based on the reason for admission, taking into account:** - **any planned interventions** - **the use of other therapies that may increase the risk of complications.**
Recommendation	**Review decisions about VTE prophylaxis for patients in critical care daily and more frequently if their clinical condition is changing rapidly. Take into account the known views of the patient, comments from their family and/or carers and the multidisiplinary team.**
Trade off between clinical benefit and harms	This is a critically ill group of patients. Survival of patients is the most immediate concern. The benefit of reducing the risk of venous thromboembolism and long term events occurring as a result of thromboembolism were considered against the risk of adverse events due to prophylaxis including major bleeding.
Economic considerations	There will be a cost in staff time to complete the assessment on admission to the critical care unit but this is outweighed by the potential benefits for reducing the risk of venous thromboembolism. No cost effectiveness analysis was completed specifically for

this population subgroup. However, the cost-effectiveness model for general medical patients included trial evidence from 1 RCT in intensive care patients. The cost-effectiveness model for medical patients found that drug prophylaxis with LMWH was cost-effective.

Given that critical care patients are likely to be at increased risk of VTE compared to general medical patients; it is likely that prophylaxis will also be cost effective for the critical care population, unless the risk of bleeding is high.

Other considerations

Admission to critical care may be from a different ward within the hospital and may represent a worsening of the patient's condition. It is important to assess the patients' VTE risk as it may have been identified as low on initial admission. A review of risk factors (chapter 5) identified admission to the critical care unit as an independent factor for increasing VTE risk.

There was a strong consensus among the Guideline Development Group members that the risk of VTE among critical care patients is higher than the normal wards. As the clinical situation changes it is necessary to reassess the risks of VTE and bleeding. The incidence of DVT in no prophylaxis arm in the study in intensive care patients was 28%, which is higher than the incidence for general medical patients (13%). Therefore the guidelind development group agreed that in the absence of bleeding risk factors and after taking into account any planned interventions or therapies which may increase complications, VTE prophylaxis should be offered.

Patients treated in the critical care may be unconscious or not capable of making decisions about their treatment. In such situations, decisions about care should take into account the known view of patients and discussions with family members, where appropriate.

As there is a lack of RCT evidence in critical care patients, consensus guidelines developed by other organisations were reviewed for relevance and quality. The International Surviving Sepsis Campaign Guideline[155] has been developed using appropriate consensus methods involving international expert panels. This guideline would be adequate for patients with severe sepsis patients in the intensive care unit.

29.7.1 Other recommendations of relevance

The specific recommendations for patients in critical care in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)

- recommendations specific to their condition where applicable (Chapters 9 to 28)
- the use of prophylaxis in general (Section 6.7 and 6.8) Note, if anti-embolism stockings are used, it should be noted that due to the changes in fluid status among critical care patients, it may be challenging to ensure a good fit.
- the provision of patient information (Section 32.5)

29.8 Summary of recommendations

- Assess all patients on admission to the critical care unit for their risks of VTE and bleeding (see section 5.9). Reassess patients' risks of VTE and bleeding daily and more frequently if their clinical condition is changing rapidly.
- Offer VTE prophylaxis to patients admitted to the critical care unit based on the reason for admission, taking into account:
  - any planned interventions
  - the use of other therapies that may increase the risk of complications.
- Review decisions about VTE prophylaxis for patients in critical care daily and more frequently if their clinical condition is changing rapidly. Take into account the known views of the patient, comments from their family and/or carers and the multidisciplinary team.
- Regard medical patients as being at increased risk of VTE if they:
  - have had or are expected to have significantly reduced mobility for 3 days or more **or**
  - are expected to have ongoing reduced mobility relative to their normal state **and** have one or more of the risk factors shown in **Box 1**.
- Regard surgical patients and patients with trauma as being at increased risk of VTE if they meet one of the following criteria:
  - surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
  - acute surgical admission with inflammatory or intra-abdominal condition
  - expected significant reduction in mobility
  - have one or more risk factors shown in **Box 1**.
- Assess all patients for risk of bleeding before offering pharmacological VTE prophylaxis*. Do not offer pharmacological VTE prophylaxis to patients with any of the risk factors for bleeding shown in **Box 2**, unless the risk of VTE outweighs the risk of bleeding.

  **Prescribers should consult the summary of product characteristics for the pharmacological VTE prophylaxis being used or planned for further details.*

Box 1 Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m^2)
- One or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
- Personal history or first-degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6 weeks post partum)

Box 2 Risk factors for bleeding

- Active bleeding
- Acquired bleeding disorders (such as acute liver failure)
- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with international normalised ratio [INR] higher than 2)
- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours
- Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours
- Acute stroke
- Thrombocytopenia (platelets less than 75 x 109/l)
- Uncontrolled systolic hypertension (230/120 mmHg or higher)
- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease)

30 Pregnancy and up to 6 weeks post partum

30.1 Introduction

Venous thromboembolism (VTE) remains the leading direct cause of maternal death in the UK. In the latest Confidential Enquiry into Maternal and Child Health (CEMACH) report 'Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer, 2003-5'[401] there were 33 deaths from pulmonary embolism (18 events occurring antenatally, 8 after vaginal delivery and 7 after caesarean section). There is an overall incidence of approximately two episodes of VTE (including non-fatal events) per 1000 deliveries[307].

The risk of VTE is present from early pregnancy because the prothrombotic and flow changes occur from this time. The prothrombotic changes of pregnancy do not revert completely to normal until up to 6 weeks after delivery [273,306,431,571] especially after an emergency Caesarean section. The time of greatest risk for VTE associated with pregnancy is the early postpartum period and, although, in absolute terms, most VTE events occur antenatally, the risk per day is greatest in the weeks immediately after delivery[150,505,548].

Indeed the Confidential Enquiries into Maternal Deaths have shown that two thirds of antenatal fatal pulmonary VTE in 2003-2005 occurred in the first trimester, and just over half of the postnatal deaths from PE were after vaginal delivery[352]. Admission to hospital in any trimester poses an increased risk of VTE.

Women with specific factors such as family history of thrombophilia or a history of VTE require specialised evaluation, ideally before conception. Advice for these patients and all women who are pregnant or postpartum but who are not admitted to hospital is outside the remit of this guideline. There are guidelines produced by the Royal College of Obstetrician and Gynaecologist's (RCOG) Green-top Guideline number 37,"Thromboprophylaxis During Pregnancy, Labour and After Vaginal Delivery" which contains a review of the evidence and recommendations for the management of women at risk of VTE in pregnancy or the postpartum period for more information. The RCOG guideline (available on the RCOG website www.rcog.org.uk/index.asp?PageID=8) was published in January 2004 and was in the process of being updated at the time of writing.

The scope for this guideline relates only to patients admitted to hospital. Women who are pregnant or postpartum are usually admitted to obstetric wards, however, some women are admitted to non-obstetric wards, particularly in early pregnancy, for reasons such as management of pre-existing disease such as diabetes, or acute surgery. Pregnancy is a highly prothrombotic state and temporary illness and/or immobilisation will lead to an increased risk of VTE. Thus any woman admitted to hospital who is pregnant or postpartum should be risk assessed for their VTE risk as per the

recommendation in section 5.9, and should be considered for thromboprophylaxis. Repeated risk assessment (as recommended in section 5.9) should be completed, particularly during the postpartum period if they develop intercurrent problems or require surgery.

The general recommendations for reducing the risks of VTE contained within section 7 which include encouraging early mobilisation and preventing dehydration are applicable to women admitted to hospital during pregnancy, labour and postpartum.

Pregnant women, who are admitted to hospital and are already receiving thromboprophylaxis on admission should still be risk assessed for their risk of VTE and bleeding. They will normally continue their prophylaxis during their stay unless they develop risk factors for bleeding, when the risk-benefit analysis of thromboprophylaxis should be reconsidered.

A full review of the RCT evidence for preventing VTE in women admitted to hospital during pregnancy or postpartum was completed (section 30.3). When a lack of evidence was identified for this population and following stakeholder comments during consultation, a group of expert advisors (Acknowledgements section, page 15) *[acknowledgements]*) were invited to discuss the issues and to develop draft recommendations which were then agreed by the guideline development group and their considerations are included in the link between evidence and recommendations in section 30.8.

30.2 Evidence for risk factors for pregnancy and postpartum

The factors increasing the risk of VTE in all patients admitted to hospital are discussed in section 5.7, which was developed after completing a full literature search for high quality systematic reviews of risk factors for all patients. No high quality systematic reviews specifically looking at the VTE risk factors for women admitted to hospital during pregnancy or postpartum period were identified.

However, the expert advisors identified that some modification of the VTE risk factor list specifically for women who are pregnant or in the postpartum period was required. These specific risk factors are discussed below:

- ***Age***. In the UK obstetric surveillance study (UKOSS) study of antenatal pulmonary embolism unadjusted odds ratio for age > 35 was 1.29 (95% CI: 0.82 – 2.06)[352]. This evidence is supported by other studies[404,603] and therefore, age >35 years is considered as a risk factor for VTE in pregnant women.
- **Excess blood loss and blood transfusion:** Excess blood loss and blood transfusion has been found to be a risk factor for VTE [143,305,307] although this will obviously need to be weighed against the risk of further bleeding and, if prophylaxis is deemed necessary, may have an impact on the timing of initiation.
- **Obesity:** Although this factor has already been mentioned in section 5.7, the expert advisors felt that it warranted particular consideration as a risk factor during pregnancy. Nearly all women (7/8) dying from VTE following vaginal delivery in the last Confidential Enquiry were overweight or obese[401]. The UKOSS study of antenatal PE demonstrated that one of the main risk factors was a BMI >30 with an adjusted odds ratio of 2.65 (95% CI 1.09-6.45)[352].

- ***Pregnancy- related risks:*** *Additional* risk factors may complicate the first trimester, for example: hyperemesis gravidarum, surgery for miscarriage, termination of pregnancy, ectopic pregnancy or ovarian hyperstimulation following IVF[23,305]. For example in one study the odds ratio for VTE in women with hyperemesis gravidarum was 2.5 (95% CI: 2.0-3.2)[307]. A recent case–control study from Norway[305] found the adjusted odds ratio for VTE in pregnancy following assisted reproductive techniques was 4.3 (95% CI, 2.0-9.4). Women with ovarian hyperstimulation syndrome (OHSS) are particularly prone to VTE in the upper body[23,482]and require consideration for thromboprophylaxis for at least the period of in-patient stay[482].

Risk factors are discussed in more detail in the RCOG guideline, from which the following table has been extracted [563].

Table 30-146: Risk factors for VTE in pregnancy and the postpartum period (adapted from RCOG guideline[563])

<table>
<tr><th colspan="4">Risk factors for VTE in pregnancy and the postpartum period</th></tr>
<tr><td rowspan="9">PRE-EXISTING</td><td colspan="3">Previous VTE</td></tr>
<tr><td rowspan="2">Thrombophilia</td><td>Inherited
Antithrombin deficiency
protein C deficiency
protein S deficiency
Factor V Leiden
prothrombin gene variant</td><td></td></tr>
<tr><td>Acquired (Antiphospholipid syndrome)</td><td></td></tr>
<tr><td colspan="3">Medical co-morbidities e.g. Heart or lung disease; acute systemic lupus erythematosus; cancer; inflammatory conditions (inflammatory bowel or joint disease) nephrotic syndrome (proteinuria > 3g/day), sickle cell disease, intravenous drug users, paraplegia, pyelonephritis, sepsis</td></tr>
<tr><td colspan="3">Age > 35 years</td></tr>
<tr><td colspan="3">Obesity (BMI >30 kg/m^2) either pre-pregnancy or in early pregnancy</td></tr>
<tr><td colspan="3">Parity ≥ 3</td></tr>
<tr><td colspan="3">Smoking</td></tr>
<tr><td colspan="3">Gross varicose veins (symptomatic or above knee or with associated phlebitis, oedema/skin changes)</td></tr>
<tr><td rowspan="4">OBSTETRIC RISK FACTORS</td><td colspan="3">Multiple pregnancy, assisted reproduction therapy [ART]</td></tr>
<tr><td colspan="3">Pre-eclampsia</td></tr>
<tr><td colspan="2">Caesarean section</td><td rowspan="2">Prolonged labour, mid-cavity rotational operative delivery</td></tr>
<tr><td colspan="2">Postpartum haemorrhage (> 1 litre) / requiring transfusion</td></tr>
<tr><td rowspan="3">NEW ONSET / TRANSIENT</td><td colspan="2">Surgical procedure in pregnancy or postpartum</td><td>e.g. ERPC, appendicectomy, postpartum sterilisation, postpartum wound infection</td></tr>
<tr><td colspan="2">Ovarian Hyperstimulation syndrome</td><td></td></tr>
<tr><td colspan="2">Immobility (>3 days bed rest)</td><td>e.g. symphysis pubis dysfunction restricting mobility</td></tr>
</table>

30.3 Evidence of methods of prophylaxis

A search was conducted for evidence from RCTs and systematic reviews for all populations (section 3.8). Any papers which included patients who pregnant or up to 6 weeks postpartum were identified from this initial search and were reviewed.

One Cochrane review of evidence (which included 8 RCTs for prophylaxis against VTE in pregnancy and the early postnatal period) was found and reviewed[215]. One additional paper[214] published after the Cochrane review was identified which contained details of two separate pilot RCTs conducted in different populations.

- Four RCTs in the Cochrane review and one of the RCTs within the additional paper evaluated antenatal, or antenatal and postnatal prophylaxis in women with increased risk (n=314). These patients received long term prophylaxis delivered in community care settings and were considered by the GDG to be outside the scope of the guideline as they were not admitted to hospital.

- Four RCTs in the Cochrane review and the second of the RCTs within the addition paper evaluated prophylaxis after caesarean section. Of these 5 studies, four were excluded; one as it did not compare interventions under consideration by the guideline, one due to VTE not being reported as an outcome and two due to VTE outcomes not being well defined. This is consistent with the criteria outlined in section 3.8. The remaining RCT[214] compared LMWH with placebo in 141 women and reported one symptomatic PE event in the placebo arm.

The Cochrane review concluded that, on the basis of trials included, it was not possible to make a conclusive recommendation for thromboprophylaxis during pregnancy and postpartum due to the small sample sizes and the small number of trials comparing the same interventions.

There is no evidence for VTE prophylaxis for pregnant women who are admitted to hospital for non-pregnancy related reasons. All of the studies comparing different types of VTE prophylaxis included in Chapter 9 to 29 excluded patients who were pregnant.A search for evidence from RCTs and systematic reviews was conducted in this patient population.

One Cochrane review of evidence (which included 8 trials) for prophylaxis against VTE in pregnancy and the early postnatal period was found and reviewed[215]. One additional study containing the results of two separate pilot trials was published subsequent to the systematic review[214].

- Four studies in the Cochrane review and one part of the pilot study evaluated antenatal, or antenatal and postnatal prophylaxis in women with increased risk (n=314). These patients were outside the scope of the guideline as they were not admitted to hospital.

- Four studies in the Cochrane review and the second part of the pilot study evaluated prophylaxis after caesarean section. Of these 5 studies, four were excluded; one as it did not compare interventions under consideration by the guideline, one due to VTE not being reported as an outcome and two due to VTE outcomes not being well defined. The remaining study[214]

compared LMWH and placebo in 141 women and reported one symptomatic PE event in the placebo arm.

The Cochrane review concluded that, on the basis of trials included, it was not possible to make a conclusive recommendation for thromboprophylaxis during pregnancy and postpartum due to the small sample sizes and the small number of trials making the same comparisons.

There is no evidence for VTE prophylaxis of pregnant women who are admitted to hospital for non-pregnancy related reasons. All of the studies comparing different types of VTE prophylaxis included in Chapter 9 to 29 excluded patients who were pregnant.

30.4 Network meta-analysis results

Network meta-analysis was not completed for this population.

30.5 Cost-effectiveness evidence

We did not prioritise this population subgroup for cost-effectiveness analysis and no relevant cost-effectiveness studies were found in the literature.

30.6 Patient views

No studies conducted specifically in pregnant women were found.

For patient views about specific prophylaxis agents, see section 6.6.

30.7 Summary of evidence

Evidence statements
A review of prophylaxis efficacy in this population did not find conclusive evidence from randomised clinical trials.
There is no relevant cost-effectiveness evidence specifically for this population subgroup.

30.8 Recommendations and link to evidence

Recommendation	**Consider offering pharmacological VTE prophylaxis with LMWH (or UFH for patients with renal failure) to women who are pregnant or have given birth within the previous 6 weeks who are admitted to hospital but are not undergoing surgery, and who have one or more of the following risk factors:** • **expected to have significantly reduced mobility for 3 or more days** • **active cancer or cancer treatment** • **age over 35** • **critical care admission** • **dehydration** • **excess blood loss or blood transfusion** • **known thrombophilias** • **obesity (pre-pregnancy or early pregnancy BMI over 30 kg/m^2)** • **one or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)** • **personal history or a first-degree relative with a history of VTE** • **pregnancy-related risk factor (such as ovarian hyperstimulation, hyperemesis gravidarum, multiple pregnancy or pre-eclampsia)** • **varicose veins with phlebitis.**
Relative Values of Outcomes	The outcomes identified as important by the Guideline Development Group included thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).
Trade off between clinical benefit and harms	The benefits of reducing the risk of VTE and long term consequences were considered against potential harmful effects to both the mother and her unborn child (if the admission was antenatal).
Economic considerations	A cost effectiveness analysis was not completed specifically for this population subgroup. However, the cost-effectiveness model for medical patients indicates that prophylaxis with LMWH is cost-effective for patients at increased risk.
Quality of evidence	No RCT studies on methods of prophylaxis were found in pregnant or postpartum women admitted to hospital not undergoing surgery.

The recommendations were developed based on the expert consensus. These are supported by epidemiological studies although no systematic review of these studies was completed.

Other considerations

Pregnancy and the postpartum period (up to and including 6 weeks after delivery) have been identified as an independent risk factor for VTE. If these patients are admitted and have one of the risk factors listed, they should be considered for prophylaxis. Most women having vaginal deliveries will not require an extended stay in hospital and women are unlikely to have restricted mobility for extended periods of time.

The risk factors for VTE within the recommendation are similar to those used for other hospitalised patients. The evidence for these factors is reviewed in section 5.7.

The risk factors added or modified are based on additional information presented within section 30.2 specifically for pregnant women and those ≤6 weeks postpartum. The age criterion of 35 was added as the evidence suggests that this is when pregnant women are at increased risk. Two other risk factors were added; excess blood loss or blood transfusion and other specific pregnancy related risk factors. The evidence for these are discussed in section 30.2

Choice of prophylactic agents

The summary of product characteristics contains further information on the use of pharmacological prophylaxis agents during pregnancy and postpartum.

LMWH: Although it has not been tested extensively in this population, low molecular weight heparin (LMWH) is regarded as the most appropriate prophylaxis for pregnant women. LMWH has been used widely in pregnancy and is considered to be relatively safe. It is preferred over over unfractionated heparin, due to its better safety profile and convenience[235] the summary of product characteristics indicates that animal studies have not shown evidence of fetotoxicity or teratogenicity. Heparin induced thrombocytopenia (HIT) with LMWH has not been reported and the risk of osteoporotic fracture with LMWH is known to be much lower than the risk with unfractionated heparin (UFH), although the actual risk is uncertain.

Fondaparinux: There is inadequate safety information for the use of fondaparinux during pregnancy and should not be prescribed unless clearly necessary.

Warfarin: has been identified to have teratogenic and bleeding risks to the foetus and should not be used without a careful risk-benefit analysis and discussion with the patient.

Prophylaxis dosing:

There is debate about the appropriate frequency and size of doses of LMWH in pregnancy due to inadequate information from clinical trials. Due to the increased plasma volume,

	increased glomerular filtration rate and, therefore, decreased half-life of LMWH during pregnancy, dose adjustment (based on weight) may be necessary. More details are available in the summary of product characteristics and the in the RCOG green-top guidelines[563].
Recommendation	**Consider offering combined VTE prophylaxis with mechanical methods and LMWH (or UFH for patients with renal failure) to women who are pregnant or have given birth within the previous 6 weeks who are undergoing surgery, including caesarean section.**
Relative values of Outcomes	The outcomes identified as important by the Guideline Development Group included thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).
Trade off between clinical benefit and harms	The benefits of reducing the risk of VTE and long term consequences were considered against potential harmful effects to both the mother and her unborn child (if the admission was antenatal).
Economic considerations	No cost effectiveness analysis was completed specifically for this population subgroup. However, the cost-effectiveness model for general surgical patients indicates that combined mechanical and pharmacological prophylaxis is cost-effective for patients at increased risk of VTE where the risk of major bleeding is less than 1%.
Quality of evidence	There was only one small randomised controlled trial included for this population which compared the use of LMWH with placebo. Only one event occurred in either arm (1 PE in the placebo) and so no firm conclusions can be drawn from these data.
Other considerations	Pregnancy and postpartum has been identified as an independent risk factor for VTE. If these patients under go surgery during this time (up to 6 weeks after delivery) they would be exposed to an additional risk of VTE which the Guideline Development Group decided should warrant combined prophylaxis with mechanical methods and LMWH. There is no evidence for mechanical methods in pregnant women but providing appropriate precautions are taken they are likely to be safe in this population.

Recommendation	**Offer mechanical and/or pharmacological VTE prophylaxis to women who are pregnant or have given birth within the previous 6 weeks only after assessing the risks and benefits and discussing these with the woman and with healthcare professionals who have knowledge of the proposed method of VTE prophylaxis during pregnancy and post partum. Plan when to start and stop pharmacological VTE prophylaxis to minimise the risk of bleeding.**
Trade off between clinical benefit and harms	The benefits of reducing the risk of VTE and long term consequences were considered against potential harmful effects to both the mother and her unborn child (if the admission was antenatal).
Economic considerations	No cost effectiveness analysis was completed specifically for this population subgroup.
Other considerations	Due to the lack of evidence in this area it was felt by the GDG that decisions for prophylaxis in pregnant women and those up to 6 weeks post partum should be made after a careful consideration of the risks and benefits and after discussion with experts in this area. **Timing of prophylaxis** The initiation of prophylaxis should generally be given as soon as it is safe to do so. Within this population the expert advisors highlighted two circumstances which need particular discussion, namely the use of anaesthesia and the timing of post partum VTE prophylaxis. ***Use of anaesthesia:*** Regional anaesthesia can only be sited after discussion with the obstetric anaesthetist in keeping with local obstetric anaesthetic protocols. It is important to discuss the implication of treatment with LMWH for regional anaesthesia/analgesia with the women prior to labour or Caesarean section. Careful planning of the timing of pharmacological prophylaxis around regional anaesthetic techniques is required to minimise the risk of epidural haematoma (see section 19.4). This should include preventing further injections of LMWH once labour has started to allow for the use of regional anaesthesia. The summary of product characteristics should be consulted according to the prophylaxis drug that is being, or is planned to be, used. There is an increased risk of wound haematoma following caesarean section with both unfractionated heparin and LMWH of around 2%[235]. Women at high risk of haemorrhage with risk factors including major antepartum haemorrhage, coagulopathy, progressive wound haematoma, suspected intra-abdominal bleeding and post partum haemorrhage may be more conveniently managed with unfractionated heparin or anti-embolism stockings (GCS). If a woman develops a haemorrhagic problem while on pharmacological VTE

prophylaxis the treatment should be stopped and expert haematological advice sought. However, excess blood loss and blood transfusion have been identified as risk factors for VTE for these women (section 30.2) and so pharmacological VTE prophylaxis should begin or be reinstituted as soon as the immediate risk of haemorrhage is reduced.

Postpartum thromboprophylaxis: The first thromboprophylactic dose of LMWH should be given as soon as possible after delivery provided there is no postpartum haemorrhage or regional analgesia (see 'regional anaesthesia' discussion above for guidance). If postpartum haemorrhage has occurred our expert advisors advised that the risk of further bleeding should be evaluated considered but that LMWH can normally be given by four hours after delivery.

Duration of prophylaxis

The duration of prophylaxis should be carefully planned. As always, decisions should be made according to individual patient characteristics and should be discussed with patients and, where doubt exists, with healthcare professionals who have knowledge of VTE in these patients.

Although decisions on duration should be made on the balance of risks and benefits for individual patients, our expert advisors proposed that 7 days thromboprophylaxis is used for all women undergoing an emergency caesarean section, all women undergoing an elective caesarean section with an additional risk factor and all women with Class 3 obesity (BMI > 40kg/m2) after delivery. This is consistent with the RCOG guideline[563].

A duration of prophylaxis of up to 6 weeks may be considered appropriate for women assessed to be at a at high risk of postpartum VTE for example those who have had a previous VTE, or women who have additional persisting (greater than 7 days) risk factors such as a wound infection. This is consistent with the RCOG guidelines and is in line with the evidence that there is an extended risk of VTE up to 6 weeks postpartum.

30.8.1 Research Recommendations

There is a lack of evidence for prophylaxis in this population, which may be due to the difficulty in conducting clinical trials in this patient group. Further research for prophylaxis for women who are pregnant or or have given birth within the previous 6 weeks post-partum and who are admitted to hospital is required.

30.8.2 Other recommendations of relevance

The specific recommendations for women who are pregnant or post partum in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)

30.9 Summary of recommendations

- Consider offering pharmacological VTE prophylaxis with LMWH (or UFH for patients with renal failure) to women who are pregnant or have given birth within the previous 6 weeks who are admitted to hospital but are not undergoing surgery, and who have one or more of the following risk factors:
  - expected to have significantly reduced mobility for 3 or more days
  - active cancer or cancer treatment
  - age over 35
  - critical care admission
  - dehydration
  - excess blood loss or blood transfusion
  - known thrombophilias
  - obesity (pre-pregnancy or early pregnancy BMI over 30 kg/m^2)
  - one or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
  - personal history or a first-degree relative with a history of VTE
  - pregnancy-related risk factor (such as ovarian hyperstimulation, hyperemesis gravidarum, multiple pregnancy or pre-eclampsia)
  - varicose veins with phlebitis.
- Consider offering combined VTE prophylaxis with mechanical methods and LMWH to women who are pregnant or have given birth within the previous 6 weeks who are undergoing surgery, including caesarean section.
- Offer mechanical and/or pharmacological VTE prophylaxis to women who are pregnant or have given birth within the previous 6 weeks only after assessing the risks and benefits and discussing these with the woman and with healthcare professionals who have knowledge of the proposed method of VTE prophylaxis during pregnancy and post

partum. Plan when to start and stop pharmacological VTE prophylaxis to minimise the risk of bleeding.

31 Patients requiring antiplatelet agents and anticoagulants for other reasons

31.1 Antiplatelet agents

Aspirin, clopidogrel and dipyridamole are prescribed for their anti-platelet actions. Aspirin has been shown to be beneficial to patients with arterial blood vessel disease at a dose of 75mg daily. At this dose it has minimal anti-thrombotic effect. Even at high doses (greater than 300mg daily) it is less efficient at reducing the risk of VTE formation than standard pharmacological methods. Clopidogrel although prescribed predominantly for its antiplatelet effect in the treatment of acute coronary syndromes and following stent insertion is not licensed for VTE prophylaxis as a single agent and is less cost effective than standard pharmacological methods (chapters 9 -1). Dipyridamole is used as an adjunct to anticoagulation for prophylaxis of thromboembolism associated with prosthetic heart valves. It is also licensed for secondary prevention of ischaemic stroke and transient ischaemic attacks. There are no trials regarding its efficacy in the prophylaxis of VTE.

Patients admitted to hospital whilst taking these medicines are required to have assessment of their VTE risk performed (chapter 5). Patients who have a clinical need for their anti-platelet agents should continue to take their medication. Patients who are assessed as being at increased risk of VTE should receive appropriate prophylaxis with low molecular weight heparin (LMWH) or fondaparinux, once the bleeding risk is reviewed and has been established as low. Mechanical methods can be used where appropriate or if the bleeding risk is considered to be too high for additional pharmacological prophylaxis.

31.2 Recommendations and link to evidence

Recommendation	**Do not regard aspirin or other antiplatelet agents as adequate prophylaxis for VTE.**
Recommendation	**Consider offering additional mechanical or pharmacological VTE prophylaxis to patients who are having antiplatelet agents to treat other conditions and who are assessed to be at increased risk of VTE (see section 5.9). Take into account the risk of bleeding (see *Box 2*) and of comorbidities such as arterial thrombosis.** • **If the risk of VTE outweighs the risk of bleeding, consider pharmacological VTE prophylaxis according to the reason for admission.** • **If the risk of bleeding outweighs the risk of VTE, offer mechanical VTE prophylaxis.**
Recommendation –from section 5.9	**Regard medical patients as being at increased risk of VTE if they:** • **have had or are expected to have significantly reduced mobility for 3 days or more, or** • **are expected to have ongoing reduced mobility relative to their normal state and have one or more of the risk factors in**
Box 1 –Risk Factors for VTE	• **Active cancer or cancer treatment** • **Age over 60 years** • **Critical care admission** • **Dehydration** • **Known thrombophilias** • **Obesity (BMI over 30 kg/m^2)** • **One or more significant medical comorbidities (such as heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions)** • **Personal history or a first degree relative with a history of VTE** • **Use of hormone replacement therapy** • **Use of oestrogen-containing contraceptive therapy** • **Varicose veins with phlebitis.** **For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and up to 6**

	weeks post partum)
Recommendation–from section 5.9	**Assess all patients for risk of bleeding before offering pharmacological VTE prophylaxis *. Do not offer pharmacological VTE prophylaxis to patients with any of the risk factors for bleeding shown in Box 2, unless the risk of VTE outweighs the risk of bleeding.** ***Consult the summary of product characteristics for the pharmacological VTE prophylaxis being used or planned for further details.***
Box 2-Bleeding Risk Factors	• **Active bleeding** • **Acquired bleeding disorders (such as acute liver failure)** • **Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR higher than 2)** • **Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours** • **Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours** • **Acute stroke** • **Thrombocytopenia (platelets less than 75 x 109/l)** • **Uncontrolled systolic hypertension (230/120 mmHg or higher)** • **Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease)**
Relative values of different outcomes	The outcomes considered important by the Guideline Development Group (GDG) were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome). Additionally patients who are receiving antiplatelet agents are likely to have additional comorbidities, such as a high arterial side thrombosis risk. These factors meant that the GDG felt that although existing antiplatelet agents should not be stopped, additional thromboprophylaxis should be considered to ensure that patients are adequately protected.
Trade off between clinical benefit and harms	The risks of developing VTE may be high and these need to be weighed up against the risks of possible side effects such as bleeding which is increased if antiplatelet agents are also being used.

Economic considerations

There is no relevant cost-effectiveness evidence specifically for this population subgroup.

In four out of five of the population subgroups that we modelled, there was enough evidence to include aspirin (Chapters 9 to 12). In all four models, aspirin alone was one of the least effective strategies at increasing quality adjusted life years (QALYs) and least cost-effective. Conversely low molecular weight heparin (LMWH) was consistently one of the most effective and cost-effective strategies. Mechanical prophylaxis in population subgroups where there is evidence, also seems to be more effective and cost-effective than aspirin alone.

Two of our models (Chapters 9 and 10) considered the combination of high dose aspirin and unfractionated heparin. In both cases the strategy reduced QALYs compared with no prophylaxis and hence the combination was neither effective nor cost-effective. This was due to a very high bleeding increase, as estimated from our network meta-analysis. However, these studies did use very high doses of aspirin (sometimes up to 1000mg per day).

Quality of evidence

All included RCTs were either individually critically appraised to be of a high quality (level 1+ or level 1++) or came from systematic reviews of RCTs which had been critically appraised to be of a high quality (level 1+ or level 1++).

The evidence for adding other pharmacological agents to aspirin is very sparse. There are two studies in general surgery patients where all patients received high dose aspirin (>300mg per day) and patient in one arm of the trial also received UFH. These trials reported a significant decrease in DVT events and a significant increase in major bleeding (Forest plots 149-151, Appendix E).

There were five studies in patients undergoing surgery (2 general surgery, 1 elective hip replacement surgery, 2 mixed surgery) which compared the addition of high dose aspirin (>300mg per day) to a background of UFH, which was received by patients in both arms of the study. The combined results of these studies do not report any statistically different findings for DVT, PE or major bleeding (Forest plots 161-163, Appendix E).

In addition, two studies in stroke patients which add UFH or LMWH to aspirin (unknown dose). Combining these studies showed that LMWH and aspirin had a statistically significant reduction in DVT events without significant increase in bleeding compared with UFH and aspirin (chapter 24, Forest plots 183-186, Appendix E).

Other considerations

The GDG found it difficult to identify situations where it was clear that pharmacological thromboprophylaxis should be used

in addition to antiplatelet agents and felt that healthcare professionals should use guidance provided in the BNF or summary of product characteristics for the agents being used or those which are planned. Individual assessment of the risks and benefits is key and this is likely to require clinical judgement.

For patients in whom additional pharmacological thromboprophylaxis was deemed inappropriate but who are considered at high risk of VTE, mechanical methods (such as anti-embolism stockings, intermittent pneumatic compression devices) can be considered as an alternative which does not increase the risk of bleeding. Where mechanical methods are provided they should be used in line with the recommendations in section 6.7.

31.3 Anticoagulant agents

Patients who are admitted who are already receiving anticoagulation therapy, or who are started on full dose anti-coagulation using heparin, do not require additional pharmacological VTE prophylaxis. Patients (including those admitted taking oral thrombin or oral Xa inhibitors) should still have a VTE assessment performed (section 5.9). Treatment should be continued unless a clinical contraindication has arisen. If treatment is stopped the patients are at risk of VTE and they should be considered for VTE prophylaxis accordingly.

31.3.1 Warfarin bridging

Some patients admitted to hospital for surgical procedures will already be receiving warfarin. Healthcare professionals involved in their care will be required to make decisions about whether to, and when to stop, the warfarin and replace with other anticoagulant agents such as low molecular weight heparin. Warfarin bridging was not prioritised for a full systematic review. However, the guideline development group considered it to be an important and complex area which will involve the assessment of risks and benefits for each patient. An example of a strategy for warfarin bridging is included in Appendix H. When unsure of the appropriate action to take, healthcare professionals should consult colleagues with specialist knowledge in this area.

31.4 Recommendations and link to evidence

Recommendation	**Do not offer additional pharmacological or mechanical prophylaxis for VTE to patients who are taking vitamin K antagonists and who are within their therapeutic range, providing anticoagulant therapy is continued.**
Relative values of different outcomes	The outcomes considered important by the GDG were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).

Trade off between clinical benefit and harms	The risk of developing venous thromboembolism is weighed against the increase risk in bleeding caused by pharmacological prophylaxis.
Economic considerations	There is no relevant cost-effectiveness evidence specifically for this population subgroup. Vitamin K antagonists (VKA) are shown to be an effective and cost-effective strategy in several groups of patient (Chapters 9 to 12). In the case of patients already on VKAs, they can obtain the benefits of prophylaxis without any additional drug and monitoring costs.
Quality of evidence	There is evidence across a number of different populations that vitamin K antagonists are effective at reducing the risk of VTE .
Other considerations	Doses of anticoagulants used for treatment are usually higher than for prophylaxis use and so are likely to be suitable for reducing VTE risk although they will increase bleeding risk. .

Recommendation	**Do not offer additional pharmacological or mechanical prophylaxis for VTE to patients who are having full anticoagulant therapy (for example, fondaparinux sodium, LMWH or UFH).**
Relative values of different outcomes	The outcomes considered important by the GDG were thromboembolic events (asymptomatic and symptomatic DVT, symptomatic pulmonary embolism and fatal pulmonary embolism), bleeding events (major bleeding, fatal bleeding and stroke) and other long term events occurring as a result of VTE (chronic thromboembolic pulmonary hypertension and post thrombotic syndrome).
Trade off between clinical benefit and harms	The risk of developing venous thromboembolism is weighed against the increase risk in bleeding caused by pharmacological prophylaxis.
Economic considerations	There is no relevant cost-effectiveness evidence specifically for this population subgroup. These drugs have been shown to be an effective and cost-effective strategy in several groups of patient (Chapters 9 to 12 and 23). In the case of patients already on these drugs, they can obtain the benefits of prophylaxis without any additional drug and costs.
Quality of evidence	There is evidence across a number of different populations that LMWH, UFH and fondaparinux are all effective at reducing the risk of VTE.
Other considerations	Doses of anticoagulants used for treatment are usually higher than for prophylaxis use and so are likely to be suitable for reducing VTE risk although they will increase bleeding risk. .

31.4.1 Other recommendations of relevance

The specific recommendations for patients already using antiplatelets and/or anticoagulants in this chapter should be read in conjunction with other relevant recommendations presented elsewhere in the guideline. These are:

- risk assessment for VTE and major bleeding (Section 5.9)
- the use of prophylaxis in general (Section 6.7 and 6.8)
- the provision of patient information (Section 32.5)
- patients undergoing cardiac surgery (Section 15.7)
- patients undergoing vascular surgery (Section 16.7)
- patients with stroke (Section 24.7)
- patients with acute coronary syndromes (Section 25.7)
- patients with cancer (Section 26.7)

31.5 Recommendations for research

A top priority research recommendation was identified for the use of prophylactic-dose anticoagulants in stroke patients (section 2.3.4).

31.6 Summary of recommendations

- Do not regard aspirin or other antiplatelet agents as adequate prophylaxis for VTE.
- Consider offering additional mechanical or pharmacological VTE prophylaxis to patients who are having antiplatelet agents to treat other conditions and who are assessed to be at increased risk of VTE (see section 5.9). Take into account the risk of bleeding (see **Box 2**) and of comorbidities such as arterial thrombosis.
  - If the risk of VTE outweighs the risk of bleeding, consider offering LMWH or UFH (for patients with renal failure).
  - If the risk of bleeding outweighs the risk of VTE, offer mechanical VTE prophylaxis.
- Regard medical patients as being at increased risk of VTE if they:
  - have had or are expected to have significantly reduced mobility for 3 days or more **or**
  - are expected to have ongoing reduced mobility relative to their normal state **and** have one or more of the risk factors in **Box 1**
- Regard surgical and trauma patients as being at increased risk of VTE if they meet one of the following criteria:

- surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb
- acute surgical admission with inflammatory or intra-abdominal condition
- expected significant reduction in mobility
- have one or more risk factors shown in **Box 1**.

➢ Assess all patients for risk of bleeding before offering pharmacological VTE prophylaxis . Do not offer pharmacological VTE prophylaxis to patients with any of the risk factors for bleeding shown in **Box 2,** unless the risk of VTE outweighs the risk of bleeding.

Box 1 Risk factors for VTE

- Active cancer or cancer treatment
- Age over 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI over 30 kg/m^2)
- One or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
- Personal history or first-degree relative with a history of VTE
- Use of hormone replacement therapy
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis

For women who are pregnant or have given birth within the previous 6 weeks see Chapter 30 (Pregnancy and 6 weeks post partum)

Box 2 Risk factors for bleeding

- Active bleeding
- Acquired bleeding disorders (such as acute liver failure)
- Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with international noramlised ratio [INR] higher than 2)
- Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours
- Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours
- Acute stroke
- Thrombocytopenia (platelets less than 75 x 109/l)
- Uncontrolled systolic hypertension (230/120 mmHg or higher)
- Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease)

- Do not offer additional pharmacological or mechanical prophylaxis for VTE to patients who are taking vitamin K antagonists and who are within their therapeutic range, providing anticoagulant therapy is continued.

- Do not offer additional pharmacological or mechanical prophylaxis for VTE to patients who are having full anticoagulant therapy (for example, fondaparinux sodium, LMWH or UFH).

32 Provision of information to patients and planning for discharge

32.1 Introduction

Medical professionals have a responsibility to inform patients under their care about their proposed interventions. In this context it means providing information on venous thromboembolism (VTE) risk, the optimal methods to prevent this, the consequences of not receiving prophylaxis and possible side effects of the prophylactic intervention. This opportunity for discussion should be made available before provision of prophylaxis, unless this is not clinically possible (for example unconsciousness) or when any delays could be seriously detrimental.

Good communication between the healthcare professionals and patients is essential. In the context of this guideline, the patients may be newly admitted to the hospital and often find the situation overwhelming. This is not the best time to assimilate complex information and make decisions, and healthcare professionals should take this into account when communicating with the patients. Patients should be encouraged to ask questions at any point during their stay and healthcare professionals may have to check that the patients understand the information from time to time.

The main class of drugs used for thromboprophylaxis is heparin; either low molecular weight heparins (LMWH) or unfractionated heparin (UFH). Heparin is a sulphated glycosaminoglycan derived from animal tissues, and those marketed in the UK are principally of porcine origin. Using animal derived products may be of concern to patients of certain religious or personal beliefs. Therefore, healthcare professionals should be prepared to discuss these concerns with the patients (or their caregivers) and provide them with information to help them to address any ethical or religious concerns. Depending on the individual clinical condition of the patients, the synthetic alternatives to heparin may be less suitable or have its disadvantages. Clinicians should ensure that patients are aware of these issues.

32.1.1 Aim

The aim of this section is two fold:

- to examine whether the education of patients who were admitted to hospital about VTE or its prophylaxis methods:

- reduced the number of DVTs and pulmonary embolisms *or*
- affected any of the outcomes identified as important by the Guideline Development Group (Section 3.5) or
- influenced patient adherence to thromboprophylaxis

- to find out what type of information might be required by patients receiving thromboprophylaxis measures.

32.1.2 Methods

We searched for studies that examined the effect of providing information to patients on VTE or on methods of prophylaxis. We also searched for studies which were designed to examine the information required by patients. This search was not limited to randomised control trials but included observational and qualitative studies as these can provide information which is applicable to current practice. The focus of this evidence review was to obtain relevant information and to interpret it in a meaningful manner. For more details about study designs and quality, see Chapter 3.

32.2 Summary of identified studies

32.2.1 Impact of providing information on VTE outcomes

No studies which examined the impact of providing patient information on reducing VTE outcomes were identified.

32.2.2 Impact of providing information on patient adherence

One observational study examined the impact of providing surgical patients with a small leaflet along with increasing nursing awareness through discussions on patient adherence [626]. The leaflet was printed with the phrase "*Please notify your nurse if your compression stockings are not on. They are important for preventing blood clots during the hospital stay*". Patient adherence to intermittent pneumatic compression devices (IPCD) did not significantly change after these interventions.

32.2.3 Information requirement for patients who need thromboprophylaxis

Two qualitative studies conducted in the UK provided some insight about areas where patients may benefit from receiving more information about VTE prevention [430,492].

A semi-structured interview study among 28 palliative care patients who received at least 5 days of LMWH prophylaxis found that most patients interviewed were not aware of the signs and symptoms of VTE. Patients in this study indicated that the main source of information about VTE was about long distance flights [492] (Evidence Table 62, Appendix D).

The other study was telephone interviews conducted to investigate what type of information should go into a patient information leaflet for anti-embolic stocking [430](Evidence table 61, Appendix D). Twelve patients who had been hospitalised within the past two months and had worn anti-embolism stockings for at least 48 hours participated; recruitment stopped when theme saturation was reached. The patients were asked about their experience and whether they had received information for specific aspects of anti-embolism stocking usage.

The study identified areas which will benefit from providing more patient information by examining aspects which went "wrong" due to patient's lack of awareness. The following are some relevant findings from the study:

- Most patients did not remember receiving information about VTE or anti-embolism stockings. Some patients did not understand why they had to wear the anti-embolism stockings; this resulted in misunderstanding that they could take them off if they did not "work" for them. Not all patients understood how or when to put on or take off the anti-embolic stockings

- Some patients had indicated that it would be useful to have some information, especially something to read. Despite that, they were unlikely to actively ask for information about anti-embolism stockings. Reasons given include:

    - They believed they would have been told, if there was something important they needed to know. Otherwise, a lot of things should be based on "common sense"

    - In the hospital setting, their role as a patient is "You do as you are told", i.e not asking questions

- Patients depended on their health care professionals, as there were few alternative sources of information other than from friends or family with history of thromboembolism and long haul flights

32.3 Conclusions on information for patients

The evidence suggests that the provision of patient information about risks of VTE and methods of VTE prophylaxis may be inadequate in some circumstances. Patients in the studies were confused about the condition and therefore unlikely to act appropriately. . Provision of relevant and adequate information is a prerequisite for the empowerment of patients, which will contribute to their acceptance and adherence to the treatment provided.

32.4 Summary of evidence

Evidence statements
No studies on the impact of patient education on venous thromboembolism outcomes were identified.
One observational study which provided only a small patient information leaflet did not find significant improvement in patient adherence to intermittent pneumatic compression devices after the intervention.
Two small qualitative studies found patients lack information about signs and symptoms of venous thromboembolism.
One small qualitative study among patients who received anti-embolism / graduated compression stockings found patients lacked certain information which could have improved their adherence or experience of care.

32.5 Recommendations and link to evidence – in hospital patient information

Recommendation	**Before starting VTE prophylaxis, offer patients and/or their families or carers verbal and written information on:** • **the risks and possible consequences of VTE** • **the importance of VTE prophylaxis and its possible side effects** • **the correct use of VTE prophylaxis (for example, anti-embolism stockings, foot impulse or intermittent pneumatic compression devices)** • **how patients can reduce their risk of VTE (such as keeping well hydrated and, if possible exercising and becoming more mobile).**
Relative values of different outcomes	Reducing the risk of venous thromboembolism and its associated short and long term consequences; and reducing unwanted effects of thromboprophylaxis methods are the most important outcomes. Increased patient awareness, adherence and correct use of prophylaxis methods could lead to a reduction in these VTE outcomes as well as improving the patient's experience and satisfaction.
Trade off between clinical benefit and harms	The Guideline Development Group considered that it was important that patients are fully aware of their VTE risks and the methods of reduction available. Opportunities for discussing and addressing any concerns about methods of thromboprophylaxis and associated risks must also be given. An informed patient would be better able to balance the benefits of thromboprophylaxis against the inconvenience or concerns. There is potential for harm if this information is not provided, for example resulting in low concordance with prophylaxis or delaying seeking medical help due to lack of symptom awareness. Improved understanding of how to reduce the risk of VTE also has the potential to reduce anxiety and improve patient participation.
Economic considerations	Information provision comes with its associated costs, such as time of health care professionals and costs associated with producing materials. However, the potential benefits of improving thromboprophylaxis adherence and reducing subsequent VTE events are likely to be cost-effective.
Quality of evidence	All studies were quality assessed using quality checklists appropriate to the study design where available. Where appropriate study design checklists were not available, attempts were made to ensure the results of the included studies were as free from bias as possible. There is not a large body of evidence to support the

recommendations.

The setting, population studied and type of intervention used are important factors which could affect the relevance of studies about provision of patient information to the various subpopulations of patients in this guideline.

Only two UK qualitative studies provided some relevant evidence about the potential issues in two intervention methods. Both studies were consistent in pointing out that patients may not be aware of signs and symptoms of VTE. An observational study was conducted in the United States and it is uncertain how applicable this evidence is.

It is particularly difficult to interpret studies on the impact of information provision. Information provision could only be expected to be effective if the information is relevant, acceptable to patients and provided using an effective medium. The study which provided limited information did not show any improvement in adherence. This could be due to limited amount of information provided or ineffective method of delivery.

Other considerations

Despite limited evidence, the Guideline Development Group considered that it was good practice and important to provide patients with information about the risk of VTE and what general methods they can do to reduce it such as early mobilisation, the importance of using prophylaxis correctly and information on the use any prophylaxis that they have been provided with..

Language barriers should not be a reason for non-provision of information. Provision on a national basis of translated documents should be undertaken.

Recommendation	**Be aware that heparins are of animal origin and this may be of concern to some patients*. For patients who have concerns about using animal products, consider offering synthetic alternatives based on clinical judgement after discussing their suitability, advantages and disadvantages with the patient.** **** See "Religion or belief: a practical guide for the NHS", website: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_093133)***
Trade off between clinical benefit and harms	Different prophylaxis methods have different levels of evidence of efficacy and safety in different populations. Ideally, the choice of agent should be based on the most evidence-based and cost-effective agent for a given population. However, in situations where there are strong

patient concerns, these need to be discussed openly.

Economic considerations

Where a choice of agents is provided within a recommendation this is based either on the results of the cost-effectiveness model for that population, or on the extrapolation of cost-effectiveness results in other populations. In these circumstances the guideline development group were unable to conclusively state which of the strategies were the most cost-effective. Another of the reasons for local factors to influence choice of drug is that the contract prices (and therefore cost-effectiveness) of some of the drugs vary considerably between NHS Trusts.

Other considerations

While it is important to offer patients alternatives if there are concerns about using animal based products, it is also important that patients are aware of the clinical benefits or disadvantages (if any) of using these alternative products. If religious beliefs are a source of concern, the patients should be aware of the official stand of religious bodies about the product. Patients will only be able to make a good decision if they have a complete picture of the pros and cons of using these products. Where information is available, it will be useful to direct the patients to these information sources. There is information for patients with specific concerns e.g: "Porcine Derived Products" booklet which is refered to in the Department of Health document titled"Religion or belief: a practical guide for the NHS" (available from http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_093133) .

If the relative risks and benefits are explained to the patient (e.g. that fondaparinux may not be as effective as heparin), and the decisions clearly documented in the patient's notes, the patient is perfectly within their rights to choose a less effective option, however difficult that might be for the clinician who wants to provide the best care.

32.6 Recommendations and link to evidence – planning for discharge

Recommendation	**As part of the discharge plan, offer patients and/or their families or carers verbal and written information on:** • **the signs and symptoms of deep vein thrombosis and pulmonary embolism** • **the correct and recommended duration of use of VTE prophylaxis at home (if discharged with prophylaxis)** • **the importance of using VTE prophylaxis correctly and continuing treatment for the recommended duration (if discharged with prophylaxis)** • **the signs and symptoms of adverse events related to VTE prophylaxis (if discharged with prophylaxis)** • **The importance of seeking help and who to contact if they have any problems using the prophylaxis (if discharged with prophylaxis)** • **the importance of seeking medical help if deep vein thrombosis, pulmonary embolism or other adverse events are suspected.**
Recommendation	**Ensure that patients who are discharged with anti-embolism stockings:** • **understand the benefits of wearing them** • **understand the need for daily hygiene removal** • **are able to remove and replace them, or have someone available who will be able to do this for them** • **know what to look for such as skin marking, blistering or discolouration, particularly over the heels and bony prominences** • **know who to contact if there is a problem.**
Recommendation	**Ensure that patients who are discharged with pharmacological and/or mechanical VTE prophylaxis are able to use it correctly, or have arrangements made for someone to be available who will be able to help them.**
Recommendation	**Notify the patient's GP if the patient has been discharged with pharmacological and/or mechanical VTE prophylaxis to be used at home.**
Relative values of different outcomes	Reducing the risk of venous thromboembolism and its associated short and long term consequences; and reducing unwanted effects of thromboprophylaxis methods are the most important outcomes. Increased patient awareness, adherence and correct use of prophylaxis methods could lead to a reduction in these

VTE outcomes as well as improving the patient's experience and satisfaction.

Trade off between clinical benefit and harms

The Guideline Development Group considered that it was important that patients are fully aware of their VTE risks and the methods of reduction available. Opportunities for discussing and addressing any concerns about methods of thromboprophylaxis and associated risks must also be given. An informed patient would be better able to balance the benefits of thromboprophylaxis against the inconvenience or concerns. There is potential for harm if this information is not provided, for example resulting in low concordance with prophylaxis or delaying seeking medical help due to lack of symptom awareness. Improved understanding of how to reduce the risk of VTE also has the potential to reduce anxiety and improve patient participation.

Economic considerations

Information provision comes with its associated costs, such as time of health care professionals and costs associated with producing materials. However, the potential benefits of improving thromboprophylaxis adherence and reducing subsequent VTE events are likely to be cost-effective.

Quality of evidence

All studies were quality assessed using quality checklists appropriate to the study design where available. Where appropriate study design checklists were not available, attempts were made to ensure the results of the included studies were as free from bias as possible.

There is not a large body of evidence to support the recommendations.

The setting, population studied and type of intervention used are important factors which could affect the relevance of studies about provision of patient information to the various subpopulations of patients in this guideline.

Only two UK qualitative studies provided some relevant evidence about the potential issues in two intervention methods. Both studies were consistent in pointing out that patients may not be aware of signs and symptoms of VTE. An observational study was conducted in the United States and it is uncertain how applicable this evidence is.

It is particularly difficult to interpret studies on the impact of information provision. Information provision could only be expected to be effective if the information is relevant, acceptable to patients and provided using an effective medium. The study which provided limited information did not show any improvement in adherence. This could be due to limited amount of information provided or ineffective method of delivery.

Other considerations

Despite limited evidence, the Guideline Development Group considered that it was good practice and important to provide patients with information about the risk of VTE and what they can do to reduce it, the signs and symptoms of VTE, how to use any prophylaxis that they will be administering at home and the importance of using these methods correctly. Additionally patients should know who to call if they have a problem with their prophylaxis and be advised to consult their GP after they are discharged from hospital if they suspect VTE, even if they are using thromboprophylaxis.

Expert advice from a general practitioner (GP) highlighted that the GP should be informed if a patient is discharged with prophylaxis to ensure that appropriate follow-up care can be offered.

Language barriers should not be a reason for non-provision of information. Provision on a national basis of translated documents should be undertaken.

32.7 Related recommendations

The specific recommendations for [provision of information to patients should be read in conjuction with other relevant recommendations presented elsewhere in the guideline. These are:

32.8 Summary of recommendations on provision of information for patients

- Before starting VTE prophylaxis, offer patients and/or their families or carers verbal and written information on:
  - the risks and possible consequences of VTE
  - the importance of VTE prophylaxis and its possible side effects
  - the correct use of VTE prophylaxis (for example, anti-embolism stockings, foot impulse or intermittent pneumatic compression devices).
  - how patients can reduce their risk of VTE (such as keeping well hydrated and, if possible exercising and becoming more mobile)

- Be aware that heparins are of animal origin and this may be of concern to some patients*. For patients who have concerns about using animal products, consider offering synthetic alternatives based on clinical judgement after discussing their suitability, advantages and disadvantages with the patient.

  * *See "Religion or belief: a practical guide for the NHS", website: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_093133)*

- As part of the discharge plan, offer patients and/or their families or carers verbal and written information on:

- the signs and symptoms of deep vein thrombosis and pulmonary embolism
- the correct and recommended duration of use of VTE prophylaxis at home (if discharged with prophylaxis)
- the importance of using VTE prophylaxis correctly and continuing treatment for the recommended duration (if discharged with prophylaxis)
- the signs and symptoms of adverse events related to VTE prophylaxis (if discharged with prophylaxis)
- the importance of seeking help and who to contact if they have any problems using the prophylaxis (if discharged with prophylaxis)
- the importance of seeking medical help if deep vein thrombosis, pulmonary embolism or other adverse events are suspected.

➢ Ensure that patients who are discharged with anti-embolism stockings:
- understand the benefits of wearing them
- understand the need for daily hygiene removal
- are able to remove and replace them, or have someone available who will be able to do this for them
- know what to look for such as skin marking, blistering or discolouration, particularly over the heels and bony prominences
- know who to contact if there is a problem.

➢ Ensure that patients who are discharged with pharmacological prophylaxis are able to use it correctly, or have arrangements made for someone to be available who will be able to help them

➢ Notify the patient's GP if the patient has been discharged with pharmacological and/or mechanical VTE prophylaxis to be used at home.

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Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital

Appendices A – D

APPENDICES

Produced by the National Collaborating Centre for Acute Care

Contents

Appendix A

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

1 Guideline title

Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital

1.1 Short title

Venous thromboembolism – prevention

2 Background

a) The National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Acute Care to develop a clinical guideline on reducing the risk of venous thromboembolism (VTE) in patients admitted to hospital, for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health (see appendix). The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

b) The Institute's clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued will have the effect of updating the Framework.

c) NICE clinical guidelines support the role of healthcare professionals in providing care in partnership with patients, taking account of their individual needs and preferences, and ensuring that patients (and their carers and families, where appropriate) can make informed decisions about their care and treatment.

3 Clinical need for the guideline

a) VTE is a spectrum of disease, ranging from asymptomatic calf vein thrombosis to symptomatic deep vein thrombosis (DVT), which may lead to potentially fatal pulmonary embolism (PE). Symptomatic VTE is common in hospital patients and brings a considerable burden of morbidity. Non-fatal VTE may produce long-term morbidity including chronic venous insufficiency, which may cause venous ulceration and development of a post-thrombotic limb (chronic pain, swelling and skin changes in the affected limb following a DVT). The incidence and prevalence of asymptomatic VTE in the community outside hospital is unknown.

b) VTE is an important cause of death in hospitalised patients, and treatment of non-fatal symptomatic VTE and related long-term morbidities is associated with a considerable cost to the health service.

c) In 2004–05, there were around 64,000 finished consultant episodes (that is, periods of care under a consultant within an NHS trust) with a diagnosis of VTE. In 2005, VTE was registered as the underlying cause of death in more than 6500 patients, although this figure is likely to be an underestimation of the true incidence.

d) The incidence of VTE in different groups of hospital patients varies greatly in the literature. The risk of PE in the absence of prophylaxis has been estimated at 5% following surgery in the highest risk groups, and around 1% in acutely ill medical patients.

e) The risk of developing VTE will depend on the condition for which the patient is admitted and on any predisposing risk factors (such as age, obesity and concomitant conditions). Both of these types of risk will be assessed within the guideline

f) Thromboprophylaxis reduces the risk of developing VTE, and a number of different interventions have been investigated. The prophylactic methods to be reviewed in this guideline are detailed in section 4.3c. The guideline will evaluate the clinical and cost effectiveness of, and risks associated with, each method.

g) There is no current worldwide consensus on which patients should receive thromboprophylaxis. The inconsistent use of preventative measures for VTE has been widely reported. A recent UK survey suggested that 71% of patients assessed to be at medium or high risk of developing DVT did not receive any form of pharmacological or mechanical thromboprophylaxis.

h) The guideline will incorporate the published NICE guideline 'Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery' (NICE clinical guideline 46). Because the 2-year review for NICE clinical guideline 46 is due during the development period for the new guideline, the review will be completed according to the latest evidence before the guideline is incorporated. A single piece of guidance will then be produced for all patients.

4 The guideline

a) The guideline development process is described in detail in two publications that are available from the NICE website (see 'Further information'). 'The guideline development process: an overview for stakeholders, the public and the NHS' describes how organisations can become involved in the development of a guideline. 'The guidelines manual' provides advice on the technical aspects of guideline development.

b) This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health (see appendix).

c) The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) Adults (18 years and older) admitted to hospital as inpatients or formally admitted to a hospital bed for day case procedures, including:

- surgical inpatients
- inpatients with acute medical illness (for example, myocardial infarction, stroke, spinal cord injury, severe infection or exacerbation of chronic obstructive pulmonary disease)
- trauma inpatients
- patients admitted to intensive care units
- cancer inpatients
- people undergoing long-term rehabilitation in hospital
- patients admitted to a hospital bed for day case medical or surgical procedures.

b) Within this population, pregnant women admitted to hospital have been identified as a group requiring special consideration.

c) During the review of the evidence, any additional groups that are shown to have particular clinical needs will be given special consideration.

4.1.2 Groups that will not be covered

a) People younger than 18 years.

b) People attending hospital as outpatients.

c) People presenting to emergency departments without admission.

d) Elderly or immobile people cared for at home, or in external residential accommodation, unless admitted to hospital.

e) Patients admitted to hospital with a diagnosis of, or suspected diagnosis of, DVT or PE.

4.2 Healthcare setting

a) Secondary and tertiary care.

b) Primary care after hospital discharge.

4.3 Clinical management

a) Risk factors associated with development of VTE in the groups listed in section 4.1.1 will be examined. The likelihood of a patient developing VTE will be assessed according to the condition for which the patient is admitted and any predisposing risk factors they may have.

b) The clinical and cost effectiveness, and possible adverse effects, of interventions to reduce the risk of VTE in patients admitted to hospital as outlined in section 4.1.1 will be evaluated.

c) Interventions that will be considered include:

- mechanical:
  - graduated elastic compression stockings
  - intermittent pneumatic compression devices, such as foot compression and calf compression
  - vena caval filters
- drugs/pharmacological:
  - low-dose unfractionated heparin
  - low molecular weight heparin

- synthetic pentasaccharides, such as fondaparinux
- oral anticoagulants, such as warfarin
- antiplatelet therapy, such as aspirin

- nursing care/physiotherapy:
  - early mobilisation
  - foot elevation
  - hydration

- recent advances, for example, drugs licensed during the course of guideline development.

Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only where clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform their decisions for individual patients.

d) The guideline development group will consider making recommendations on the principal complementary and alternative interventions or approaches to care relevant to the guideline topic.

e) The guideline development group will take reasonable steps to identify ineffective interventions and approaches to care. If robust and credible recommendations for re-positioning the intervention for optimal use, or changing the approach to care to make more efficient use of resources, can be made, they will be clearly stated. If the resources released are substantial, consideration will be given to listing such recommendations in the 'Key priorities for implementation' section of the guideline.

4.4 Status

4.4.1 Scope

This is the final scope.

Associated NICE guidance:

4.4.1.1 Published

- Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery. NICE clinical guideline 46 (2007). Available from www.nice.org.uk/CG046

- Caesarean section. NICE clinical guideline 13 (2004). Available from www.nice.org.uk/CG013

4.4.1.2 Under development

- Stroke: the diagnosis and acute management of stroke and transient ischaemic attacks. NICE clinical guideline (publication expected July 2008.

4.4.2 Guideline

The development of the guideline recommendations will begin in September 2007.

5 Further information

Information on the guideline development process is provided in:

- 'The guideline development process: an overview for stakeholders, the public and the NHS'
- 'The guidelines manual'.

These booklets are available as PDF files from the NICE website (www.nice.org.uk/guidelinesmanual). Information on the progress of the guideline will also be available from the website.

6 Referral from the Department of Health

The Department of Health asked the Institute:

> 'To prepare a clinical guideline on the prevention of VTE in all patients admitted to hospital.'

Appendix B

1 Declarations of interests

1.1 Introduction

All members of the GDG and all members of the NCC-AC staff were required to make formal declarations of interest at the outset, and these were updated at every subsequent meeting throughout the development process. No interests were declared that required action.

1.2 Declarations of interests of the GDG members

1.2.1 Tom Treasure (Chair)

GDG meeting	Declaration of Interests
First GDG meeting **(13th September 2007)**	None
Second GDG Meeting **(29th October 2007)**	None
Third GDG Meeting **(28th November 2007)**	None
Fourth GDG Meeting **(9th January 2008)**	None
Fifth GDG Meeting **(21st February 2008)**	None
Sixth GDG Meeting **(2nd April 2008)**	None
Seventh GDG Meeting **(13th May 2008)**	None
Eight GDG Meeting **(27th June 2008)**	None
Ninth GDG Meeting **(2nd September 2008)**	None
Tenth GDG Meeting **(8th October 2008)**	None
Eleventh GDG Meeting **(14th November 2008)**	None
Twelfth GDG Meeting **(16th December 2008)**	Not attended

GDG meeting	Declaration of Interests
Thirteenth GDG Meeting **(18th May 2009)**	None
Fourteenth GDG Meeting **(8th July 2009)**	None
Fifteenth GDG meeting **(3rd November 2009)**	None

1.2.2 Kim Carter

GDG meeting	Declaration of Interests
First GDG meeting **(13th September 2007)**	KC declared no personal pecuniary interest. She declared that she knew of no personal family interest. KC declared a non-personal pecuniary interest; the Trust that she works for has received a grant from Sanofi Aventis to develop a computerised assessment tool for VTE. Additionally she is a director of the Lifeblood Charity which receives some donations from the pharmaceutical industry. This is not a paid position. She declared a personal non-pecuniary interest; she is a member of Thrombosis Committee at Portsmouth Hospitals NHS Trust and has helped develop Trust VTE guidelines.
Second GDG Meeting **(29th October 2007)**	No change to declarations
Third GDG Meeting **(28th November 2007)**	KC declared that she knew of no personal pecuniary interest, personal family interest or personal non-pecuniary interest. She declared a non-personal pecuniary interest; the thrombosis committee at Portsmouth Hospitals Trust, of which she is a member, was nominated for, and was runner up at the hospital doctor team of the year award for thrombosis prophylaxis. The award was sponsored by Sanofi.
Fourth GDG Meeting **(9th January 2008)**	No change to declarations
Fifth GDG Meeting **(21st February 2008)**	No change to declarations
Sixth GDG Meeting **(2nd April 2008)**	Not attended
Seventh GDG Meeting **(13th May 2008)**	No change to declarations
Eight GDG Meeting **(27th June 2008)**	No change to declarations
Ninth GDG Meeting **(2nd September 2008)**	No change to declarations
Tenth GDG Meeting **(8th October 2008)**	No change to declarations
Eleventh GDG Meeting **(14th November 2008)**	No change to declarations
Twelfth GDG Meeting **(16th December 2008)**	No change to declarations

GDG meeting	Declaration of Interests
Thirteenth GDG Meeting **(18th May 2009)**	Not attended
Fourteenth GDG Meeting **(8th July 2009)**	Not attended
Fifteenth GDG meeting **(3rd November 2009)**	No change to declarations

1.2.3 Nandam Gautam

GDG meeting	Declaration of Interests
First GDG meeting **(13th September 2007)**	NG declared a personal pecuniary interest; he was paid to give Bristol-Myers Squibb lectures on unstable coronary syndrome. He declared that he knew of no personal family interest. NG declared a non-personal pecuniary interest; his unit received money from Sanofi Aventis for a short term DVT audit nurse. He declared a person non-pecuniary interest; he has established local policy guideline.
Second GDG Meeting **(29th October 2007)**	No change to declarations
Third GDG Meeting **(28th November 2007)**	Not attended
Fourth GDG Meeting **(9th January 2008)**	No change to declarations
Fifth GDG Meeting **(21st February 2008)**	NG declared a non-personal pecuniary interest, Bristol-Myers Squibb have donated £200 to an academic fund of which he is a director but not an exclusive cheque writer. He declared that he knew of no personal pecuniary, personal family interest or personal non-pecuniary interest above those already declared.
Sixth GDG Meeting **(2nd April 2008)**	No change to declarations
Seventh GDG Meeting **(13th May 2008)**	Not attended
Eight GDG Meeting **(27th June 2008)**	No change to declarations
Ninth GDG Meeting **(2nd September 2008)**	Not attended
Tenth GDG Meeting **(8th October 2008)**	Not attended
Eleventh GDG Meeting **(14th November 2008)**	NG declared a personal non-pecuniary interest. The department of acute medicine had a meeting sponsored by Bristol Myers Squibb. No financial benefit was gained. He declared he know of no personal pecuniary interest, personal family interest or non-personal pecuniary interest.
Twelfth GDG Meeting **(16th December 2008)**	No change to declarations
Thirteenth GDG Meeting **(18th May 2009)**	Not attended
Fourteenth GDG Meeting	Not attended

(8th July 2009)	
Fifteenth GDG meeting **(3rd November 2009)**	Not attended

1.2.4 Aroon Hingorani

GDG meeting	Declaration of Interests
First GDG meeting **(13th September 2007)**	AH declared a personal pecuniary interest; he is on the editorial board of Drug and Therapeutics Bulletin. He holds a Medical Research Council project grant with Pfizer as a collaborating co-funder. He has receives fellowship funding from British Heart Foundation. Has received honoraria for speaking at educational meetings (donated in full to charity). He declared that he knew of no personal family interest, non-personal pecuniary interest or personal non-pecuniary interest.
Second GDG Meeting **(29th October 2007)**	No change to declarations
Third GDG Meeting **(28th November 2007)**	No change to declarations
Fourth GDG Meeting **(9th January 2008)**	No change to declarations
Fifth GDG Meeting **(21st February 2008)**	Not attended
Sixth GDG Meeting **(2nd April 2008)**	Not attended
Seventh GDG Meeting **(13th May 2008)**	No change to declarations
Eight GDG Meeting **(27th June 2008)**	No change to declarations
Ninth GDG Meeting **(2nd September 2008)**	Not attended
Tenth GDG Meeting **(8th October 2008)**	Not attended
Eleventh GDG Meeting **(14th November 2008)**	Not attended
Twelfth GDG Meeting **(16th December 2008)**	Not attended
Thirteenth GDG Meeting **(18th May 2009)**	Not attended
Fourteenth GDG Meeting **(8th July 2009)**	Not attended
Fifteenth GDG meeting **(3rd November 2009)**	Not attended

1.2.5 Rodney Hughes

GDG meeting	Declaration of Interests
First GDG meeting **(13th September 2007)**	None
Second GDG Meeting **(29th October 2007)**	None
Third GDG Meeting **(28th November 2007)**	None
Fourth GDG Meeting **(9th January 2008)**	RH declared a non-personal pecuniary interest; his unit is involved in a trial where Sanofi-Aventis are reimbursing the cost of the drugs, although no grant is provided. He declared that he knew of no personal pecuniary interest, personal family interest or personal non-pecuniary interest.
Fifth GDG Meeting **(21st February 2008)**	No change to declarations
Sixth GDG Meeting **(2nd April 2008)**	No change to declarations
Seventh GDG Meeting **(13th May 2008)**	Not attended
Eight GDG Meeting **(27th June 2008)**	No change to declarations
Ninth GDG Meeting **(2nd September 2008)**	No change to declarations
Tenth GDG Meeting **(8th October 2008)**	Not attended
Eleventh GDG Meeting **(14th November 2008)**	No change to declarations
Twelfth GDG Meeting **(16th December 2008)**	No change to declarations
Thirteenth GDG Meeting **(18th May 2009)**	Not attended
Fourteenth GDG Meeting **(8th July 2009)**	Not attended
Fifteenth GDG meeting **(3rd November 2009)**	No change to declarations

1.2.6 Beverley Hunt

GDG meeting	Declaration of Interests
First GDG meeting **(13th September 2007)**	BH declared a personal pecuniary interest; she has been paid for giving lectures and taking part in drug advisory boards for Sanofi Aventis, Bayer and Boehringer Ingelheim within the last 12 months. She has been paid to script write and story board a set of cartoons on coagulation and VTE. She has attended a meeting which was funded by Bayer with journalists to develop user friendly words about VTE. She declared that she knew of no personal family interest. She declared a non-personal pecuniary interest; she is a director of British Society for Haematology Ltd and a director of Lifeblood, the Thrombosis Charity Ltd which receives money

GDG meeting	Declaration of Interests
	donated from industry for set projects. This is not a paid position. BH declared a personal non-pecuniary interest; she will appear before Health Select Committee on 18th October for a discussion about NICE processes.
Second GDG Meeting **(29th October 2007)**	BH declared a personal pecuniary interest; she has received a grant to her research funds from Bayer to pay for flights to attend the American Society of Haematology meeting in December 2007. She declared a non-personal pecuniary interest; a contribution to Lifeblood: the thrombosis charity was made in return for attending a meeting with journalists to discuss VTE terminology. She declared that she knew of no personal family interest or personal non-pecuniary interest above those she declared at the previous meeting.
Third GDG Meeting **(28th November 2007)**	No change to declarations
Fourth GDG Meeting **(9th January 2008)**	BH declared a non-personal pecuniary interest, meeting on 10 January 2008 organised by Bayer to discuss how to set-up thrombosis committees in trusts for which Lifeblood will receive payment. She declared that she knew of no personal pecuniary, personal family interest, non-personal pecuniary interest or personal non-pecuniary interest.
Fifth GDG Meeting **(21st February 2008)**	BH declared a non-personal pecuniary interest, Lifeblood for which she is a trustee has received educational grants from Bayer and Boehringer Ingelheim to develop the website. She declared a personal non-pecuniary interest, lecturing at a symposium at the British Society for haematology sponsored by Boehringer Ingelheim in April 2008, for which the fee was given to Lifeblood. She declared that she knew of no personal pecuniary interest or personal family interest above those declared at the previous meeting.
Sixth GDG Meeting **(2nd April 2008)**	No change to declarations
Seventh GDG Meeting **(13th May 2008)**	BH declared a personal non-pecuniary interest; she gave media interviews for the launch of Dabigaran to BBC, ITN, Radio 5 Live and Sky giving an independent view. During the media day the PR company working for Boehringer Ingelheim produced a press release on the Lifeblood's behalf without agreement from them. Lifeblood have made a formal complaint to The Association of the British Pharmaceutical Industry (ABPI), the Medicines and Healthcare products Regulatory Agency (MHRA) and NICE have been copied in. BH did not declare a personal pecuniary interest, personal family interest or non-personal pecuniary interests above those declared at the previous meeting.
Eight GDG Meeting **(27th June 2008)**	No change to declarations
Ninth GDG Meeting **(2nd September 2008)**	BH declared a non-personal pecuniary interest; Lifeblood: the thrombosis charity received money from Bayer for a lecture that she gave to journalists on VTE. She declared that she knew of no personal pecuniary interest, family interest or personal non-pecuniary interest, above those declared at the previous meeting.
Tenth GDG Meeting **(8th October 2008)**	No change to declarations
Eleventh GDG Meeting **(14th November 2008)**	BH declared a non-personal pecuniary interest; she was sponsored by Bayer to give a talk, monies received were given to Lifeblood, the thrombosis charity. She declared she knew of no personal pecuniary interest, personal family interest or personal non-pecuniary interest above those declared at the previous meeting.
Twelfth GDG Meeting **(16th December 2008)**	No change to declarations

GDG meeting	Declaration of Interests
Thirteenth GDG Meeting **(18th May 2009)**	No change to declarations
Fourteenth GDG Meeting **(8th July 2009)**	No change to declarations
Fifteenth GDG meeting **(3rd November 2009)**	BH declared a non-personal pecuniary interest; she accepted travel expenses for running a meeting for LGO and gave the remaining fee to charity. She declared that she knew of personal pecuniary interest, personal family interest or personal non-pecuniary interest, above those declared at the previous meeting.

1.2.7 Nigel Langford

GDG meeting	Declaration of Interests
First GDG meeting **(13th September 2007)**	NL declared a personal pecuniary interest; he received an honorarium from the University of Birmingham for lecturing on anticoagulation courses. He declared that he knew of no personal family interest. He declared a non-personal pecuniary interest; his department has received a grant into research looking at cellulitis as well as a service evaluation into the nurse led DVT/PE service from Sanofi Aventis. He declared a personal non-pecuniary interest; he is a member of a thrombosis committee, and has had a paper on venometers published in 'Acute Medicine'.
Second GDG Meeting **(29th October 2007)**	NL declared a non-personal pecuniary interest; his unit received a gift of single use tourniquets from Sanofi Aventis for an audit project. He declared he knew of no other personal pecuniary interest, personal family interest, non-personal pecuniary interest or personal non-pecuniary interest, above those he declared at the previous meeting
Third GDG Meeting **(28th November 2007)**	No change to declarations
Fourth GDG Meeting **(9th January 2008)**	Not attended
Fifth GDG Meeting **(21st February 2008)**	No change to declarations
Sixth GDG Meeting **(2nd April 2008)**	No change to declarations
Seventh GDG Meeting **(13th May 2008)**	No change to declarations
Eight GDG Meeting **(27th June 2008)**	No change to declarations
Ninth GDG Meeting **(2nd September 2008)**	No change to declarations
Tenth GDG Meeting **(8th October 2008)**	No change to declarations
Eleventh GDG Meeting **(14th November 2008)**	No change to declarations
Twelfth GDG Meeting **(16th December 2008)**	No change to declarations

GDG meeting	Declaration of Interests
Thirteenth GDG Meeting **(18th May 2009)**	Not attended
Fourteenth GDG Meeting **(8th July 2009)**	Not attended
Fifteenth GDG Meeting **(3rd November 2009)**	No change to declarations

1.2.8 Donald McBride (Joined the main guideline development group in Sep 2008)

GDG meeting	Declaration of Interests
Ninth GDG Meeting **(2nd September 2008)**	None
Tenth GDG Meeting **(8th October 2008)**	None
Eleventh GDG Meeting **(14th November 2008)**	None
Twelfth GDG Meeting **(16th December 2008)**	None
Thirteenth GDG Meeting **(18th May 2009)**	None
Fourteenth GDG Meeting **(8th July 2009)**	None
Fifteenth GDG meeting **(3rd November 2009)**	None

1.2.9 Gordon McPherson (Resigned from the guideline development group in Feb 2008)

GDG meeting	Declaration of Interests
First GDG meeting **(13th September 2007)**	None
Second GDG Meeting **(29th October 2007)**	None
Third GDG Meeting **(28th November 2007)**	Not attended
Fourth GDG Meeting **(9th January 2008)**	Not attended
Mr Gordon McPherson resigned from the GDG in Feburary 2008. He was replaced by Mr Peter Walton	

1.2.10 Paul Mainwaring

GDG meeting	Declaration of Interests
First GDG meeting **(13th September 2007)**	None

Second GDG Meeting **(29th October 2007)**	None
Third GDG Meeting **(28th November 2007)**	Not attended
Fourth GDG Meeting **(9th January 2008)**	Not attended
Fifth GDG Meeting **(21st February 2008)**	Not attended
Sixth GDG Meeting **(2nd April 2008)**	None
Seventh GDG Meeting **(13th May 2008)**	Not attended
Eight GDG Meeting **(27th June 2008)**	Not attended
Ninth GDG Meeting **(2nd September 2008)**	PM declared a personal non-pecuniary interest; he has been involved in running focus groups for several PCTs to look at world class commissioning and some of the pathways involved around: A&E redesign, Community Based Anticoagulation Monitoring Service, Community Chronic Kidney Disease Service, Community Dermatology Service He declared that he knew of no personal pecuniary interest, family interest or personal non-pecuniary interest, above those declared at the previous meeting.
Tenth GDG Meeting **(8th October 2008)**	Not attended
Eleventh GDG Meeting **(14th November 2008)**	Not attended
Twelfth GDG Meeting **(16th December 2008)**	Not attended
Thirteenth GDG Meeting **(18th May 2009)**	Not attended
Fourteenth GDG Meeting **(8th July 2009)**	Not attended
Fifteenth GDG meeting **(3rd November 2009)**	Not attended

1.2.11 Simon Noble

GDG meeting	Declaration of Interests
First GDG meeting **(13th September 2007)**	SN declared a personal pecuniary interest; he received honoraria from Leo Pharma for a talk given from in October 2006, and from Sanofi Aventis for a talk given in June 2006. He declared that he knew of no personal family interest. He declared a non-personal pecuniary interest; he is a grant holder (but not administrator/manager) for a study of dalteparin on lung cancer $1,000,000 from Pfizer. He declared that he knew of no personal non-pecuniary interest.
Second GDG Meeting **(29th October 2007)**	SN declared a personal non-pecuniary interest; he has been involved with the Welsh Assembly on a committee to promote safe prevention of VTE in association with Lifeblood. He declared he knew of no other personal pecuniary interest, personal family interest, non-personal pecuniary interest or personal non-pecuniary interest, above those he declared at the previous meeting.

GDG meeting	Declaration of Interests
Third GDG Meeting **(28th November 2007)**	No change to declarations
Fourth GDG Meeting **(9th January 2008)**	SN declared a non-personal pecuniary interest; he has accepted and invitation to become a trustee of Lifeblood. He declared that he knew of no personal pecuniary interest, personal family interest or personal non-pecuniary interest.
Fifth GDG Meeting **(21st February 2008)**	No change to declarations
Sixth GDG Meeting **(2nd April 2008)**	No change to declarations
Seventh GDG Meeting **(13th May 2008)**	No change to declarations
Eight GDG Meeting **(27th June 2008)**	Not attended
Ninth GDG Meeting **(2nd September 2008)**	SN declared a personal non-pecuniary interest; he has been invited to be a member of a thromboprophylaxis forum, supported by an unrestricted educational grant from Boerhinger Ingelheim. He declared that he knew of no personal pecuniary interest, personal family interest or non-personal pecuniary interest, above those declared at the previous meeting.
Tenth GDG Meeting **(8th October 2008)**	No change to declarations
Eleventh GDG Meeting **(14th November 2008)**	Not attended
Twelfth GDG Meeting **(16th December 2008)**	No change to declarations
Thirteenth GDG Meeting **(18th May 2009)**	No change to declarations
Fourteenth GDG Meeting **(8th July 2009)**	No change to declarations
Fifteenth GDG meeting **(3rd November 2009)**	Not attended

1.2.12 Gerard Stansby

GDG meeting	Declaration of Interests
First GDG meeting **(13th September 2007)**	GS declared a personal pecuniary interest; he has received speaker's fees from Sanofi Aventis and Bristol-Myers Squibb for chairing and speaking at meetings on peripheral arterial disease. He declared that he knew of no personal family interest. GS declared a non-personal pecuniary interest; he is co-chair of TARGET-PAD a lobbying group for peripheral arterial disease which is sponsored by Bristol-Myers Squibb. GS declared a personal non-pecuniary interest; he is an author on Cochrane review on combined therapies for DVT prophylaxis (not yet published).
Second GDG Meeting **(29th October 2007)**	No change to declarations

GDG meeting	Declaration of Interests
Third GDG Meeting **(28th November 2007)**	No change to declarations
Fourth GDG Meeting **(9th January 2008)**	No change to declarations
Fifth GDG Meeting **(21st February 2008)**	No change to declarations
Sixth GDG Meeting **(2nd April 2008)**	No change to declarations
Seventh GDG Meeting **(13th May 2008)**	No change to declarations
Eight GDG Meeting **(27th June 2008)**	No change to declarations
Ninth GDG Meeting **(2nd September 2008)**	No change to declarations
Tenth GDG Meeting **(8th October 2008)**	No change to declarations
Eleventh GDG Meeting **(14th November 2008)**	No change to declarations
Twelfth GDG Meeting **(16th December 2008)**	No change to declarations
Thirteenth GDG Meeting **(18th May 2009)**	No change to declarations
Fourteenth GDG Meeting **(8th July 2009)**	No change to declarations
Fifteenth GDG meeting **(3rd November 2009)**	No change to declarations

1.2.13 Peter Walton (Joined the guideline development group in Feb 2008)

GDG meeting	Declaration of Interests
Peter Walton was recruited to the GDG in February 2008 to replace Mr. Gordon McPherson as patient representative.	
Fifth GDG Meeting **(21st February 2008)**	None
Sixth GDG Meeting **(2nd April 2008)**	None
Seventh GDG Meeting **(13th May 2008)**	None
Eight GDG Meeting **(27th June 2008)**	None
Ninth GDG Meeting **(2nd September 2008)**	None

Tenth GDG Meeting **(8th October 2008)**	None
Eleventh GDG Meeting **(14th November 2008)**	None
Twelfth GDG Meeting **(16th December 2008)**	None
Thirteenth GDG Meeting **(18th May 2009)**	Not attended
Fourteenth GDG Meeting **(8th July 2009)**	Not attended
Fifteenth GDG meeting **(3rd November 2009)**	None

1.2.14 Annie Young

GDG meeting	Declaration of Interests
First GDG meeting **(13th September 2007)**	None
Second GDG Meeting **(29th October 2007)**	AY declared a personal pecuniary interest; she was paid by GlaxoSmithKline to attend the European Cancer Nursing Advisory Board in September 2007. She declared a personal non-pecuniary interest; she is the President of the UK Oncology Nursing Society which is supported by pharmaceutical companies. She declared she knew of no personal family interest or non-personal pecuniary interest above those she declared at the previous meeting.
Third GDG Meeting **(28th November 2007)**	No change to declarations
Fourth GDG Meeting **(9th January 2008)**	No change to declarations
Fifth GDG Meeting **(21st February 2008)**	AY declared a non-personal pecuniary interest; she has been invited onto the National Collaborating Centre for Cancer management group for cancer drugs. She declared that she knew of no personal pecuniary interest, personal family interest or non-personal pecuniary interests, above those declared at the previous meeting.
Sixth GDG Meeting **(2nd April 2008)**	AY declared a personal pecuniary interest; she will be writing for travel grant to attend International Society of Nurses in Cancer Care (ISNCC) meeting in August in Singapore. She did not declare a personal family interest, non-personal pecuniary interest or personal non-pecuniary interest, above those declared at the previous meeting.
Seventh GDG Meeting **(13th May 2008)**	No change to declarations
Eight GDG Meeting **(27th June 2008)**	No change to declarations
Ninth GDG Meeting **(2nd September 2008)**	AY declared a personal pecuniary interest; she received a travel grant from 10 pharmaceutical companies for herself and 5 nurses to attend the society of nurses in cancer care conference. She declared that she knew of no personal family interest, non-personal pecuniary interest or personal non-pecuniary interest, above those declared at the previous meeting.

Tenth GDG Meeting **(8th October 2008)**	No change to declarations
Eleventh GDG Meeting **(14th November 2008)**	Not attended
Twelfth GDG Meeting **(16th December 2008)**	No change to declarations
Thirteenth GDG Meeting **(18th May 2009)**	No change to declarations
Fourteenth GDG Meeting **(8th July 2009)**	AY declared travelling expenses to MASCC meeting (Multiagency in Supportive Cancer Care) Rome 24th June 2009 GSK paid for.
Fifteenth GDG meeting **(3rd November 2009)**	AY declared a personal pecuniary interest; she recieved travel expenses to ECCO Berlin from GSK, as well as travel and accommodation expenses to attend a conference in Brighton from MSD and Pfizer. AY declared a personal non-pecuniary interest: she participated at the NCRI conference and Thrombosis and Cancer workshop (no fee received). She declared that she knew of no personal family interest, or non-personal pecuniary interest, above those declared at the previous meeting.

1.2.15 Declarations of interests of the NCC-AC members

GDG meeting	Declaration of Interests
First GDG meeting **(13th September 2007)**	JH, DW, CS declared they worked on the 1st VTE guildeline.
Second GDG Meeting **(29th October 2007)**	None
Third GDG Meeting **(28th November 2007)**	None
Fourth GDG Meeting **(9th January 2008)**	None
Fifth GDG Meeting **(21st February 2008)**	None
Sixth GDG Meeting **(2nd April 2008)**	None
Seventh GDG Meeting **(13th May 2008)**	None
Eight GDG Meeting **(27th June 2008)**	None
Ninth GDG Meeting **(2nd September 2008)**	None
Tenth GDG Meeting **(8th October 2008)**	None
Eleventh GDG Meeting **(14th November 2008)**	None
Twelfth GDG Meeting **(16th December 2008)**	None

Thirteenth GDG Meeting **(18th May 2009)**	None
Fourteenth GDG Meeting **(8th July 2009)**	None
Fifteenth GDG meeting **(3rd November 2009)**	None

1.3 Declarations of interests of the Orthopaedic Subgroup Members

1.3.1 Tom Treasure (Chair)

GDG meeting	Declaration of Interests
First GDG meeting **(2nd June 2008)**	None
Second GDG Meeting **(30th July 2008)**	None
Third GDG Meeting **(17th October 2007)**	None
Fourth GDG Meeting **(9th January 2009)**	None
Fifth GDG Meeting **(22nd May 2009)**	None

1.3.2 Kim Carter

GDG meeting	Declaration of Interests
First GDG meeting **(2nd June 2008)**	None
Second GDG Meeting **(30th July 2008)**	None
Third GDG Meeting **(17th October 2007)**	None
Fourth GDG Meeting **(9th January 2009)**	None
Fifth GDG Meeting **(22nd May 2009)**	None

1.3.3 Simon Carter

GDG meeting	Declaration of Interests
First GDG meeting **(2nd June 2008)**	None
Second GDG Meeting **(30th July 2008)**	None
Third GDG Meeting **(17th October 2007)**	None

Fourth GDG Meeting **(9th January 2009)**	None
Fifth GDG Meeting **(22nd May 2009)**	Not attended

1.3.4 Nick Fiddian

GDG meeting	Declaration of Interests
First GDG meeting **(2nd June 2008)**	None
Second GDG Meeting **(30th July 2008)**	None
Third GDG Meeting **(17th October 2007)**	Not attended
Fourth GDG Meeting **(9th January 2009)**	None
Fifth GDG Meeting **(22nd May 2009)**	Not attended

1.3.5 Simon Frostick

GDG meeting	Declaration of Interests
First GDG meeting **(2nd June 2008)**	SF declared a personal pecuniary interest; he received an honorarium from Boehringer Ingelheim. He declared a non-personal pecuniary interest; he has received funds from Bayer. He declared that he knew of no personal family interest or personal non-pecuniary interest.
Second GDG Meeting **(30th July 2008)**	No change to declarations
Third GDG Meeting **(17th October 2007)**	No change to declarations
Fourth GDG Meeting **(9th January 2009)**	No change to declarations
Fifth GDG Meeting **(22nd May 2009)**	Not attended

1.3.6 Paul Gregg

GDG meeting	Declaration of Interests
First GDG meeting **(2nd June 2008)**	None
Second GDG Meeting **(30th July 2008)**	None
Third GDG Meeting **(17th October 2007)**	None
Fourth GDG Meeting **(9th January 2009)**	PG declared he knew of no personal pecuniary interest, personal non-pecuniary interest, personal family interest, but indicated that he took part in a debate and

	received funds from Boerhinger Ingelheim.
Fifth GDG Meeting **(22nd May 2009)**	Not attended

1.3.7 Donald McBride

GDG meeting	Declaration of Interests
First GDG meeting **(2nd June 2008)**	None
Second GDG Meeting **(30th July 2008)**	Not attended
Third GDG Meeting **(17th October 2007)**	Not attended
Fourth GDG Meeting **(9th January 2009)**	None
Fifth GDG Meeting **(22nd May 2009)**	None

1.3.8 David Warwick

GDG meeting	Declaration of Interests
First GDG meeting **(2nd June 2008)**	DWk declared a personal pecuniary interest; he has received payments from Sanofi Aventis to lecture (April 2008), Boehringer Ingelheim to lecture (May 2008), Johnson & Johnson Registry to participate in Advisory Boards (May 2008 - ongoing), Ramsey Healthcare to review VTE guidelines. He declared that he knew of no personal family interest or non-personal pecuniary interest. He declared a personal non-pecuniary interest; he has published in the journal of bone and joint surgery (*Insufficient duration of venous thromboemolism prophylaxis* – June 2007, *Orthopaedic thromboprophylaxis – limitations of current guidelines* – Feb 2008).
Second GDG Meeting **(30th July 2008)**	No change to declarations
Third GDG Meeting **(17th October 2007)**	No change to declarations
Fourth GDG Meeting **(9th January 2009)**	No change to declarations
Fifth GDG Meeting **(22nd May 2009)**	No change to declarations

1.3.9 Nick Welch

GDG meeting	Declaration of Interests
First GDG meeting **(2nd June 2008)**	Not attended
Second GDG Meeting **(30th July 2008)**	NW declared personal non-pecuniary interest; he worked for 36 years in the pharmaceutical industry prior to retirement. This included 18 years with Boehringer Ingelheim. He declared he knew of no personal pecuniary interest, personal family interest, non-personal pecuniary interest.
Third GDG Meeting **(17th October 2007)**	Not attended

Fourth GDG Meeting **(9th January 2009)**	No change to declarations
Fifth GDG Meeting **(22nd May 2009)**	No change to declarations

1.3.10 Claire Young

GDG meeting	Declaration of Interests
First GDG meeting **(2nd June 2008)**	None
Second GDG Meeting **(30th July 2008)**	None
Third GDG Meeting **(17th October 2007)**	None
Fourth GDG Meeting **(9th January 2009)**	None
Fifth GDG Meeting **(22nd May 2009)**	None

1.4 Declarations of interests of expert advisors

1.4.1 David Fitzmaurice (General practitioner – post-discharge prophylaxis)

DOI Date	Declaration of Interests
25th November 2008	DF declared personal pecuniary interests: he has attended advisory board meetings for Bayer, Boehringer Ingelheim and would be attending board meeting for Sanofi Aventis.

1.4.2 Ian A Greer (Dean of medical school -- Pregnancy and postpartum)

DOI Date	Declaration of Interests
22nd May 2009	IG declared personal pecuniary interests: he has received honoraria for speaking at conferences and for advisory boards from Leo Pharma and Sanofi Aventis

1.4.3 Nihal Gurusinghe (Neurosurgeon – Neurosurgery and spinal surgery)

DOI Date	Declaration of Interests
1st December 2008	None

1.4.4 Mike Laffan (Haematologist – Pregnancy and postpartum)

DOI Date	Declaration of Interests
24th May 2009	None

1.4.5 Lucy Mackillop (Obstetric physician – Pregnancy and postpartum)

DOI Date	Declaration of Interests
26th May 2009	LM declared a personal non-pecuniary interest: She was the co-author of the Royal College of Obstetricians Gynaecologists guidelines on thromboprophylaxis which was due to be published in November 2009.

1.4.6 Peter McCallum (Haematologist – Pregnancy and postpartum)

DOI Date	Declaration of Interests
25th May 2009	PM declared personal pecuniary interests: he has received honorarium for lecturing from Pfizer, and paid honorarium for an advisory board meeting by Boehringer Ingelheim. He also declared non-personal pecuniary interest: his unit received funding from Boehringer Ingelheim to participate in a clinical trial of dabigatran in which he was a principal investigator. PM declared personal non-pecuniary interest: he was the co-author of guidelines that were being written for the Royal College of Obstetricians and Gynaecologists on reducing the risk of thromboembolism during pregnancy, birth and the puerperium.

1.4.7 Catherine Nelson-Piercy (Obstetric physician – Pregnancy and postpartum)

DOI Date	Declaration of Interests
22nd May 2009	None

1.4.8 Douglas Wardlaw (Neurosurgery – Neurosurgery and other orthopaedic surgery)

DOI Date	Declaration of Interests
6th July 2007	D Wardlaw declared personal non-pecuniary interests: he has a research interest in the topic and had papers accepted for publication in the European Spine Journal.

Appendix C

Search Strategies

1.1 Search Strategies

Searches were constructed by using the following groups of terms. These groups are expanded in full in Section 1.2 below.

All searches were run in Medline, Embase and Cochrane Library (Central Register of Controlled Trials) and additionally Cinahl and the Cochrane Database of Systematic Reviews were searched where this was deemed appropriate. Economic searches were conducted in Medline and Embase and additionally in HEED (Health Economic Evaluations Database) and the HTA (Health Technology Reports) database from the Cochrane Library.

Economic searches

Simplified VTE terms
AND
Prophylaxis terms
AND
Economic filter

Incidence

Simplified VTE terms
AND
Incidence terms
NOT
Animal/publication filter

Prophylaxis searches

VTE terms
AND
Prophylaxis terms
(general, pharmacological, mechanical, nursing and physiotherapy, anaesthesia)
AND
RCT filter or systematic review filter
NOT
Animal/publication filter

Patient education

VTE terms
AND
Patient education terms

Patient views

VTE terms
AND
Patient view terms

Risk factors

VTE terms
AND
Risk factor terms
AND
Systematic review filter

1.2 Search terms

1.2.1 Animal/publication filter

Animal/publication filter Medline

1 (Case-Reports NOT Randomized-Controlled-Trial OR Letter OR Historical-Article OR Review-Of-Reported-Cases).PT. OR (exp Animals/ NOT Humans/)

Animal/publication filter Embase

1 Case-Study/ or Abstract-Report/ or Letter/ or (case adj report).tw. or ((exp Animal/ or Nonhuman/ or exp Animal-Experiment/) not exp Human/)

1.2.2 Economic

Economic filter MEDLINE

1 exp "Costs and Cost Analysis"/
2 Economics/
3 Economics, Nursing/ or Economics, Medical/ or Economics, Hospital/ or Economics, Pharmaceutical/
4 exp "Fees and Charges"/
5 exp Budgets/
6 budget$.tw.
7 cost$.ti.
8 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab.
9 (economic$ or pharmacoeconomic$ or pharmaco-economic$).ti.
10 (price$ or pricing$).tw.
11 (financial or finance or finances or financed).tw.

12 (fee or fees).tw.
13 (value adj2 (money or monetary)).tw.
14 Value of Life/
15 quality adjusted life.tw.
16 (qaly$ or qald$ or qale$ or qtime$).tw.
17 disability adjusted life.tw.
18 daly$.tw.
19 Health Status Indicators/
20 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
21 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
22 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
23 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
24 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
25 (euroqol or euro qol or eq5d or eq 5d).tw.
26 (hql or hqol or h qol or hrqol or hr qol).tw.
27 (hye or hyes).tw.
28 (hui or hui1 or hui2 or hui3).tw.
29 utilit$.tw.
30 disutilit$.tw.
31 rosser.tw.
32 quality of wellbeing.tw.
33 qwb.tw.
34 willingness to pay.tw.
35 standard gamble$.tw.
36 time trade off.tw.
37 time tradeoff.tw.
38 tto.tw.
39 exp models, economic/
40 models, theoretical/ or models, organizational/
41 economic model$.tw.
42 markov chains/
43 markov$.tw.
44 Monte Carlo Method/
45 monte carlo.tw.
46 exp Decision Theory/
47 (decision$ adj2 (tree$ or anlay$ or model$)).tw.
48 or/1-47

Economic filter Embase

1 exp economic aspect/
2 cost$.tw.
3 (price$ or pricing$).tw.
4 (fee or fees).tw.
5 (financial or finance or finances or financed).tw.
6 (value adj2 (money or monetary)).tw.
7 resourc$ allocat$.tw.
8 expenditure$.tw.
9 (fund or funds or funding or fundings or funded).tw.

10 (ration or rations or rationing or rationings or rationed).tw.
11 (saving or savings).tw.
12 or/1-11
13 Quality of Life/
14 quality of life.tw.
15 life quality.tw.
16 quality adjusted life.tw.
17 (qaly$ or qald$ or qale$ or qtime$).tw.
18 disability adjusted life.tw.
19 daly$.tw.
20 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
21 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
22 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
23 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
24 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
25 (euroqol or euro qol or eq5d or eq 5d).tw.
26 (hql or hqol or h qol or hrqol or hr qol).tw.
27 (hye or hyes).tw.
28 health$ equivalent$ year$.tw.
29 (hui or hui1 or hui2 or hui3).tw.
30 health utilit$.tw.
31 disutilit$.tw.
32 rosser.tw.
33 (quality of wellbeing or quality of well being).tw.
34 qwb.tw.
35 willingness to pay.tw.
36 standard gamble$.tw.
37 time trade off.tw.
38 time tradeoff.tw.
39 tto.tw.
40 factor analy$.tw.
41 preference based.tw.
42 (state adj2 valu$).tw.
43 Life Expectancy/
44 life expectancy$.tw.
45 ((duration or length or period of time or lasting or last or lasted) adj4 symptom$).tw.
46 or/13-46
47 exp model/
48 exp Mathematical Model/
49 markov$.tw.
50 Monte Carlo Method/
51 monte carlo.tw.
52 exp Decision Theory/
53 (decision$ adj2 (tree$ or anlay$ or model$)).tw.
54 model$.tw.
55 or/47-55
56 12 or 46 or 55

1.2.3 Incidence

Incidence OVID Medline

1 Incidence/
2 incidence.ti,ab.
3 Epidemiology/
4 epidemiolog$.tw.
5 Registries/
6 or/1-5

Incidence OVID Embase

1 Incidence/
2 incidence.ti,ab.
3 Epidemiology/
4 epidemiolog$.tw.
5 Registries/
6 or/1-5

Incidence Cochrane

#1 MeSH descriptor Incidence, this term only
#2 incidence
#3 MeSH descriptor Epidemiology, this term only
#4 epidemiolog*
#5 MeSH descriptor Registries, this term only
#6 #1 or #2 or #3 or #4 or #5

1.2.4 Patient education

Patient education OVID Medline

1 Patients/ or Inpatients/ or Outpatients/
2 Caregivers/ or exp Family/ or exp Parents/ or exp Legal-Guardians/
3 (patients or carer$ or famil$).tw.
4 or/1-3
5 Popular-Works-Publication-Type/ or exp Information-Services/ or Publications/ or Books/ or Pamphlets/ or Counseling/ or Directive-Counseling/
6 4 or 5
7 ((patient or patients) adj3 (education or educate or educating or information or literature or leaflet$ or booklet$ or pamphlet$)).ti,ab.
8 Patient-Education/ or Patient-Education-Handout-Publication-Type/
9 or/6-8

Patient education OVID Embase

1 Patient/ or Hospital patient/ or Outpatient/
2 Caregiver/ or exp Family/ or exp Parent/
3 (patients or carer$ or famil$).tw.
4 or/1-3
5 Information Service/ or Information center/ or Publication/ or Book/ or Counseling/ or Directive counseling/
6 4 or 5
7 ((patient or patients) adj3 (education or educate or educating or information or literature or leaflet$ or booklet$ or pamphlet$)).ti,ab.

8 Patient information/ or Patient education/
9 or/6-8

1.2.5 Patient views

Patient views OVID Medline

1 exp Consumer-Satisfaction/ or Personal-Satisfaction/ or exp Patient-Acceptance-Of-Health-Care/ or exp Consumer-Participation/ or exp Patient-Rights/ or Health Care Surveys/ or Questionnaires/ or Interview/ or Focus groups/
2 (patient$ adj3 (view$ or opinion$ or awareness or tolerance or perception or persistenc$ or attitude$ or compliance or satisfaction or concern$ or belief$ or feeling$ or position or idea$ or preference$ or choice$)).tw.
3 (Discomfort or comfort or inconvenience or bother$4 or trouble or fear$ or anxiety or anxious or worr$3).tw.
4 or/1-3

Patient views OVID Embase

1 Consumer attitude/ or patient satisfaction/ or patient compliance/ or patient right/ or health survey/ or questionnaire/ or interview/
2 (patient$ adj3 (view$ or opinion$ or awareness or tolerance or perception or persistenc$ or attitude$ or compliance or satisfaction or concern$ or belief$ or feeling$ or position or idea$ or preference$ or choice$)).tw.
3 (Discomfort or comfort or inconvenience or bother$4 or trouble or fear$ or anxiety or anxious or embarrass$4).tw.
4 or/1-3

1.2.6 Prophylaxis terms

Prophylaxis: general terms OVID Medline/Embase

1 thromboprophyla$.ti,ab.
2 (prophylaxis or prevention).ti,ab.
3 pc.fs.
4 or/1-3

Prophylaxis Cochrane

#1 thromboprophyla*:ti,ab
#2 (prophylaxis or prevention):ti,ab
#3 pc.fs.
#4 #1 or #2 or #3

Prophylaxis: pharmacological OVID Medline/Embase

1 exp anticoagulants/ or exp fibrinolytic agents/ or exp platelet aggregation inhibitors/
2 exp Antithrombins/
3 (anticoagula$ or anti coagula$ or antithromb$ or anti thromb$ or antiemboli$ or anti emboli$ or thrombin inhibit$ or direct thrombin).ti,ab.
4 (Dabigatran or dabigatran etexilate or Rendix or lepirudin or refludan).mp.
5 heparin/ or heparin, low-molecular-weight/ or dalteparin/ or enoxaparin/ or nadroparin/ or heparinoids/

6 (Calciparine or Monoparin or Calcium Multiparin or Bemiparin or Zibor or Dalteparin or Fragmin or Enoxaparin or Clexane or Lovenox or Tinzaparin or Innohep or Antixarin or CY 222 or Embolex or monoembolex or Fragmin or Tinzaparin or Suleparoide or Ardeparin or Certoparin or Nadroparin or Parnaparin or Reviparin or Tedelparin).mp.
7 coumarins/ or warfarin/
8 (fondaparinux or idraparinux or rivaroxaban or arixtra or xarelito or apixaban).mp.
9 (acenocoumarol or brodifacoum or bromadiolone or cloricromen or coumafos or coumadin or coumarin or coumatetralyl or coumetarol or dicoumarol or difenacoum or ethyl-biscoumacetate or flocoumafen or galbanic-acid or nicoumalone or phenindione or phenprocoumon or phepromaron or tioclomarol or sinthrone or warfarin).mp.
10 (pentasaccharide or pentasaccharides).ti,ab.
11 Aspirin/
12 (aspirin or acetylsalicylic acid or antiplatelet or anti platelet).mp.
13 or/1-12

Prophylaxis: pharmacological Cochrane

#1 exp anticoagulants/ or exp fibrinolytic agents/ or exp platelet aggregation inhibitors/
#2 exp Antithrombins/
#3 (anticoagula* or anti coagula* or antithromb* or anti thromb* or antiemboli* or anti emboli* or thrombin inhibit* or direct thrombin):ti,ab
#4 (Dabigatran or dabigatran etexilate or Rendix or lepirudin or refludan):ti,ab
#5 heparin/ or dalteparin/ or enoxaparin/ or nadroparin/ or heparinoids/
#6 MeSH descriptor Heparin, Low-Molecular-Weight, this term only
#7 (Calciparine or Monoparin or Calcium Multiparin or Bemiparin or Zibor or Dalteparin or Fragmin or Enoxaparin or Clexane or Lovenox or Tinzaparin or Innohep or Antixarin or CY 222 or Embolex or monoembolex or Fragmin or Tinzaparin or Suleparoide or Ardeparin or Certoparin or Nadroparin or Parnaparin or Reviparin or Tedelparin):ti,ab
#8 coumarins/ or warfarin/
#9 (fondaparinux or idraparinux or rivaroxaban or arixtra or xarelito or apixaban):ti,ab
#10 (acenocoumarol or brodifacoum or bromadiolone or cloricromen or coumafos or coumadin or coumarin or coumatetralyl or coumetarol or dicoumarol or difenacoum or ethyl-biscoumacetate or flocoumafen or galbanic-acid or nicoumalone or phenindione or phenprocoumon or phepromaron or tioclomarol or sinthrone or warfarin):ti,ab
#11 (pentasaccharide or pentasaccharides):ti,ab
#12 Aspirin/
#13 (aspirin or acetylsalicylic acid or antiplatelet or anti platelet):ti,ab
#14 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13

Prophylaxis: mechanical and others OVID Medline/Embase

1 Bandages/
2 mechanical.ti,ab.
3 Intermittent Pneumatic Compression Devices/
4 (stocking or stockings or hose).ti,ab.

5 (((calf or elastic or graded or limb or leg or pneumatic or plantar or foot) adj compression) or (compression adj device)).ti,ab.

6 (((foot adj pump) or foot) adj pumps).ti,ab.

7 flowtron.ti,ab.

8 Motion Therapy, Continuous Passive/

9 Early Ambulation/

10 (mobilisation or mobilization or physiotherapy or ambulation or kinetic therapy or ((continuous or lateral) adj rotation) or ((therapeutic or specialised or specialized) adj bed) or air loss mattress or bedrest or bed rest or immobili$ or leg exercises).ti,ab.

11 Hindlimb Suspension/

12 ((foot or feet or limb or leg or legs) adj3 (elevat$ or raise$ or suspend$)).ti,ab.

13 Fluid Therapy/

14 Rehydration Solutions/

15 (hydrat$ or rehydrat$).ti,ab.

16 or/1-15

Prophylaxis: mechanical and others Cochrane

#1 Bandages/

#2 mechanical:ti,ab

#3 Intermittent Pneumatic Compression Devices/

#4 (stocking or stockings or hose):ti,ab

#5 (((calf or elastic or graded or limb or leg or pneumatic or plantar or foot) NEAR compression) or (compression NEAR device)):ti,ab

#6 (((foot near pump) or foot) near pumps):ti,ab

#7 flowtron:ti,ab

#8 MeSH descriptor Motion Therapy, Continuous Passive, this term only

#9 Early Ambulation/

#10 (mobilisation or mobilization or physiotherapy or ambulation or kinetic therapy or ((continuous or lateral) NEAR rotation) or ((therapeutic or specialised or specialized) NEAR bed) or air loss mattress or bedrest or bed rest or immobili* or leg exercises):ti,ab

#11 Hindlimb Suspension/

#12 ((foot or feet or limb or leg or legs) NEAR (elevat* or raise* or suspend*)):ti,ab

#13 Fluid Therapy/

#14 Rehydration Solutions/

#15 (hydrat* or rehydrat*):ti,ab

#16 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15

Prophylaxis: anaesthesia Medline

#1 Anesthesia-and-Analgesia/ or Analgesia-Epidural/ or Anesthesia/ or exp Anesthesia-Conduction/

#2 (anaesthesia or anesthesia or anaesthetic$ or anesthetic$ or anaesthetise$ or anesthetise$ or analgesi$ or spinal or epidural or extradural).ti,ab.

#3 #1 or #2

Prophylaxis: anaesthesia Embase

#1 Anesthesia/ or exp Epidural-Anesthesia/ or exp Local-Anesthesia/ or exp Regional-Anesthesia/

#2 (anaesthesia or anesthesia or anaesthetic$ or anesthetic$ or anaesthetise$ or anesthetise$ or analgesi$ or spinal or epidural or extradural).ti,ab.

#3 #1 or #2

Prophylaxis: anaesthesia Cochrane

#1	MeSH descriptor Anesthesia, this term only
#2	MeSH descriptor Anesthesia and Analgesia, this term only
#3	MeSH descriptor Analgesia, Epidural, this term only
#4	MeSH descriptor Anesthesia, Conduction explode all trees
#5	(anaesthesia or anesthesia or anaesthetic* or anesthetic* or anaesthetise* or anesthetise* or analgesi* or spinal or epidural or extradural):ti
#6	(anaesthesia or anesthesia or anaesthetic* or anesthetic* or anaesthetise* or anesthetise* or analgesi* or spinal or epidural or extradural):ab
#7	(#9 OR #10 OR #11 OR #12 OR #13 OR #14)
#8	(#8 AND #15)
#9	(#8 AND #15), from 2006 to 2008

1.2.7 RCT filter

RCT filter Medline

1	Randomized-Controlled-Trials/ or Random-Allocation/ or Double-Blind-Method/ or Single-Blind-Method/ or exp Clinical-Trials as topic/ or Cross-Over-Studies/ or Prospective-Studies/ or Placebos/
2	(Randomized-Controlled-Trial or Clinical-Trial or Controlled-Clinical-Trial).pt.
3	((((((((clinical or control or controlled) adj (study or trial)) or (single or double or triple)) adj (blind$3 or mask$3)) or randomised or randomized or random$) adj (assign$ or allocat$ or group or grouped or patients or study or trial or distribut$)) or crossover) adj (design or study or trial)) or placebo or placebos).ti,ab.
4	or/1-3

RCT filter Embase

1	Clinical-Trial/ or Randomized-Controlled-Trial/ or Randomization/ or Single-Blind-Procedure/ or Double-Blind-Procedure/ or Crossover-Procedure/ or Prospective-Study/ or Placebo/
2	((((((((clinical or control or controlled) adj (study or trial)) or (single or double or triple)) adj (blind$3 or mask$3)) or randomised or randomized or random$) adj (assign$ or allocat$ or group or grouped or patients or study or trial or distribut$)) or crossover) adj (design or study or trial)) or placebo or placebos).ti,ab.
3	1 or 2

1.2.8 Risk factors

Risk factors OVID Medline

1	Risk/ or Risk Factors/
2	risk*.ti,ab.
3	exp Cohort Studies/
4	Case-Control Studies/
5	or/1-4

Risk factors OVID Embase

1	RISK FACTOR/ or RISK/
2	risk*.ti,ab.
3	exp Cohort Analysis/
4	Case Control Study/
5	or/1-4

Risk factors Cochrane

#1 MeSH descriptor Risk, this term only
#2 MeSH descriptor Risk Factors, this term only
#3 risk:ti
#4 risk:ab
#5 MeSH descriptor Cohort Studies explode all trees
#6 MeSH descriptor Case-Control Studies, this term only
#7 #1 or #2 or #3 or #4 or #5 or #6

1.2.9 Simplifed VTE terms

Simplified VTE terms OVID Medline

1 pulmonary embolism/ or venous thrombosis/
2 (((venous or vein) adj (thrombosis or thrombus or thromboembolism)) or (dvt or vte) or ((pulmonary or lung) adj6 (embolism or emboli))).ti,ab.
3 1 or 2

Simplified VTE terms OVID Embase

1 Thromboembolism/ or Vein Thrombosis/
2 (((venous or vein) adj (thrombosis or thrombus or thromboembolism)) or (dvt or vte) or ((pulmonary or lung) adj (embolism or emboli))).ti,ab.
3 1 or 2

Simplified VTE terms Cochrane

#1 MeSH descriptor Pulmonary Embolism, this term only
#2 MeSH descriptor Venous Thrombosis, this term only
#3 (((venous or vein) near (thrombosis or thrombus or thromboembolism)) or (dvt or vte) or (((pulmonary or lung) near (embolism or emboli))))
#4 #1 or #2 or #3

1.2.10 Systematic review filter

Systematic review filter Medline

1 meta-analysis/
2 (metaanalys$ or meta-analys$ or meta analys$).tw.
3 exp "review literature"/
4 (systematic$ adj3 (review$ or overview$)).tw.
5 (selection criteria or data extraction).ab. and review.pt.
6 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or bids or cancerlit).ab.
7 (reference list$ or bibliograph$ or hand search$ or hand-search$ or manual search$ or relevant journals).ab.
8 or/1-7

Systematic review filter Embase

1 meta analysis/
2 (metaanalys$ or meta-analys$ or meta analys$).tw.

3 systematic review/
4 (systematic$ adj3 (review$ or overview$)).tw.
5 (selection criteria or data extraction).ab. and Review.pt.
6 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or bids or cancerlit).ab.
7 (reference list$ or bibliograph$ or hand search$ or manual search$ or relevant journals).ab.
8 or/1-7

1.2.11 VTE terms

VTE terms OVID Medline

1 pulmonary embolism/ or thromboembolism/ or venous thrombosis/ or thrombophlebitis/
2 (((venous or vein) adj (thrombosis or thrombus or thromboembolism)) or (dvt or vte) or (((pulmonary or lung) adj6 (embolism or emboli)) or thrombophlebitis)).ti,ab.
3 1 or 2

VTE terms OVID Embase

1 Thromboembolism/ or Venous Thromboembolism/ or Vein Thrombosis/ or Deep Vein Thrombosis/ or Leg Thrombosis/ or Postoperative Thrombosis/ or Lung Embolism/ or Thrombophlebitis/
2 (((venous or vein) adj (thrombosis or thrombus or thromboembolism)) or (dvt or vte) or (((pulmonary or lung) adj6 (embolism or emboli)) or thrombophlebitis)).ti,ab.
3 1 or 2

VTE terms Cochrane

#1 MeSH descriptor Thromboembolism, this term only
#2 MeSH descriptor Venous Thrombosis, this term only
#3 MeSH descriptor Pulmonary Embolism, this term only
#4 MeSH descriptor Thrombophlebitis, this term only
#5 ((*venous OR *vein) NEXT (thrombosis OR thrombus OR thromboembolism) OR dvt OR vte OR (pulmonary OR lung) NEAR (embolism or emboli) OR thrombophlebitis):ti
#6 ((*venous OR *vein) NEXT (thrombosis OR thrombus OR thromboembolism) OR dvt OR vte OR (pulmonary OR lung) NEAR (embolism or emboli) OR thrombophlebitis):ab
#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6

Appendix D

Evidence tables

Abbreviations

BMI	Body mass index
CT	Computed tomography
CVC	Central venous catheter
DVT	Deep vein thrombosis
FID	Foot impulse device
FU	Follow-up
FUT	^{125}I-Fibrinogen uptake test
GCS	Graduated compression stockings
HRQL	Health related quality of life
HRT	Hormone replacement therapy
IBS	Irritable bowel syndrome
INR	International normalized ratio
IPCD	Intermittent pneumatic compression device
LDUH	Low density unfractionated heparin
LE	Life expectancy
LMWH	Low molecular weight heparin
LoS	Length of stay (in hospital)
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NA	Not available
NR	Not reported
OAC	Oral anticoagulant
PE	Pulmonary embolism
PTS	Post-thrombotic limb syndrome
PVT	Proximal vein thrombosis
QoL	Quality of life
RCT	Randomised controlled trial
THR	Total hip replacement
TKR	Total knee replacement
UFH	Unfractionated heparin
US	Ultrasound
VKA	Vitamin K antagonists
VTE	Venous thromboembolism
V/Q	Ventilation and Quantitative Scan

Surgical Risk

Evidence Table 1: Surgical risk of VTE: incidence studies

Paper	Asymptomatic DVT	Symptomatic VTE	Fatal PE	PE	Type of prophylaxis	Type of Surgery	Notes
Andtbacka et al., 2006[19]	Not reported	within 60 days: 7/3898 (0.16%) VTE 3/3898 (0.07%) DVT only	No deaths.	3/3898 (0.07%)	No prophylaxis:	General (breast cancer)	3898 breast cancer patients. 4416 operations. Length of operation given as a risk factor, result broken down using this. N/A Study draws correlation between operation length and development of VTE. Mean operative time (in patients dev VTE) = 278 mins Mean operative time (no VTE) = 256 P = 0.7
Auguste et al., 2003[25]	6/180 (3.3%) (Exact one-tailed 95% upper CL 6.5%) developed VTE. Of these: 3 (1.7% exact one-tailed 95% upper CL 4%) developed contralateral DVT 1 (0.6% exact one-tailed 95% upper CL 2%) developed ipsilateral DVT	6/180 (3.3%) (Exact one-tailed 95% upper CL 6.5%) developed VTE.	No deaths.	2/180 (1.1%) (Exact one-tailed 95% upper CL 4.8%)	Intraoperative: antiembolism stocking plus compression device. Post operative: bilateral mechanical prophylaxis (compression stockings)	Neurosurgery: Craniotomy and motor mapping for glioma	180 patients – all diagnosed with glioma, no history of DVT. Mean operation length given as 7.7 hrs, further info in paper. Wilcox test demonstrated no significance between clinical VTE and age, duration of surgery, preoperative values for prothrombin time and partial thromboplastin time. Obesity, BMI, smoking not included in analysis.

Surgical risk of VTE: incidence studies

Paper	Asymptomatic DVT	Symptomatic VTE	Fatal PE	PE	Type of prophylaxis	Type of Surgery	Notes
Bjornara et al., 2006[63]	Not reported	**Total:** 150/5607 (2.7%, CI 2.2-3.1) Confirmed DVT: **Hip fracture surgery:** 36/2420 (1.5%) CI 1.0 to 2.1 **THR:** 39/2512 (1.6%) CI 1.1 to 2.1 **TKR:** 11/675 (1.6%) CI 0.8-2.9 **TOTAL:** 1.5% (95%CI 2.2-3.1)		**Hip fracture surgery:** 32/2420 (1.3%) CI 0.9 -1.9 **THR:** 28/2512 (1.1%, CI 0.7-1.9) **TKR:** 4/675 (0.6% CI 0.2-1.5) **TOTAL:** 1.1% (95%CI 0.9-1.4) 7 patients developed DVT and PE 0.1%, 95% CI 0.9-0.2	Thromboprophylaxis LMWH for approx ten days or until discharge. Subcutaneous dalteparin (5000 IU) or enoxaparin (40 mg) 12 hours preoperatively.	Orthopaedic	All patients undergoing major hip and knee surgery who were diagnosed with objectively confirmed VTE within 6 months of surgery. Broken down by time of diagnosis (during initial hospitalisation/after discharge) Also broken down by type of surgery.
Fletcher and Batiste, 1997[187]	14/121 (9.8%) DVT incidence 9.1% incidence for reconstructive surgery 14.3% for amputation.	Not reported	Not reported	1/121 (0.7%)	5000 unit of unfractionated heparin 3x daily, preoperative-mobile, and intraoperative sequential compression devices.	Vascular Repair of abdominal aortic aneurysm, reconstruction of lower extremity arterial occlusive disease or amputation.	Major bleeding 3/121
Gordon-Smith et al., 1972[229]	**Control:** 9/32 (28%) **Intervention:** 9/30 (30%) Not significant.	Not reported	1 fatality in control from MI 1 fatality in control from PE 1/30 (3.3%)	**Control:** 1/32 (3%) **Intervention:** 2/30 (6%) Not significant.	6g EACA in the intervention group 5 hours preoperatively.	Urology (prostatectomy)	RCT: 32 control, 30 int., 50yrs+

Surgical risk of VTE: incidence studies

Paper	Asymptomatic DVT	Symptomatic VTE	Fatal PE	PE	Type of prophylaxis	Type of Surgery	Notes
Howie et al., 2005[288]	Not reported	DVT (including fatal PE) At 90 days: Hip: 22.0/1000 (2.2%) (OR 14.8 (95% CI, 12.9 to 16.9) Knee: 17.3/1000 (1.7%) (OR 11.62 (95% CI, 10.0 to 13.5) Cataract: 1.5/1000 (0.15%) At 365 days: Hip: 25.8/1000 Knee:20.8/1000 Cataract: 4.9/1000	At 90 days: Hip: 2.2/1000 Knee:1.5/1000 Cataract: 0.3/1000 At 365 days: Hip: 2.7/1000 Knee:2.0/1000 Cataract: 1.24/1000	Not reported	Not reported.	Orthopaedic: Knee arthoplasty:: (n=27503) hip (n=44785) cataract (n=176520)	Data retrieved from the Scottish Morbidity Record (SMRO1) system between 1992-2001 of all patients that had hip or knee arthroplasty or cataract surgery. Majority of fatal PE after arthroplasty is significantly higher than for cataract cases with majority of deaths occurring between discharge and six weeks post-operatively. Low incidence of autopsy (<10%) in this study. Cataract patients were slightly older than those undergoing arthroplasty. * NHSSCOTLAND2006[485] reports on DVT/PE incidences from SMRO1 records but only in graphical form and not exact figures.

Surgical risk of VTE: incidence studies

Paper	Asymptomatic DVT	Symptomatic VTE	Fatal PE	PE	Type of prophylaxis	Type of Surgery	Notes
Joffe, 1975[309]	10/23 (43%) postoperative DVT **Breakdown:** 6/10 (60%) of spinal operations developed DVT 4/13 (38%) of craniotomy operations (p<0.2)	1/23 (4%) developed symptomatic DVT	Not reported	None	No prophylaxis reported	Neurosurgery	23 patients. Age, sex, length of hospital stay given as not affecting results. Obesity and previous DVT history as risk factors. Study aims to compare screening techniques: Doppler/ I fibrinogen. No conclusions drawn about efficacy of screening technique or prophylaxis
Keeney et al., 2006[334]	25/705 (3.5%) asymptomatic week after surgery Of whom 17/25 (68%) had proximal DVT. 5/705 (0.7%) presented with pain within 3 months, all proximal DVT. 4.2% Total of which: 1.1% distal 3.1% proximal	Not reported	Not reported	1/705 nonfatal PE. (0.1%)	Pneumatic compression, adjusted dose warfarin (7 days), early mobilisation.	Orthopaedic (elective hip)	Increased age (p=0.008), male sex (p=0.005), DVT history (p=0/0005) identified as risk factors significantly associated with DVT.
Martino et al., 2006[428]	Not reported	Not reported	Not reported	Cancer patients: 21/507 (4.1%) Benign patients: 1/332 (0.3%) p<0.001 95% CI 1.9-102.1 minor/non-abdominal surgery: 2/536 (0.4%)	Prophylaxis with intermittent compression and early mobilisation, preoperatively extending through discharge.	Major abdominal surgery in Gynaecological oncology	1373 surgery patients, 839 (507 cancer diagnosis, 332 benign) major abdominal surgery cases, 534 minor abdominal surgery cases Cancer, age of 60+ identified as risk factors (p = 0.009 95%CI) Data also given on different types of oncological surgery.

Surgical risk of VTE: incidence studies

Paper	Asymptomatic DVT	Symptomatic VTE	Fatal PE	PE	Type of prophylaxis	Type of Surgery	Notes
Mayo et al., 1971[432]	Open prostatectomy 21/41 (51%) Transurethral resection 2/20 (10%) Total: 32/61 (38%) 0.001<p<0.01	Not reported			6g EACA in first 12 hours postoperatively	Urology (prostatectomy)	61 patients. Operation type, length, age, bed rest, blood given all entered into analyses as risk factors. See p 741.
Moreano et al., 1998[461]	Total: 34/12805 (0.3%) **DVT:** 0.03% (general otolaryngology) 6% (in patients with low dose heparin) General otolaryngology (GO) 3/4563 (0.1%) Head and Neck (H&N) 21/3463 (0.6%) Otology/Neurology (O/N) 8/2526 (0.3%) Trauma and Plastic Surgery (T/P) 2/2254 (0.1%)	Not reported	0.02% (general otolaryngology) 0.21% (in patients with low dose heparin) H&N 0.06%	Total: 24/12805 (0.2%) 0.52% (in patients with low dose heparin) GO 2/4563 (0.04%) H&N 14/3463 (0.4%) O/N 6/2526 (0.2%) T/P 2/2254 (0.1%)	In the 34 patients who developed DVT: No prophylaxis: 12 (34%) Prophylaxis: 22 (65%) Of which: 11 (32%) preoperative compression device 2 (6%) postoperative compression device 9 (26%) stockings only.	Various Incidence broken down by surgery type. Effectiveness data on GO group by type of prophylaxis.	12805 operations Number of patients not given. Discussion of development of risk-categorisation for patients.
Phillips et al., 2003[518]	Not reported	Not reported	Not reported	0.9% within 3 months	No prophylaxis reported	Orthopaedic (elective hip)	Medicare records for total hip replacements for one year (retrospective study) 71477 patients. Incidence for various time periods given, calculated as number of events per 10, 000 person-weeks Broken down by weeks and also compares primary with revision hip replacements.

Surgical risk of VTE: incidence studies

Paper	Asymptomatic DVT	Symptomatic VTE	Fatal PE	PE	Type of prophylaxis	Type of Surgery	Notes
Saarinen et al., 1995[566]	Not reported	Not reported	Not reported	34/7533 (0.45%) postoperative DVT (21 Male, 13 female, mean age 63)	Not reported.	Vascular	FINNVASC (Finnish vascular registry) data. Breaks down incidence by risk factor see p 127, e.g. hyperlipidaemia, smoking, etc. Compares DVT patients with non-DVT patients for distribution of vascular operations and risk. 94% of PEs had undergone vascular procedure involving infrarenal aorta or lower extremity.
Sinclair et al., 1976[604]	No significant difference between groups. 20/40 (50%) evidence of DVT of which: 13/19 (68%) of prostatectomy patients developed DVT 7/21 (33%) of transurethral resections	Not reported	Not reported	Not reported	EACA in the intervention group, 0.5g per hour for twelve hours, then 6g twice daily for ten days.	Urology (Elective retro-pubic prostatectomy)	Double blind RCT to assess effectiveness of EACA. Incidence broken down by intervention groups and also by type of surgery. I-fibrinogen test used to identify DVT.
Valladares and Hankinson, 1980[652]	29/100 (29%) developed DVT Of whom: 16/36 (44%) of those with known risk factors developed DVT. Of those without risk factors, 13/64 (20.3%)	Not reported	Not reported	Not reported	No prophylaxis reported	Neurosurgery (major cranial or spinal operations)	100 patients undergoing major cranial or spinal operations. Broken down by specific type of surgery, and also by risk factor, e.g. age,."leg weakness", length of op, given as particular risk factors

Surgical risk of VTE: incidence studies

Paper	Asymptomatic DVT	Symptomatic VTE	Fatal PE	PE	Type of prophylaxis	Type of Surgery	Notes
Warwick et al., 1995[677]	Not reported	Overall venographically proven DVT rate 22/1162 (1.89%, CI 1.11-2.76)	4/1162 (0.34%) CI 0.09-0.88	14/1162 (1.20%, CI 0.657 to 2.02)	Standard practice: stockings and early mobilisation, Anticoagulant prophylaxis was not used routinely but reserved for those considered to be at the greatest risk of thromboembolism.	Orthopaedic	Review of records of 1112 patients who had 1162 primary or revision THR Total early morbidity from VTE 3.4% In-patient, all cause mortality rate of 0.86% (10/1162) 90-day mortality rate 1.3% (1.1%, 15/1162) Total thromboembolitic morbidity : 3.4% (95%, CI 2.5%-4.7%)

Medical Risk

Evidence Table 2: Medical risk of VTE: incidence studies

Paper	Population	Type of prophylaxis	Asymptomatic DVT	Symptomatic DVT	PE	Fatal PE	Notes
Bosson et al., 2006[77] **Country of study:** France **Study design:** prospective cohort **Recruitment period:** Oct 2002 – June 2003	**Study setting:** General Practice, nationwide **Population:** Patients with an 'acute medical event' & reduced mobility managed in the community. **Inclusion criteria:** Outpatients aged at least 40yrs anticipated to have reduced mobility for at least 48h due to an acute medical event **Exclusion critieria:** Patients administered anticoagulants, reduced mobility before the start of the study due to surgery in the previous 6/52, bedridden for > 1month, incapable of complying with the protocol. 662 (3.9%) patients excluded due to administration of therapeutic or non-reported doses of anticoagulants, no follow-up visit, or occurrence of VTE at the or before the inclusion visit	Initiated in 35% (n = 5782) patients: LMWH in 96.5% (n = 5582), UFH in 3.5% (n = 200). Median duration 10 (range 1-90) days. Results by 'risk group': in the major risk group incidence of DVT 2.5% (42/1664) in the treated patients compared with 1.2% (16/1318) in the non-treated pts. In the low risk group 1.4% (35/2499) vs 0.5% (35/6843)	Not specified	128 patients had DVT confirmed by duplex ultrasonography (note another 36 pts *not* confirmed on USS). Authors calculate incidence density for total of 164 patients as 0.50 (95% CI 0.42 - 0.58) events/1000 patient days; incidence rate 1% (95% CI 0.84 - 1.14)	27 patients had imaging confirmed PE. A total of 33 patients reported to have symptomatic PE. Based on 33 patients, authors report incidence density 0.1 events/1000 patient-days (95% CI 0.07 - 0.14). Incidence rate 0.2% (95% CI 0.13 - 0.27)	8 fatal PE (none confirmed at autopsy)	**Duration of follow up:** Planned second visit at 3 weeks +/- 7 days. Duration of follow-up < 10 days in 98 pts (0.6%), 10-14days in 16 pts (0.1%) and between 14-28days in 16138 pts (99.3%) Time to VTE: Median time from inclusion to event 7 days (range 1-28 days) for DVT and 11 days (range 1-23 days) for PE **Notes:** **Population:** Severe acute infection 4727 (28.6%); acute rheumatism 4446 (26.9%); falls without # 2705 (16.4%); acute inflammatory episode 1934 (11.7%); decompensated cardiac insufficiency (NYHA III/IV) 825 (5%); decompensated respiratory insufficiency 752 (4.5%) **Limitations:** Patients managed in the community – ma not represent patients hospitalised with an acute medical illness. Does not report baseline characteristics of the groups that did and did not receive prophylaxis. Fatal PE not confirmed at autopsy and some cases of VTE did not have imaging confirmed diagnosis

Paper	Population	Type of prophylaxis	Asymptomatic DVT	Symptomatic DVT	PE	Fatal PE	Notes
	(n= 16,532) **Risk factors** Male:female: 39.4%: 60.6% Race: not specified Age: 71 year						

Medical risk of VTE: incidence studies

Paper	Population	Type of prophylaxis	Asymptomatic DVT	Symptomatic DVT	PE	Fatal PE	Notes
Blom et al., 2004[67] **Country of study:** Holland **Study design:** Retrospective cohort **Recruitment period:** 1990-2000	**Study setting:** Single centre hospital study **Population** Lung cancer patients **Inclusion criteria:** Patients identified from oncology database: first diagnosis of non-small cell lung cancer **Exclusion critieria:** 57 medical records could not be traced, 50 patients not included as visited hospital only for laser therapy, 34 patients not included as they had a diagnosis of lung ca before 1990 or a primary diagnosis of lung ca could not be confirmed **(n=537)** **Risk factors** Male:female: 429:108 Race: Not recorded Age: Mean 65 years	Not recorded	Not reported	17 (3.2%) Method of diagnosis not reported	22 (4.1%) (this includes DVT and PE) Method of diagnosis not reported	Not analysed	**Duration of follow up:** Total 879 person-years of follow-up **Time to VTE:** Median time from first admittance for lung cancer until development of VTE = 5.3 months (range 0 - 56.5 months) **Notes:** **Limitations:** Not necessarily in-hospital events. No description of other medical risk factors. ? Ongoing smoking. Potential loss to follow-up and sudden death at home - fatal PE

Medical risk of VTE: incidence studies

Paper	Population	Type of prophylaxis	Asymptomatic DVT	Symptomatic DVT	PE	Fatal PE	Notes
Blom et al., 2006[68] **Country of study:** Holland **Study design:** Retrospective cohort **Recruitment period:** 1990-2000	**Study setting:** Single centre hospital study **Population** pancreatic cancer patients **Inclusion criteria:** Patients identified from oncology database: all patients admitted with a tumour of the pancreas **Exclusion critieria:** 27 patients excluded as only breifly visited for diagnosis or therapy; 7 patients excluded as they had a diagnosis of pancreatic cancer before 1990 or a primary diagnosis of pancreatic ca which could not be confirmed. 16 medical records could not be traced **(n=202)** **Risk factors** Male:female: 115:87 Race: Not recorded Age: Mean 64 years	Not recorded	Not reported	21 (10.4%) Method of diagnosis not reported	6 (3.0%) (this includes DVT and PE) Method of diagnosis not reported	Not analysed	**Duration of follow up:** Total 176 person years of follow-up **Time to VTE:** For patients with distant metastasis, median time for development of VTE 92 days. Data not supplied for patients without metastasis. **Notes:** **Limitations:** Not necessarily in-hospital events. No description of other medical risk factors. Potential loss to follow-up and sudden death at home - fatal PE

Medical risk of VTE: incidence studies

Paper	Population	Type of prophylaxis	Asymptomatic DVT	Symptomatic DVT	PE	Fatal PE	Notes
Cook et al., 2005[134] **Country of study:** Canada **Study design:** Prospective cohort **Recruitment period:** Jan 2001- Jan 2002	**Study setting:** Single university affiliated ICU **Population** Mixed critical care **Inclusion criteria:** ≥ 18 years of age; anticipated to be in ICU for ≥ 72 hours **Exclusion critieria:** Admitting diagnosis of trauma; orthopaedic surgery; pregnancy; life support withdrawal **(n= 262)** **Risk factors** Male:female: 59.8%:40.2% Race:Not specified Age: 66.9 (SD 15.1)	Routine medical-surgical ICU patients received UFH 2000 IU SC BD. Pts in whom heparin contraindicated recived pneumatic compression stockings. If contraindications to both, given antiembolic stocks. Ten patients (3.8%) had active bleeding and so were ineligible for anticoag prophylaxis. Of remaining 251, 233 (92.8%) received anticoagulants: 201 (81.7%) received UFH SC; 17 (6.8%) received UFH IV; 10 (4%) received LMWH; 1 (0.4%) received warfarin	Clinically unsuspected DVTs at ICU admission (prevalence): 4 patients. Clinically unsuspected DVTs occurring during ICU stay, identified by US (incidence): 22 patients Bilateral lower extremity compression US within 48h of admission to ICU to determine DVT prevalence at admission. To determine incidence, bilateral lower extremity US twice weekly or if clinically suspected	Clinically suspected DVTs at ICU admission (prevalence): 3 patients. Clinically suspected DVTs occurring during ICU stay, identified by US (incidence): 3 patients	3 patients with PE Diagnosis with VQ/helical CT/pulmonary angiogram	Not specified	**Duration of follow up:** Up to hospital discharge. Median duration of hospital stay 25 days, IQR 13-52 days **Time to VTE:** DVTs which developed in ICU occurred at median ICU day 8, interquartile range 4 - 14) **Notes:** **Risk factors:** Mean APACHE II score 25.5 (SD 8.4); BMI 27.1 (SD7.3); central venous catheter in 221 patients (84.7%). Additional details provided re mechanical ventilation, admitting diagnosis, mortality etc but not broken down into VTE vs non-VTE grouping

Medical risk of VTE: incidence studies

Paper	Population	Type of prophylaxis	Asymptomatic DVT	Symptomatic DVT	PE	Fatal PE	Notes
Darze et al., 2005[144] **Country of study:** Brazil **Study design:** Prospective Cohort **Recruitment period:** July 2001 – March 2003	**Study setting:** Coronary care unit of a tertiary care hospital **Population** Patients with congestive heart failure **Inclusion criteria:** Patients admitted to CCU with decompensated congestive heart failure F **Exclusion critieria:** Acute STEMI; admitting diagnosis other than congestive heart failure **(n=198)** **Risk factors** Male:female: Not reported Race: Not reported Age: Not reported	Thromboprophylaxis was used by 12 of 18 patients (66.7%) with PE and 126 of 180 patients (70%) without PE (p = 0.77). All patients received enoxaparin, 40 mg qd, and none received unfractionated heparin or mechanical methods. There was no significant difference in the incidence of PE between patients who did or did not receive prophylaxis (8.7% vs 10%, p = 0.769)	Not reported	Not reported	18 (9.1%) The diagnosis of PE was confirmed by high prob lung scintigraphy in 14 patients (78%) and positive spiral CT in 4 patients (22%)	Not analysed	**Duration of follow up:** Not reported **Time to VTE:** DVTs which developed in ICU occurred at median ICU day 8, interquartile range 4 - 14) **Notes:** **Limitations:** No length of stay recorded. Not clear that these were incidence cases occurring on the unit compared with cases precipitating admission

Medical risk of VTE: incidence studies

Paper	Population	Type of prophylaxis	Asymptomatic DVT	Symptomatic DVT	PE	Fatal PE	Notes
De Silva et al, 2006[149] **Country of study:** Singapore **Study design:** Prospective Cohort **Recruitment period:** June 2002 – December 2002	**Study setting:** Single centre hospital **Population** Patients with ischaemic stroke **Inclusion criteria:** (1) acute ischemic stroke (diagnosed by a consultant neurologist based on clinical presentation and CT or MR brain imaging done within 48 h of symptom onset) and (2) a National Institute of Health Stroke Scale (NIHSS) score of >/= 1 for the lower limb affected by the acute stroke at time of recruitment screening which was carried out within 48 h of hospital admission **Exclusion critieria:** Past history of stroke or DVT **(n=105)** **Risk factors** Male:female: 49: 62 Race: Chinese 92 (83%); Malay 9 (8%); Indian 9 (8%); Indian 9 (8%); Caucasian 1 (1%) Age: Median 72 years	No patients on UFH or LMWH prior to first Doppler scan at day 7-10 All patients on anitplatelet therapy unless contraindicated - majority aspirin 100mg OD.	23 (22%) patients distal DVT, another 8 patients with proximal DVT (30%) Doppler USS - routine at days 7-10 and 25-30 post stroke	None of the patients were symptomatic or had clinical signs on examination for DVT at the time of the first or second Doppler scans.	1 (0.95%) diagnosed by spiral CT	None	**Duration of follow up:** Functional assessment at 6 months. Followed up re DVT for 25-30 days post stroke **Time to VTE:** Routine doppler scans at 7-10 days and 25-30 days post stroke **Notes:**

Medical risk of VTE: incidence studies

Paper	Population	Type of prophylaxis	Asymptomatic DVT	Symptomatic DVT	PE	Fatal PE	Notes
Erelel et al., 2002[173] **Country of study:** Turkey **Study design:** Prospective Cohort **Recruitment period:** Not stated	**Study setting:** Hospital setting **Population** Acute exacerbation COPD **Inclusion criteria:** One criterion for hospitalisation in an acute exacerbation COPD (as defined by American Thorax Society/European Resp Soc) **Exclusion critieria:** Clinical/radiological finding of lung ca; other haematological/solid malignancy; other systemic disease; other function limiting disease; other 'risk grouping' for DVT/PE **(n= 56)** **Risk factors** Male:female: 46:10 Race: not reported Age: not reported	Not reported	4 (7.1%) on admission detected by colour doppler ultrasonography/ venography	Not reported	5 (9%) (of these: 3 PE + 2 PE w/ DVT. These DVTs are additional to those recorded previously) detected by V/Q scan	Not reported	**Duration of follow up:** Not reported **Time to VTE:** Not reported **Notes:** **Limitations:** This is only a point prevalence of DVT/PE at the point of admission to hospital with DVT. Does not analyse VTE over time while in hospital. Problems - no analysis of population risk factors, confounding by prophylaxis?

Medical risk of VTE: incidence studies

Paper	Population	Type of prophylaxis	Asymptomatic DVT	Symptomatic DVT	PE	Fatal PE	Notes
Guijarro et al., 2005[241] **Country of study:** Spain **Study design:** Database review **Recruitment period:** 1998-2001	**Study setting:** 32 hospitals in Spain **Population:** All hospital inpatients **Inclusion criteria:** Primary or secondary diagnosis with ICD-9-CM coding for embolism, pulmonary infarction, phlebitis, thrombophlebitis, thrombophlebitis/venous thrombosis in pregnancy and childbirth **Exclusion critieria:** Primary or secondary diagnosis with ICD-9-CM coding for Superficial phlebitis; thrombophlebitis of the upper limbs **(n=2,228,894)** **Risk factors** Male:female: Not reported Race: Not reported Age: Not reported	No information provided	Not analysed	2162 with PE as secondary diagnosis at discharge (0.1%)	5559 cases with DVT as the secondary diagnosis (0.25%) Database coding used as confirmation of event	Not analysed	**Duration of follow up:** Not reported **Time to VTE:** Not reported **Notes:** **Limitations:** Events were confirmed by coding, which is unreliable as secondary events may not always be reported appropriately. This may explain why the DVT rate appears to be low. There is no mention made of the prophylaxis strategy used in the patients.

Medical risk of VTE: incidence studies

Paper	Population	Type of prophylaxis	Asymptomatic DVT	Symptomatic DVT	PE	Fatal PE	Notes
Joynt et al., 2000[320] **Country of study:** Hong Kong **Study design:** Prospective cohort **Recruitment period:** January 1996 – Feburary 1998	**Study setting:** Critical care unit **Population** Medical/surgical patients in critical care requiring a femoral line **Inclusion criteria:** Femoral line in mixed medical/surgical ICU **Exclusion critieria:** Infection/inflammation at insertion site, existing/previous DVT, recent pelvic/abdo trauma, lower extremity ischaemia, documented hypercoagulable state (protein C/S deficiency, antithrombin III deficiency, lupus anticoagulant), prior femoral catheterisation, survival < 24h post insertion of line **(n=124)** **Risk factors** Male:female: Not reported Race: Not reported Age: Not reported	None	12 (9.68%) ileofemoral DVT on side with femoral line; 2 (1.61%) ileofemoral on side without femoral line. Of the total of 14 DVTs, 2 were clinically obvious Doppler USS - routine before insertion, within 12 hours after insertion, daily up to discharge, 24 hours after removal and at 1 week post removal	12 (9.68%) ileofemoral DVT on side with femoral line; 2 (1.61%) ileofemoral on side without femoral line. Of the total of 14 DVTs, 2 were clinically obvious	None	None	**Duration of follow up:** 1 week after discharge from ICU **Time to VTE:** Not reported **Notes:**

Medical risk of VTE: incidence studies

Paper	Population	Type of prophylaxis	Asymptomatic DVT	Symptomatic DVT	PE	Fatal PE	Notes
Kishimoto et al., 2005[349] **Country of study:** Japan **Study design:** Retrospective cohort **Recruitment period:** 1987-1999	**Study setting:** Single tertiary referral centre **Population** All hospital inpatients **Inclusion criteria:** None stated **Exclusion critieria:** None stated **(n=131,060)** **Risk factors** Male:female: 46.3%:53.7% Race: 99.5% Japanese Age: Not stated	"There was no fixed policy for prophylaxis during the study period. Compression stockings rarely used, other forms (pneumatic compression devices, heparin, warfarin) were never used"	Not analysed in this study	128 patients were diagnosed with symptomatic DVT by venography or ultransound (0.1%)	41 patients were diagnosed with symptomatic PE Pulmonary perfusion scintigraphy and/or contrast enhanced CT (0.03%)	Not analysed	**Duration of follow up:** Hospital stay **Time to VTE:** 44% of VTE diagnosed while an inpatient. Time from admission to diagnosis was mean 21.3 days +/- 21.2 S.D. **Notes:** **Population:** The breakdown of the population included is not provided. Given that this population was admitted to a tertiary referral unit it is difficult to determine how representative the population is. **Limitations:** The VTE figures are divided up into those diagnosed on admission and those diagnosed as an inpatient, but these are not in turn broken down into DVT and PE.

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Paper	Population	Type of prophylaxis	Asymptomatic DVT	Symptomatic DVT	PE	Fatal PE	Notes
Misra et al., 2005[453] **Country of study:** USA **Study design:** Retrospective cohort **Recruitment period:** July 2001 – July 2002	**Study setting:** Mixed intensive care unit in a single hospital **Population** Medical, surgical, cardiac , transplant intensive care patients **Inclusion criteria:** Not stated **Exclusion critieria:** Not neurosurgery patients. **(n=4223)** **Risk factors** Male:female: 49.1%: 50.9% Race: not analysed Age: 55.3 years	Not reported	Not analysed	238 patients (5.62%) Diagnosed with Doppler ultrasound when clinically indicated	45 patients (1.06%) Diagnosed using Chest CT scan	Not reported	**Duration of follow up:** Duration of ICU stay **Time to VTE:** Not reported **Notes:** **Limitations:** No details of prophylaxis, no analysis of patient group/risk factors. Not clear what the prevalence of DVT/PE was at the point of admission to ICU, vs how many acquired in the unit

Medical risk of VTE: incidence studies

Paper	Population	Type of prophylaxis	Asymptomatic DVT	Symptomatic DVT	PE	Fatal PE	Notes
Muscadere et al., 2007[469] **Country of study:** Canada **Study design:** Retrospective cohort **Recruitment period:** Jan 2001 – Feb 2002	**Study setting:** Single centre intensive care unit **Population** **Inclusion criteria:** ICU patients (medical, surgical and trauma) > 18 years with an ICU stay > 48 hours **Exclusion critieria:** Treatment for VTE diagnosed before the time of ICU admissions; therapeutic anticoagulation for other reasons during ICU stay **(n=600)** **Risk factors** Male:female: 60.2%: 39.8 Race: Not analysed Age: 59.5 years	Prophylaxis recorded for ICU stay and ward stay post-ICU: On ICU patients received prophylaxis for 87.6% (95% CI 81.5 - 93.7%) days in the unit. This was made up of 42.1% (39.8-45.4) low dose UFH; 11.2% (9.0-13.4%) LMWH; 34.3% (29.8-38.8) pneumatic compression stockings. On the ward, prophylaxis for 59.8% days (55.1-65.7), made up of 41.9% (38.2-45.6) low dose UFH; 9.4% (6.7-12.1) LMWH; 3.5% (2.8-4.2) pneumatic compression stockings.	Not analysed in the study	17 patients proximal DVT and an additional 19 patients proximal DVT & PE (recorded in PE box as well here) (6.0%) Diagnosed by duplex ultrasonography	12 patients had proximal DVT and PE (also recorded in DVT box here) and an additional 13 patients had PE only (4.2%) Diagnosed by CTPA/VQ scan/Pulmonary angiography	2 patients (0.3%) had fatal PE confirmed at autopsy	**Duration of follow up:** In hospital length of stay **Time to VTE:** Not analysed **Notes:** Note that 32 of 50 VTE events occurred after discharge from ICU to the ward. Prolonged duration of mechanical ventilation (8.8+/- 7.9 vs 6.4 +/- 6.4 days p = 0.05); prolonged ICU stay (14.8 vs 8.8 days, p <0.01) and prolonged duration of hospitalisation (47.5 +/-34.2 vs 23.6 +/- 20.8 days p < 0.001) associated with VTE. Rates of prophylaxis similar between group of patients receiving prophylaxis and those not

Medical risk of VTE: incidence studies

Paper	Population	Type of prophylaxis	Asymptomatic DVT	Symptomatic DVT	PE	Fatal PE	Notes
Oger et al., 2002[501] **Country of study:** France **Study design:** Prospective cohort **Recruitment period:** April 1999 – Jan 2000	**Study setting:** Single centre, internal medical centre **Population** General medical patients **Inclusion criteria:** All patients admitted under internal medicine **Exclusion critieria:** Under 18 years of age; clinical suspicion of VTE; hospitalisation scheduled for < 4 days; patients referred from another hospital; any type of anticoagulant therpay for more than 48h prior to admissions; diseases requiring anticoagulants such as cardiac arrhythmias, ACS, or stroke; inability to give informed consent eg neuropsychiatric disorder **(n=234)** **Risk factors** Male:female: 50.9%: 49.1% Race: not analysed Age: 66 years (SD = 16)	Unclear regarding whether prophylaxis was given.	Prevalence of asymptomatic DVT at point of admission: 13 patients (5.5%, 95% CI 3.1-9.5). Incidence of asymptomatic DVT at day 5 and day 10 for patients negative on admission: 3/134 patients (day 5); 1/133 patients (day 10). Overall incidence of asymptomatic DVT during hospital follow-up was 2.6 per 1000 person-days (95% CI 0.0 to 5.2) Diagnosed by compression ultrasonography	Not analysed in the study	Not analysed	Not analysed	**Duration of follow up:** Median follow up 6 days **Time to VTE:** Not reported **Notes:** No information about provision of prophylaxis.

Medical risk of VTE: incidence studies

Paper	Population	Type of prophylaxis	Asymptomatic DVT	Symptomatic DVT	PE	Fatal PE	Notes
Patel et al, 2005[512] **Country of study:** Canada **Study design:** Retrospective cohort **Recruitment period:** Jan – Dec 2000	**Study setting:** 12 intensive care units **Population** Mixed medical and surgical patients admitted to intensive care unit. **Inclusion criteria:** ICU patients > 18 years **Exclusion critieria:** None stated **(n=12338)** **Risk factors** Male:female: Not reported Race: not reported Age: Not reported	Prophylaxis only recorded for patients *with* VTE. Among pts with VTE, pharmacological or mechanical prophylaxis administered for 70.4% (95% CI 57.8-73.2%) of eligible ICU days. Details of drugs given or doses not recorded.	TOTAL DVTs: 166 events, of which 44 were prevalent (present at/within 48h of admission) and 122 were incident cases after admission to ICU up to 8 weeks after discharge. 16.3% of DVTs were 'clinically unsuspected' and detected by screening. Authors report prevalent DVT in 0.4% (95%CI 0.3-0.5%) and incident DVT in 1.0% (95% CI 0.8-1.2%) Screening by duplex ultrasonography or venography	See asymptomatic DVT box	TOTAL PEs: 111 events, of which 54 were prevalent and 57 were incident. 1.8% of PE events were clinically unsuspected. Authors report prevalent PE in 0.4% (95% CI 0.3-0.6%) and incident PE 0.5% (95% CI 0.4-0.6%) VQ/CTPA/echocardiocardiography/ECG/autopsy	Not reported	**Duration of follow up:** In hospital length of stay up to a maximum of 8/52 post ICU discharge **Time to VTE:** Not analysed. "Most events occurred within 2 weeks of ICU admission" **Notes:** **Population:** **Limitations:** No analysis of the patients which did not have VTE no analysis of classical risk factors; results not presented by prophylaxis; ECG and echo used for diagnosis of PE

Medical risk of VTE: incidence studies

Paper	Population	Type of prophylaxis	Asymptomatic DVT	Symptomatic DVT	PE	Fatal PE	Notes
Sachdev et al., 2006[567] **Country of study:** USA **Study design:** Prospective cohort **Recruitment period:** 1997-2000	**Study setting:** Mixed surgical/medical rehabilitation unit **Population** Rehabilitation - mixed medical/surgical **Inclusion criteria:** All patients admitted to rehabilitation programme **Exclusion critieria:** Pts receiving anticoagulation; patients with symptomatic or clinically suspected DVT **(n=380)** **Risk factors** Male:female: 191:189 Race: not reported Age: 64.7 yrs with DVT, 55.8 years without.	364 patients receiving prophylaxis at the point of first screening (admission to rehab programme) - either UFH or LMWH	Total DVT = 128 (34%) patients. In 25 patients (7%), DVT was found in both the thigh and calf veins; in 87 patients (23%), DVT was limited to the calf veins; and in 16 patients (4%), DVT was limited to the thigh veins Duplex USS on admission to rehab programme. Follow-up USS achieved for 60 of the patients with positive initial scan within 6/52 of initial scan, after a mean of 13 days after first scan	Not reported	Not reported	Not reported	**Duration of follow up:** Up to second ultrasound scan **Time to VTE:** Not reported **Notes:** **Limitations: High loss to follow up**

Medical risk of VTE: incidence studies

Paper	Population	Type of prophylaxis	Asymptomatic DVT	Symptomatic DVT	PE	Fatal PE	Notes
Skaf et al., 2005[606] **Country of study:** USA **Study design:** Database review **Recruitment period:** 1979-2003	**Study setting:** Multicentre study across hospitals in the USA **Population** Ischaemic or haemorrhagic stroke **Inclusion criteria:** NHDS codes for ischaemic stroke, DVT and PE **Exclusion critieria:** None reported **(n=** Ischaemic = 14,109,000; haemorrhagic = 1,606,000) **Risk factors** Male:female: Not reported Race: not reported Age: not reported	Not analysed although the authors state: "we assume most patients with ischaemic stroke received antithrombotic therapy"	Not analysed	Ischaemic stroke: 104,000 (0.74%) Haemorrhagic stroke: 22,000 (1.37%) Method of diagnosis was not reported.	Ischaemic stroke: 72,000 (0.51%) Haemorrhagic stroke: 11,000 (0.68%) Method of diagnosis was not reported.	Not reported	**Duration of follow up:** Until discharge (length of stay not analysed) **Time to VTE:** Not analysed **Notes:** **Limitations:** rates presented were from discharge coding and may not always have been accurate. Methods of diagnosis of DVT and PE were not reported

Medical risk of VTE: incidence studies

Paper	Population	Type of prophylaxis	Asymptomatic DVT	Symptomatic DVT	PE	Fatal PE	Notes
Stein et al., 1999[624] **Country of study:** USA **Study design:** Retrospective cohort **Recruitment period:** Jan 1993 – Sep 1997	**Study setting:** All hospital inpatients **Population** Mixed medical and surgical patients **Inclusion criteria:** Discharge coding ICD-9-CM for PE and infarction; iatrogenic PE and infarction; PE (other); PE with abortion; PE with ectopic pregnancy, childbirth, in the puerperium **Exclusion critieria:** None stated **(n=175,730)** **Risk factors** Male:female: Not reported Race: not reported Age: not reported	Not analysed. Hospital had no specific policy for prophylaxis during study period.	Not analysed in this study	Not analysed in this study	400 patients of 175,730, ie 0.23% (95% CI 0.21 to 0.25%). Incidence per year = 0.05% Diagnosed by Positive VQ or pulmonary angiogram	Not analysed separately	**Duration of follow up:** In hospital stay. No information reported on length of stay **Time to VTE:** Not analysed **Notes:** **Limitations:** No information on prophylaxis, no analysis of risk factors. Analysis of discharge coding does not restrict to in hospital VTE - may apply to patients who have VTE in the community and present to hospital

Medical risk of VTE: incidence studies

Paper	Population	Type of prophylaxis	Asymptomatic DVT	Symptomatic DVT	PE	Fatal PE	Notes
Stein et al., 2006 [623] **Country of study:** USA **Study design:** Database revuew **Recruitment period:** 1979-1999	**Study setting:** Multicentre study across hospitals in the USA **Population** Mixed medical and surgical patients all with cancer. **Inclusion criteria:** NHDS codes for 19 malignancies, DVT and PE **Exclusion critieria:** None stated **(n=40,787,000)** **Risk factors** Male:female: not reported Race: not reported Age: not reported	Not reported	Not reported	643000 (1.6%) (1.6 DVT per 100 hospitalisations). This is the average rate for patients with cancer Method of diagnosis was not reported.	245000 (0.6%) (0.6 per 100 hospitalisations). This is the average rate for patients with cancer Method of diagnosis was not reported	Not reported	**Duration of follow up:** Until discharge (length of stay not analysed) **Time to VTE:** Not reported **Notes:** Incidence for 19 different malignancies presented. Average rates recorded within the paper. **Limitations:** ncludes community DVT and PE of the patients who presented to hospital. Unclear whether the database review data includes information on patients who died Information regarding surgery, metastasis, chemotherapy, radiotherapy, etc not available. No adjustment of cancer population re age/sex/medical comorbidities compared with the general hospital population for direct comparison

Patient Risk Factors

Evidence Table 3: Patient Risk Factors - age

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Edmonds et al., 2004[169]	Systematic review 6 cohort studies	2+	1927	Patients undergoing general, gynaecological, elective hip replacement and 1 study did not specify the type of surgery. Other inclusion criteria: 2 studies - >40 yrs 1 study – 40-80 yrs 3 studies – no other specific patient group	Age Different age bands used for different studies	Varied 6 to 8 postoperative days or for duration of hospital-isation	Percentage of population with postoperative DVT	40 to 60 year olds 24.4% 61 to 80 year olds 45.7% significant (1 study)	Pooled risk estimate not possible because of different categorisation of age 3 studies had reported no prophylaxis used, 3 studies did not report the prophylaxis used, 1 study did not control for prophylaxis. Diagnosis of DVT: 5 studies fibrinogen uptake test 1 study bilateral ascending venography.
							Percentage of population with postoperative DVT	Under 60 year olds 19% Over 60 year olds 36% p<0.0005 (1 study)	
							Mean ±SD age (years) groups with and without postoperative DVT	With DVT 58 ±3 Without DVT: 44 ±2 Significant (1 study)	
							Mean ±SD age (years) groups with and without postoperative DVT	With DVT 71.7 ±9.8 Without DVT: 59.5 ±10.8 Significant (1 study)	
							Incidence of postoperative DVT. (continuous range of age)	Constant risk below 45 years, increases with each year older (1 study)	
							Risk estimate for postoperative DVT	Odds ratio: 1.21 CI: 1.04 to 1.42 (1 study)	

Age

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Rocha et al., 2007[556]	Systematic review 5 studies 3 cohort 2 registry studies	2+	Unclear	General population, immobilised hospital population Other inclusion criteria: 1 studies >65 yrs 1 study >75 yrs 1 study >80 yrs 1 study >85 yrs	Age Different age bands used for different studies	Unclear	Relative risk of VTE (no further description)	Relative risk of 1.75 for age >65 no 95%CI given Significant (1 study; general population) Relative risk of 1.51 for age >75 no 95%CI given significant (1 study; immobilised general population) Relative risk of 2.0 for age > 85 no 95%CI given significant (1 study; general population) Doubled at each decade from the 5th decade (RR = 1.9)	Pooled risk estimate not possible because of different categorisation of age 1 study reported on the use of prophylaxis. No other studies reported prophylaxis use
							Prevalence of asymptomatic DVT (Doppler ultrasound) (n=234)	Medical patients >80years 17.8% (95% CI: 8.5-32.6) (1 study)	
							Incidence of asymptomatic DVT (Doppler ultrasound) (n=234)	Medical patients >80years 6 per 1000 patients (95% CI: 0-12.7) (1 study)	

Evidence Table 4: Patient Risk Factors - obesity

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Edmonds et al., 2004[169]	Syste-matic review 7 cohort studies	2+	4804	Patients undergoing general, gynaecological, thoracic, orthopaedic, neurological or urologic surgery. Other inclusion criteria: 1 study - adults 2 studies - >40 yrs 1 study – 40-80 yrs 3 studies – no other specific patient group	Obesity Different definitions used to classify obesity	Varied 6 to 8 postoperative days or for duration of hospital-isation	Risk estimate for postoperative DVT (BMI>30 vs BMI ≤30)	Odds ratio: 2.04 CI 1.04 to 4.02 (1 study)	Pooled risk estimate not possible because of different ways of defining obesity. Diagnosis of DVT: 5 studies fibrinogen uptake test 1 study bilateral ascending venography 1 study Doppler ultrasound and clinical diagnosis
							Risk estimate for postoperative DVT (definition for obesity not stated)	Relative risk: 1.43 p<0.025 on univariate analysis (1 study)	
							Risk estimate for postoperative DVT (weight height analysis used, definition of obesity not stated)	Relative risk: 1.95 p<0.01 (higher incidence in overweight patients) (1 study)	
							Weight & obesity (definition not stated) as a risk for postoperative DVT	Increased weight a risk p=0.02 Obesity significant risk factor (no data provided) (1 study)	
							Incidence of postoperative DVTs (% overweight for height used, definition not stated)	With DVT: 13 ±3% Without DVT: 5 ±1% Significant (1 study)	
							Incidence of postoperative DVTs (% overweight, definition not stated)	Non-significant difference (1 study)	
							Incidence of postoperative	Non-significant difference	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
							DVTs (Definition of obesity not recorded)	(1 study)	

Obesity

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Rocha et al., 2007[556]	Syste-matic review 8 cohort studies 1 case control study	2+	Unclear	General medical patients. Other inclusion criteria: 5 studies – Obesity not defined 1 study – women with BMI >27 1 study – 30% excess above ideal body weight 1 study – obesity at autopsy 1 study – obese women using hormonal contraceptives	Obesity Different definitions used to classify obesity (see patient characteristics)	Unclear	Risk estimate for VTE (Obese medical patients not defined)	Relative risk ranges from 1.04 (95% CI: 0.69-1.60) Not significant (1 study)	Pooled risk estimate not possible because of different ways of defining obesity. Definition of VTE is not well described in any of the studies.
							Risk estimate for VTE (women with body mass index >27)	Not significant (1 study)	
							Risk estimate for clinical suspicion of VTE (outpatient with 30% excess above ideal body weight)	Not significant (1 study)	
							Risk estimate for VTE (no definition provided)	RR: 2.97 (95% CI: 1.78-4.93) (1 study) RR ranging from 2.0 to 3.92 Significant (4 studies)	
							Risk estimate for hormonal contraceptives in obese patients	RR rises from 2-10 Significant (1 study)	

Evidence Table 5: Patient Risk Factors – history of VTE

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Edmonds et al., 2004[169]	Syste-matic review 4 cohort studies	2+	1362	Patients undergoing major gynaecological, non-lower limb elective surgery. 1 study with 624 patients did not specify the type of surgery. Other inclusion criteria: 1 study - >40 yrs 3 studies – no other specific patient group	History of venous thrombosis	Varied: 6 postoperati ve days, for duration of hospital-isation or not specified	Risk estimate for postoperative DVT	Relative risk: 5.18 CI: 3.16 to 8.49 (3 studies. 1 study did not provide enough data)	Diagnosis of DVT by fibrinogen uptake test

History of VTE

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Rocha et al., 2007[556]	Syste-matic review 2 cohort studies 4 cohort studies	2+	Unclear	Hospitalised and ambulatory patients and general population Other inclusion criteria: 1 study >64 yrs 1 study > 40 yrs	History of venous thrombosis	Not specified	New thrombotic events (ambulatory patients with previous VTE)	Odds ratio: 15.6 No 95% CI Significant (1 study)	Pooled risk estimate not attempted Definition of VTE is not well described in any of the studies. DVT confirmed with venography in 1 study
							DVT (medical patients with previous VTE and a suspected DVT)	Odds ratio: 1.7 No 95% CI Significant (1 study)	
							VTE (Individuals with previous VTE)	Odds ratio: 6.8 No 95% CI Significant (1 study)	
							VTE (hospitalised medical patients with previous VTE)	Odds ratio: 4.7 No 95% CI Significant (1 study)	
							VTE (hospitalised medical patients >64yrs with previous VTE)	Odds ratio: 3.4 No 95% CI Significant (1 study)	
							VTE (medical patients in hospital >40yrs with previous VTE)	Associated with VTE in: Univariate analysis RR = 1.8, p=0.02 Multivariate analysis: RR 2.1, p = 0.02	

Evidence Table 6: Patient Risk Factors - thrombophilias

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Edmonds et al., 2004[169]	Syste-matic review 2 cohort studies	2+	1125	Patients undergoing elective hip or knee replacement Other inclusion criteria: 1 study - 40 -80 yrs 1 study – no other specific patient group	Factor VS Leiden (FVL)	8 to 14 days post-operatively in 1 study, 3 months in other study	Risk estimate for activated protein C resistance (95% cases had FVL) & postoperative DVT.	Relative risk: 4.9 CI: 1.1 to 22.1 (1 study)	Diagnosis of DVT: 1 study bilateral ascending venography 1 study clinical diagnosis.
							Risk estimate for FVL mutation & postoperative DVT	Odds ratio: 3.18 CI: 0.99 to 10.2 (1 study)	
							Risk estimate for low sensitivity of FVL to APC & postoperative DVT	Odds ratio: 2.97 CI: 1.27 to 6.92 (1 study)	

Thrombophilias

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
den Heijer et al., 2005[156]	Systematic review of 24 studies: 3 prospective 21 retrospective	2+	3765 cases 5297 controls	Any population Excluded studies in diseased populations (irritable bowel syndrome, systemic lupus erythematosis or Behcet's Syndrome)	Raised homocysteine levels	Not reported	Risk estimate for venous thrombosis for a 5µmol/L increase in measured plasma total homocysteine	Odds ratio: 1.27 95% CI: 1.01 to 1.59 (3 prospective studies) Odds ratio: 1.60 95% CI: 1.10 to 2.34 (21 retrospective studies)	Not reported how venous thrombosis was diagnosed.
den Heijer et al., 2005[156]	Systematic review of 53 studies	2+	8364 cases 12,468 controls	Any population Excluded studies in diseased populations (irritable bowel syndrome, systemic lupus erythematosis or Behcet's Syndrome)	MTHFR 677TT geno-type compared to MTHFR 677CC geno-type	Not reported	Risk estimate for venous thrombosis for TT vs CS genotype for MTHFR	Odds ratio: 1.20 CI: 1.08 to 1.32 (53 studies)	Not reported how venous thrombosis was diagnosed.

Thrombophilias

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Galli et al., 2003[206]	Syste-matic review of 25 studies 11 case–control, 3 cross-section-al 2 ambi-spectiv e 9 pro-spectiv e	2+	4184 patients 3151 controls	Medical patients	Antiphospholipid syndrome - lupus anticoagulants and/or anticardiolipin antibodies	Not reported	Risk estimate for DVT in studies of lupus anticoagulants and anticardiolipin antibodies*	Odds ratios varied from 5.91 (any event) to 9.4 (first event) (5 studies) Significant	Thrombosis verified by computerised ultrasonography, venography for DVT, angiography or radionuclide lung scanning for pulmonary embolism Pooled odds ratios for studies were classified by type of event (first event, recurrent or any event, which means no distinction was possible between first and recurrent events) * None of the studies found anticardioplatin to be a significant risk factor for thrombosis
							Risk estimate for DVT in studies of lupus anticoagulants alone	Odds ratios varied from 4.09 (recurrent event) to 16.2 (any event) (4 studies) Significant	
							Risk estimate for DVT in studies of anticardiolipin antibodies (only G istope measured)	Significant association No value given (6 studies) Significant	
							Risk estimate for DVT in studies of IgG and/or IgM anticardiolipin antibodies	4 studies with 8 associations. Only 1 IgG anticardiolipin association significant	

Thrombophilias

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Rocha et al., 2007[556]	Syste-matic review 6 cohort studies 3 case control studies	2+	20665	Unclear (data presented in paper as table only)	Factor VS Leiden (FVL)	Unclear	Relative Risk estimate for medical patients with FVL mutation and VTE.	Relative risk ranges in studies from 2.2-6.6 No confidence intervals (5 studies)	Definition and diagnosis of VTE is not provided.
							Risk estimate for medical patients with FVL mutation and VTE	Odds ratio ranges in studies from 3.2 to 5.8 No confidence intervals (4 studies)	

Thrombophilias

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Rocha et al., 2007[556]	Syste-matic review 4 cohort studies 1 case control study	2+	31871	Unclear (data presented in paper as table only)	Protein C deficiency	Unclear (1 study followed patients for 8.1 years)	Relative Risk estimate for medical patients with protein C deficiency and VTE.	Relative risk ranges in studies from 3.36 to 7.3 No confidence intervals (2 studies)	Definition and diagnosis of VTE is not provided.
							Risk estimate for medical patients with protein C deficiency and VTE	Odds ratio ranges in studies from 1.7 to 12.6 No confidence intervals (3 studies)	

Thrombophilias

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Rocha et al., 2007[556]	Syste-matic review 2 cohort studies 2 case control studies	2+	3048	Unclear (data presented in paper as table only)	Protein S deficiency	Unclear	Relative Risk estimate for medical patients with protein S deficiency and VTE.	Relative risk: 8.5 No confidence intervals (1 study)	Definition and diagnosis of VTE is not provided.
							Risk estimate for medical patients with protein S deficiency and VTE	Odds ratio ranges in studies from 0.7 to 19.9 No confidence intervals (3 studies)	

Thrombophilias

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Rocha et al., 2007[556]	Syste-matic review 1 cohort study 7 case control studies	2+	4475	Unclear (data presented in paper as table only)	Mutation of the pro-thrombin gene	Unclear	Risk estimate for medical patients with mutation of the pro-thrombin gene and VTE	Odds ratio ranges in studies from 2.0 to 11.5 No confidence intervals (3 studies)	Definition and diagnosis of VTE is not provided.

Thrombophilias

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Rocha et al., 2007[556]	Syste-matic review 2 cohort studies 1 case control study	2+	2404	Unclear (data presented in paper as table only)	Anti-thrombin III deficiency	Unclear	Relative Risk estimate for medical patients with anti-thrombin III deficiency and VTE.	Relative risk: 8.1 No confidence intervals (1 study)	Definition and diagnosis of VTE is not provided.
							Risk estimate for medical patients with anti-thrombin III deficiency and VTE	Odds ratio ranges in studies from 2.2 to 21.2 No confidence intervals (3 studies)	

Evidence Table 7: Patient Risk Factors – varicose veins

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Edmonds et al., 2004[169]	Syste-matic review 7 cohort studies	2+	4804	Patients undergoing general, gynaecological, thoracic, orthopaedic, neurological or urologic surgery. Other inclusion criteria: 1 study - adults 2 studies - >40 yrs 1 study - 40 -80 yrs 3 studies – no other specific patient group	Varicose veins	Varied 6 to 8 postoperative days or for duration of hospital-isation	Risk estimate for postoperative DVT	Relative risk: 2.39 CI: 1.69 to 3.37 (6 studies. (1 study had no data)	Diagnosis of DVT: 5 studies fibrinogen uptake test 1 study bilateral ascending venography 1 study Doppler ultrasound and clinical diagnosis.

Varicose veins

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Rocha et al., 2007[556]	Syste-matic review 4 cohort studies 4 case control studies	2+	Unclear	Medical patient and general population	Varicose veins Venous Insufficiency Peripheral arterial disease	Unclear	Risk estimate for VTE in medical patients with varicose veins according to age	Odds ratio: Age 45: 4.2 Age 60: 1.9 Age 75: 0.9 No confidence intervals (1 study)	Definition and diagnosis of VTE is not provided. One study showed that after adjusting for counfounders such as hosptialisation, trauma, cancer and chemotherapy, chronic heart failure, stroke, central venous catheter the risk associated with varices became zero.
							Risk estimate for VTE in medical patients with varicose veins	Odds ratio: ≥2.5 No confidence intervals Significant (4 studies) No association (2 studies)	
							Risk estimate for VTE in medical patients with venous insufficiency	Odds ratio: ≥1.7 No confidence intervals Significant (4 studies)	
							Risk estimate for VTE in ambulatory patients with clinical suspicion of DVT or PE and peripheral arterial disease	Odds ratio: 1.9 No confidence intervals (1 study)	

Evidence Table 8: Patient Risk Factors – cardiovascular factors

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Edmonds et al., 2004[169]	Syste-matic review 1 cohort study	2+	411	Patients undergoing major gynaecological surgery	Recent myocardial infarction	Until discharge	Risk estimate for postoperative DVT	Relative risk: 2.51 p=0.10 (1 study)	Diagnosis of DVT by fibrinogen uptake test
Edmonds et al., 2004[169]	Syste-matic review 2 cohort studies	2+	3288	Patients undergoing general, gynaecological, thoracic, orthopaedic, neurological or urologic surgery. Other inclusion criteria: 1 study - adults 1 study - no specific patient group.	Hypertension	Up to 14 days or until discharge	Risk of postoperative DVT	Not significant, no data given (1 study)	Diagnosis of DVT: 1 study fibrinogen uptake test 1 study Doppler ultrasound and clinical diagnosis.
							Risk estimate for postoperative DVT	Relative risk: 1.30 p=0.22 (1 study)	

Cardiovascular factors

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Edmonds et al., 2004[169]	Syste-matic review 2 cohort studies	2+	3288	Patients undergoing general, gynaecological, thoracic, orthopaedic, neurological or urologic surgery. Other inclusion criteria: 1 study - adults 1 study - no specific patient group.	Congestive cardiac failure	Up to 14 days or until discharge	Risk estimate for postoperative DVT	Non-lower limb surgery Relative risk: 1.32 Lower limb surgery Relative risk: 0.42 (1 study, neither relative risk significant)	Diagnosis of DVT: 1 study fibrinogen uptake test 1 study Doppler ultrasound and clinical diagnosis. 1 of the studies showed a significant relationship in a univariate analysis but not in a multivariate analysis, the other study showed no difference. The figures were not provided.
							Risk estimate for postoperative DVT	Relative risk: 1.33 p=0.59 (1 study)	

Cardiovascular factors

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Rocha et al., 2007[556]	Syste-matic review 2 RCTs	2+	181	Medical patients with acute myocardial infarction	Acute myocardial infarction	14-21 days	Incidence of DVT after myocardial infarction with no prophylaxis	Incidence: 62.5% No confidence intervals Significant (1 study)	Diagnosis of DVT by fibrinogen uptake test Diagnosis of PE is not given and it is unclear if only symptomatic events were included.
							Incidence of PE after myocardial infarction with no prophylaxis	Incidence: 2.2% No confidence intervals (1 study)	

Cardiovascular factors

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Rocha et al., 2007[556]	Syste-matic review 3 cohort studies 2 case control studies	2+	Unclear	Medical patients with congestive heart failure	Congestive Heart Failure	Unclear	Risk estimate for VTE in medical patients with CHF	Odds ratio: 2.6 (95% CI: 1.4-4.7) (1 study)	Definition and diagnosis of VTE not provided. 1 of the studies showed a significant relationship in a univariate analysis but not in a multivariate analysis, the other study showed no difference. The figures were not provided. *NYHA = New York Heart Association
							Risk estimate for VTE in medical patients with CHF with different ejection fractions	Odds ratio: Ejection fraction <20%: OR 38.3 Ejection fraction 20-40%: OR 2.8 Ejection fraction >45%: OR 1.7 No confidence intervals (1 study)	
							Risk estimate for fatal PE at autopsy in medical patients with CHF	Odds ratio: 2.8 (95% CI: 1.8-4.2) (1 study)	
							Risk estimate for VTE in ambulatory patients	Odds ratio: 2.9 (95% CI: 1.5-5.6) (1 study)	
							Risk estimate for VTE in patients with CHF treated with anticoagulants for a previous VTE episode	Odds ratio: 2.3 (95% CI: 1.1 – 5.0) (1 study)	
							Risk estimate for VTE in medical patients with CHF by severity of functional compromise	Relative risks: NYHA class III: RR: 0.87 (95% CI 0.6-1.3) NYHA class IV RR: 1.3 (95% CI: 0.74 – 2.34) (1 study)	

Evidence Table 9: Patient Risk Factors – oral contraceptives

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Edmonds et al., 2004[169]	Syste-matic review with 2 case control studies and 5 cohort studies	2+	Not stated for all studies	Patients undergoing general, elective gynaecological, emergency gynaecological, thoracic, orthopaedic, neurological or urologic surgery. Other inclusion criteria: 1 study - adults 1 study – 15-44 yrs 2 studies – /16-40 yrs olds 1 study – 40-80 yrs 3 studies – no other specific patient group	Oral contraceptives Non-users of oral contraceptives	3 days to 3 months or entire postoperati ve hospital-isation	Risk estimate for postoperative DVT	Odds ratio: 2.48 CI: 1.53 to 4.02 (3 studies)	A pooled risk estimate was only possible for three of the studies due to deficiencies in reported data. Diagnosis of DVT: 3 studies fibrinogen uptake test 1 study Doppler ultrasound and clinical diagnosis 2 studies used discharge data for diagnosis of DVT 1 study not specified

Oral contraceptives

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Kemmeren et al., 2001[336]	Syste-matic review 3 cohort studies 9 case-control studies 3 nested case-control studies	2+	1598 cases 3265 controls	Current oral contraceptive users. Data collected from Western countries.	3rd generation oral contraceptives: desogestral gestodene 2nd generation oral contraceptives levonorgestrel	Not reported	Risk estimate for venous thrombosis 3rd vs 2nd generation contraceptives	Unadjusted odds ratio: 1.6 (CI: 1.3 to 1.9) (4 studies) Adjusted odds ratio: 1.7 (CI: 1.4 to 2.0) (3 studies)	Author reports: some studies reported only frequencies, some only unadjusted or adjusted odds ratios. They performed an overall analysis based on the adjusted odds ratios and on the 2x2 tables separately. *Diagnosis confirmed by ultrasound, plethysmography or venography. Not all studies in used an objective test to diagnose venous thrombosis.
							Risk estimate for venous thrombosis desogestrel vs levonorgestrel	Unadjusted odds ratio: 1.9 (CI: 1.5 to 2.3) (6 studies) Adjusted odds ratio: 1.7 (CI: 1.2 to 2.6) (4 studies)	
							Risk estimate for venous thrombosis gestodene vs levonorgestrel	Unadjusted odds ratio: 1.7 (CI: 1.3 to 2.2) (5 studies) Adjusted odds ratio: 1.5 (CI: 1.3 to 2.2) (3 studies)	
							Risk estimate for venous thrombosis 3rd vs 2nd generation (type of progestagen unspecified)l	Unadjusted odds ratio: 1.5 (CI: 1.2 to 1.8) (4 studies) Adjusted odds ratio: 1.4 (CI: 1.1 to 1.9) (3 studies)	

Oral contraceptives

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Rocha et al., 2007[556]	Syste-matic review 2 system atic review s 5 case control studies 1 study unclear	2+	Unclear	Unclear	Oral contraceptives	Unclear	See comments section	See comments section	Results not reported as all studies except 1 were included in Kemmeren et al., 2001[336]. The only study not reported was a systematic review which reached the same conclusion as Kemmeren et al., 2001[336]

Evidence Table 10: Patient Risk Factors – hormone replacement therapy

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Miller et al., 2002[444]	Syste-matic review 12 studies 3 RCTs 1 cohort 8 case-control studies	2+	RCTs: 3919 Cohort studies: 476,008 Case-control studies: 22,137	Post-menopausal women **Excluded**: women with a history of thrombotic events or conditions associated with high risk for thrombosis Women in 1 RCT were healthy Women in 2 RCTs had heart disease Health status not recorded for cohort or case control studies	Hormone replacement therapy Post menopausal oestrogen replacement Oestrogen alone or oestrogen plus progestin RCTs and the cohort study were outpatient studies. The RCTs used a placebo for the control group. 4 case control studies used hospital based controls 4 case control studies used population based controls	Not reported for all studies. RCTs: one not specified, other two 3 or 4 years. Cohort: compared >5 year use with < 5years Case controls: not reported	Risk estimate for venous thromboembolism	Relative risk: 2.14 Cred Int: 1.64 to 2.81 (all studies)	Mehtod of diagnosis for thromboembolism diagnosis varied. Most rigorous venography, ultrasonography or Doppler ultrasonography for DVT, venography or perfusion scan for PE. 3 studies did not state the method of diagnosis. Relative risks and credible intervals (Cred Int) calculated using a bayesian meta-analysis.
							Risk estimate venous thromboembolism	Relative risk: 3.75 Cred Int: 1.23 to 10.26 (3 RCTs)	
							Risk estimate venous thromboembolism	Relative risk: 2.1 Cred Int: 1.2 to 3.8 (1 cohort study)	
							Risk estimate venous thromboembolism	Relative risk: 2.05 Cred Int: 1.40 to 2.95 (8 case control studies)	
							Risk estimate venous thromboembolism first year use vs subsequent years	Relative risk in 1st year of use: 3.49 Cred Int: 2.33 to 5.59 Relative risk after 1 year of use:: 1.91 Cred Int: 1.18 to 3.52 (6 studies)	

Hormone replacement therapy

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Rocha et al., 2007[556]	Syste-matic review 6 studies 3 RCTs 3 case control studies	2+	Unclear	Post-menopausal women	Hormone replacement therapy	Not reported for all studies.	Risk estimate for VTE in group receiving HRT compared with placebo group	Relative risk: 2.1 (95% CI 1.6-2.8) (1 RCT)	Definition and diagnosis of VTE not provided. Only results presented are those not already reported in Miller et al. 2002 [444]
							Risk estimate for VTE with oral administration of HRT (compared to transdermic administration)	Odds ratio: 4.0 (95% CI 1.9 – 8.3) (1 study)	

Hormone replacement therapy

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Royal College of Obstetricians and Gynaecologists, 2004[562]	System atic review includ-ing 9 studies	2+	Not reported	Women on hormone replacement therapy Exact inclusion/exclusion criteria not reported.	Hormone replacement therapy (oestrogen) No description of the control groups	Not reported	Risk estimates reported for each study, no pooled estimate	Relative risks varied from: 1.22 up to 6.9	

Evidence Table 11: Patient Risk Factors – cancer

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Edmonds et al., 2004[169]	Syste-matic review 6 cohort studies 3 RCTs	2+	1867	Patients undergoing general and gynaecological, surgery for malignancy. Other inclusion criteria: 5 studies - >40 yrs 3 studies – no other specific patient group 1 study included 3 groups – a control, oral contraceptive users and cervical cancer patients	Cancer 3 RCTs with 628 participants included prophylaxis: 1 study - heparin and electical calf stimulation 1 study – IPCD calf stimulation 1 study - GCS	Varied 6 to 7 postoperative days or for duration of hospital-isation	Risk estimate for postoperative DVT	Odds ratio: 2.94 CI: 2.01 to 4.29 (9 studies)	Diagnosis of DVTwith fibrinogen uptake test for all the studies.

Cancer

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Rocha et al., 2007[556]	Syste-matic review 2 registry studies 2 cohort studies 1 unknown study design	2+	>9,000,000	Medical patients (unclear if patients had surgery although it is suspected that a certain proportion will have)	Cancer	Unclear	Risk estimate for VTE inpatients with different cancers	* See table below (2 studies)	Definition and diagnosis of VTE not provided.

Origin	Patients with VTE	Total Patients	Relative Risk	95% CI
Head and neck	35	20924	0.29	0.2-0.4
Bladder	180	74517	0.42	0.36-0.49
Breast	469	186273	0.44	0.4-0.48
Esophagus	64	14742	0.76	0.58-0.97
Cervix	53	10236	0.90	0.68-1.18
Liver	121	22938	0.92	0.76-0.11
Prostate	1230	218743	0.98	0.93-1.04
No cancer	46,848	8177634	1.0	
Rectum	417	65837	1.11	1.0-1.22
Lung	1504	232764	1.13	1.07-1.19
Colon	1320	168832	1.36	1.29-1.44
Renal	278	34376	1.41	1.25-1.59
Stomach	280	32655	1.49	1.33-1.68
Lymphoma	537	52042	1.80	1.65-1.96
Pancreas	488	41551	2.05	1.87-2.24
Ovarium	327	26406	2.16	1.93-2.41
Leukaemia	591	47234	2.18	2.01-2.37
Brain	184	13529	2.37	2.04-2.74
Uterus	226	11606	3.34	2.97-3.87

Evidence Table 12: Patient Risk Factors – chemotherapy

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Braithwaite et al., 2003[79]	Syste-matic review 32 RCTs	1+	52, 929	Patients receiving tamoxifen for treatment or prevention of cancer. Mean age: 54.8 years 4 RCTs – risk reduction for breast cancer 25 RCTs – treatment of breast cancer 3 RCTs - treatment of metastatic melanoma	Tamoxifen Compared to no chemotherapy agent Mean length of years receiving tamoxifen: 4.3 years	Varied from 2.8 to 15 years	Risk estimate for DVT	Relative risk: 1.87 CI: 1.33 to 2.66 (15 studies)	Method of diagnosis for DVT not reported.
							Risk estimate for pulmonary embolism	Relative risk: 1.88 CI: 1.17 to 3.01 (11 studies)	

Chemotherapy

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Rocha et al., 2007[556]	Syste-matic review 1 cohort 5 RCTs	2+	3842	Patients receiving chemotherapy with or without tamoxifen for Breast cancer or multiple myeloma 1 cohort	Tamoxifen Chemotherapy Compared to no chemotherapy agent	Unclear	VTE in patients with breast cancer 'on chemotherapy regimen' vs. 'off chemotherapy regimen'	Signficantly increased risk of VTE when patients were 'on chemotherapy therapy' ($p<0.05$). No magnitude of risk provided. (1 cohort)	Definition and diagnosis of VTE not provided.
							VTE in patients with breast cancer with either 'on therapy' or 'off therapy'	Significantly increased risk of VTE whilst 'on therapy' vs. 'off therapy' (2 studies).	
							VTE in pateints with breast cancer receiving chemotherapy with tamoxifen or chemotherapy without tamoxifen	No significant difference between the two regimens when 'on therapy' (1 study) <u>Pre-menopausal</u> 2.8% (with tamoxifen) vs 0.8% (without tamoxifen) ($p=0.03$) <u>Post-menopausal</u> 8.0% (with tamoxifen) vs 0.4% (without tamoxifen) ($p<0.001$) (1 study)	
							VTE in pateints with breast cancer receiving tamoxifen or tamoxifen with	<u>Post menopausal</u> 2.6% (tamoxifen alone) vs 13.6% (tamoxifen and chemotherapy)	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
							chemotherapy	(p<0.001) (1 study)	
							DVT in multiple myeloma patients either with 'chemotherapy plus thalidomide' vs 'chemotherapy without thalidomide'	28% (chemotherapy with thalidomide) vs 4% (chemotherapy without thalidomide) (p=0.02) (1 study)	

Evidence Table 13: Patient Risk Factors – prolonged travel

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Aryal and Al-khaffaf, 2006[24]	Systematic review 2 cohort studies 4 prospective case-control studies 3 incidence studies	2+	Cohort studies: 2497 Case control studies: 3084 Incidence studies: 182.87 million	Air passengers	Air travel or long distance travel	Not reported	Risk estimate for VTE for air travel	Odds ratio: 1.59 CI: 1.04 to 2.43 (3 case-control studies)	Not all studies stated method of diagnosis
							Risk estimate for VTE for air travel	Relative risk: 2.93 CI: 1.58 to 5.58 (2 cohort studies)	
							Risk estimate for VTE for any long distance travel	Odds ratio: 2.6 CI: 1.79 to 3.79 (2 case-control studies)	
							Incidence of symptomatic pulmonary embolism after long haul flights	varied from 0.41 per million to 2.57 per million (3 incidence studies)	

Evidence Table 14: Patient Risk Factors – Admission to ICU

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Rocha et al., 2007[556]	Syste-matic review 3 RCTs 1 cohort study 1 inci-dence study	2+	RCTs = 534 Cohort = 102 Incidencestudy = 100	Critical care patients	Admission to the critical care unit	Not reported	Incidence of DVT in the absence of prophylaxis	DVT by fibrinogen uptake test = 29% (1 study) DVT by contrast venography = 26% (1 study) DVT by ultrasound = 33% (1 study) DVT (no diagnosis gven) = 28% (1 study)	One study indicated that patients had an average of 4.4 risk factors for VTE The Rocha systematic review indicates that admission to ICU was a risk factor for VTE with a relative risk of 1.8-2.9 although it is unclear from the included studies where this figure came from.
							Incidence of DVT in the presence of prophylaxis	DVT by ultrasound = 12%	

Evidence Table 15: Patient Risk Factors – Active rheumatologic Diseases

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Rocha et al., 2007[556]	Syste-matic review 8 studies 6 cohorts 2 case control	2+	Unclear	Unclear if patients are hospitalised	Systemic lupus erythematosus (SLE) (n=2089) (2 cohorts, 1 case control study) Acute rheumatologic diseases (n=1102) (1 cohort) Lupus anticoagulant (n=173) (1 cohort) Bechets disease (n=85) (1 cohort study) Irritable bowel disease Crohn's disease (n=2857) Ulcerative colitis (n=2672) (1 cohort study) Irritable bowel syndrome (n = 613) Rheumatoid arthritis (n=486) (1 case control)	Unclear	Risk estimate for VTE in patients with SLE	Odds ratio: 4.3 (95%CI: 3.1-5.5) (1 study) Odds ratio 0.6 to 1.7 No 95% CI given but not significant (2 studies)	Definition and diagnosis of VTE not provided. No diagnosis method for DVT and PE are reported.
							Risk estimate for VTE in patients with acute rheumatologic diseases	Relative risk: 1.6 (95% CI: 0.96 – 2.69) p = 0.11 (1 study)	
							Risk estimate for VTE inpatients with SLE with lupus anticoagulant	Odds ratio: 6.4 (95% CI: 2.7-15.4) (1 study)	
							Risk estimate for VTE in patients with bechets disease and HLA-B52 positive	Odds ratio: 4.2 (95% CI: 1.1-16.3) (1 study)	
							Risk estimate for VTE in patients with bechets disease and HLA-B35 positive	Odds ratio: 0.2 (95% CI: 0.004-0.92) (1 study)	
							Risk estimate for DVT in patients with crohn's disease	Relative risk: 4.7 (95% CI: 3.5-6.3) (1 study)	
							Risk estimate for PE in patients with crohn's disease	Relative risk: 2.9 (95% 1.8 - 4.7) (1 study)	
							Risk estimate for DVT in ulcerative	Relative risk: 2.8 (95% CI: 2.1 – 3.7)	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
							colitis	(1 study)	
							Risk estimate for PE in ulcerative colitis	Relative risk: 3.6 (95% CI: 2.5 – 5.2) (1 study)	
							Risk estimate for VTE in irritable bowel disease	Odds ratio: 3.6 (95% CI: 1.7-7.8) (1 study)	
							Risk estimate for VTE in rheumatoid arthritis	Odds ratio: 0.7 (95% CI: 0.2 – 2.9) Not significant (1study)	

Evidence Table 16: Patient Risk Factors – Stroke

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Rocha et al., 2007[556]	Syste-matic review 1 RCT 1 cohort study	2+	RCTs = unclear Cohort = 17552	Hospitalised patients with acute stroke	Ischaemic or haemorrhagic stroke	Not reported	Incidence of DVT in the absence of prophylaxis	DVT by fibrinogen uptake test= 75% (No confidence intervals) (1 study)	Definition and diagnosis of VTE not provided. No diagnosis method for DVT and PE are reported.
							Risk estimate for VTE in haemorrhagic stroke compared with ischaemic stroke	Odd ratio: 2.6 (95% CI: 1.5-4.6) (1 study)	

Evidence Table 17: Patient Risk Factors – Infections

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Rocha et al., 2007[556]	Syste-matic review 1 case control 2 cohorts 1 registr y	2+	Cohorts = 1203 Case control = 1272 Registry = 5451	Ambulant and hospitalised patients	Infections including pneumonia or cardiac diseases	Not reported	Risk estimate for ambulatory patients with infection (site not recorded)	Odds ratio: 1.95 (95% CI: 1.31-2.92) (1 study)	Definition and diagnosis of VTE not provided. .
							Incidence of DVT (detected by fibrinogen uptake test) in patients with various infections	Pneumonia: 4/22 (18.2%) No patients with the following infections developed DVT: urinary tract infection, bronchitis, acute entercolitis or sepsis. (1 study)	
							Incidence of infections as a comorbidity in patients with DVT (detected by ultrasound)	Infection as comorbidity identified in 22% of patients with DVT (pneumonia in 7%, sepsis in 5%, other infections in 10%) (1 study)	
							Risk estimate for DVT in patients with acute infection (compared with patients with no infection)	Relative risk: 1.47 (95% CI: 1.47-2.14) (1 study)	

Evidence Table 18: Patient Risk Factors – Nephrotic Syndrome

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Rocha et al., 2007[556]	Syste-matic review 2 unclear	2+	Unclear	Patients in hospital	Nephrotic syndrome	Not reported	Incidence of PE and DVT in patients with nephritic syndrome	11% (no confidence intervals are provided) (1 study)	Definition and diagnosis of VTE not provided. No diagnosis method for DVT and PE are reported.
							Incidence of PE in patients with nephritic syndrome	14% (95% CI: 9-21%) (1 study)	

Evidence Table 19: Patient Risk Factors – Paresis/Paralysis of lower extremities

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Rocha et al., 2007[556]	Syste-matic review 1 cohort 2 case control	2+	N = 1213	Medical patients admitted to hospital	Acute hemiplegia	Unclear	Incidence of VTE in patients who developed acute hemiplegia	26% (no 95% CI given) (1 study)	Definition and diagnosis of VTE not provided.
							Risk estimate for VTE in hospitalised medical patients with paralysis (compared to without paralysis)	Odds ratio: 12.5 (95%CI: 1.5-104.5) (1 study)	
							Risk estimate for VTE in patients older than 65 years with paralysis (compared to no paralysis)	Odds ratio: 2.1 (95% CI: 1.0 – 4.1)	

Evidence Table 20: Patient Risk Factors – Pregnancy and Post partum

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Rocha et al., 2007[556]	Syste-matic review 1 registr y study	2+	N = 24,000	Patients identified from hospital records.	Pregnancy and post partum (no definition)	Unclear	Incidence of VTE in pregnancy and post partum	103:100,000 (95% CI: 55-177)	Definition and diagnosis of VTE not provided.

Evidence Table 21: Patient Risk Factors – Reduced Mobility

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Rocha et al., 2007[556]	Syste-matic review 1 cohort 3 case controls	2+	N = 35222	Medical patients admitted to hospital	Reduced mobility	Unclear	Risk estimate for VTE in patients standing for more than 6 hours	Odds Ratio: 1.9 (95% CI: 1.1-3.1) (1 study)	Definition and diagnosis of VTE not provided. One study (results not reported) of 1000 patients with suspected DVT identified a significant correlation between loss of mobility for more than 3 days and development of DVT (identified by Doppler ultrasound). Systematic review concludes that reduced mobility should be defined as staying in bed or char for more than half of the day (excluding sleep time)
							Risk estimate for VTE in patients resting in bed or chair	Odds ratio: 5.6 (95% CI: 2.3-13.7) (1 study)	
							Risk estimate for VTE in patients who are hospitalised or admitted to a long-term care facility	Odds ratio: 8.0 (95% CI: 4.5-14.2) (1 study)	
							Risk estimate for VTE in hospitalised patients older than 65 with reduced mobility (compared with no reduce mobility)	Odds ratio 1.73 to 5.64 (no confidence intervals given) (1 study) Risk was higher in patients with more severe limitation of mobility.	

Evidence Table 22: Patient Risk Factors – Respiratory Diseases

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Exposure	Length of follow up/ exposure	Outcome measures	Effect size	Comments
Rocha et al., 2007[556]	Syste-matic review 6 cohorts	2+	Unclear in one study N=2451	Patients admitted to hospital	Chronic Obstructive Pulmonary Disease (COPD) Or Chronic respiratory disease	Unclear	Incidence of COPD in patients with DVT	18% (no confidence intervals given) (1 study)	Definition and diagnosis of VTE not provided.
							Incidence of COPD in patients with PE	34% (no confidence intervals given) (1 study)	
							Incidence of DVT (fibrinogen uptake test) in patients admitted to hospital with decompensated COPD	9% (no confidence intervals given) (1 study)	
							Incidence of DVT (Doppler ultrasound) in patients admitted to hospital with acute COPD	11% (no confidence intervals given) (2 studies)	
							Incidence of PE (lung perfusion scan) in patients admitted to hospital with non-infective exacerbations of COPD	29% (no confidence intervals given) (2 studies)	
							Risk estimate for recurrence of VT in patients with chronic respiratory disease	Odds ratio 1.91 (95% CI: 0.85-4.26)	
							Risk estimate for VTE in patients with chronic respiratory diseases	Odds ratio: 0.6 (95% CI: 0.38 – 0.92) (1 study)	

Effectiveness - Prophylaxis vs no prophylaxis

Evidence Table 23: GCS vs no prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Amaragiri and Lees, 2000[15] 7 RCTs included: [13,284,290,593,643,644,649] All of these studies were included in the guideline review.	Systematic Review	1+	**Total:** 16 studies, 7 with 1027 participants **Intervention:** GCS alone n = 536 **Control:** no stockings n = 491	General surgery, orthopaedics, neurosurgery and obstetrics and gynaecology. **Age:** > 16 years	Graduated compression stockings(GCS) (thigh-length 4 studies, length not stated 2 studies, thigh and knee-length 1 study) **Timing:** start time varied from day of admission to same day as surgery, end time varied from 4 to 5 days to 9 days postoperatively to day of discharge.	No prophylaxis **Additional non-comparative prophylaxis:** Not reported	Not stated	**DVT** Confirmed by: venogram, US, isotope studies	**Int:** 81/536 **Control:** 144/491 **p value:** <0.00001 (Significant)	**Not reported:** PEs, type of DVT, side effects, QoL and LoS.

GCS vs no prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
CLOTS2009 [158] **Country of study:** Multicentre study of 64 centres in 3 countries **Study design:** RCT **List who was masked to interventions:** Investigator completing DVT scans. Positive scans obtained for central verification. **Evidence level:** 1+ **Duration of follow-up:** 30 days	**Patient group:** Acute Stroke patients 2145/2518 (85%) had ischaemic stroke, 232/2518 (9%) had haemorrhagic stroke, 141/2518 (6%) had an uncertain or non-stroke diagnosis. **Setting:** Hospital admission **Inclusion criteria:** Patients admitted within 1 week of acute stroke and who were immobile (defined as being unable to walk independently to the toilet). **Exclusion criteria:** Patients with peripheral vascular disease, and those with diabetic sensory neuropathy, when the responsible clinician or nurse judged that GCS might cause skin damage. Patients with subarachnoid haemorrhage. **<u>All patients</u>** **N:** 2518 **Age (mean):** 76 (range: 68-83) **M/F:** 1242: 1276 **Additional risk factors:** **Gp1** **Gp 2** Previous DVT or PE 55 56 Diabetes 191 165 Peripheral vascular disease 36 26 Overweight 320 343 Cigarette Smoker 235 235 Able to lift both legs off bed	**Group 1** Thigh length graduated Compression Stockings (GCS) (Tyco Healthcare [Covidien]) – no compression profile given. Start time: as soon as possible after randomisation. Worn day and night End time: independently mobile around the ward, discharged, patient refused to wear them or the staff became concerned about the patient's skin. **Group 2** Routine care plus avoidance of GCS. **Additional non-comparative prophylaxis:** No information about thus use of aspirin provided. 381/1256 (30.3%) patients received post randomisation anticoagulants (warfarin, heparin or LMWH) in the	**All cause mortality** **Symptomatic pulmonary embolism** (confirmed by: imaging or autopsy) **Symptomatic DVT** (confirmed by: screening compression Doppler ultrasound) **DVT, asymptomatic or symptomatic** (screened for by: compression Doppler ultrasound at 7-10 days and then again at 25-30 days) **Thigh DVT**(screened for by: compression Doppler ultrasound at 7-10 days and then again at 25-30 days) **Medical complications of GCS** (skin breaks/ulcers/blisters/skin necrosis) **Lower limb Ischaemia / amputation**	**Group1:** 122/1256 **Group 2:** 110/1262 **P value:** 0.409** **Group1:** 13/1256 **Group 2:** 20/1262 **P value:** 0.293** **Group1:** 55/1256 **Group 2:** 61/1262 **P value:** 0.635** **Group1:** 205/1256 **Group 2:** 224/1262 **P value:** 0.341** **Group1:** 90/1256 **Group 2:** 90/1262 **P value:** Not significant **Group1:** 64/1256 **Group 2:** 16/1262 **P value:** <0.001* **Group1:** 7/1249 **Group 2:** 2/1262 **P value:** 0.108*	**Funding:** Medical research council (UK), Chief Scientist office of Scottish Government, Chest Heart and Stroke Scotland, Tyco Healthcare, UK Stroke Research Network **Limitations:** No information about the use of aspirin although it would be expected that most patients would have received this. Significantly more participants received post randomisation anticoagulants (when all forms combined) in the no stockings group compared with the stockings group (34.3 vs. 30.3%, chi squared = 4.729; p = 0.03). Stockings were removed in order to blind the investigator completing the ultrasound scan but no mention of how long before the scan this was completed and so it may have been unblended and a cause for bias. Other outcomes, such as adverse events were not blinded. Only positive scans were obtained for central verification. Screening was planned at between 7-10 days and 25-30 days but it is not clear whether the 7-10 day diagnosis was used in the final results if no further screening was completed. Diagnosis of PE was 'confirmed

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	542 550 Prescribed heparin, warfarin or alteplase at baseline 98 109 **Group 1** **No. randomised:** 1256 **No. of dropouts:** 39 (3.1%) were not compliant with allocation* **Group 2** **No. randomised:** 1262 **No. of dropouts:** 70 (5.5%) were not compliant with allocation*	stocking group compared with 434/1262 (34.3%) in the no stockings group.			on imaging or autopsy' which is not clear. Intention to treat analysis has been completed, but it is unclear about the number of patients screened for in the DVT outcomes in the results. **Outcomes not reported:** Asymptomatic PE, Asymptomatic calf DVT, any bleeding results, heparin induced thrombocytopenia, post thrombotic syndrome, pulmonary hypertension, quality of life, length of stay. **Additional outcomes reported:** One fatal PE was identified in both group but it is unclear whether all those who died had an autopsy. Adverse events related to the use of stockings (see effect size column for results). Compliance was reported as a secondary outcome but no mention was made, despite a statistical difference being identified. **Notes:** * Compliance with allocation is not clearly defined within the paper. ** Calculated by the NCC using fishers exact test.

GCS vs no prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Roderick et al., 2005[557] Two RCTs included [561,599] 1 of these studies was included in the guideline review[599]	Systematic Review	1+	**Total:** 302 Int: 151 Control: 151	**Type of surgery:** General surgery	**Intervention :** **Type:** Graduated compression stockings (GCS) (knee-length 1 study; thigh-length 1 study) **Timing:** started preoperatively and continued until mobile or discharged	**Type:** no prophylaxis	14 days in one study, not stated in other	**DVT** Confirmed by fibrinogen uptake test	**Int1:** 13/151 **Cont** 25/151 **p value:** 0.03	**Not reported:** PE, LoS, QoL, or PTS. Event rates reported here are for all studies as published in the systematic review
								Proximal DVT:	**Int1:** 0/25 **Control:** 0/25 **p value:** 1.0	

Evidence Table 24: IPCD or FID devices vs no prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Prasad et al., 1982[538] **Country of study:** UK **Study design:** RCT **List who was masked to interventions:** None mentioned **Evidence level:** 1+ **Duration of follow-up:** 10 days	**Patient group:** Stroke **Setting:** Geriatric ward **Inclusion criteria:** • All patients admitted for acute stroke within 72 hours • Anyone with weakness up to 2/6 motor power (MRC grade) in one or both limbs on either side **Exclusion criteria:** • Patients in a coma or with another clinically unacceptable condition **<u>All patients</u>** **N:** 26 **Age (mean):** NR Age group 1 = 78 ± 4 Age group 2 = 80 ± 6 **M/F:** 12/14 **Additional risk factors:** NR **<u>Group 1</u>** **No. randomised:** 13 **No. of dropouts:** 2 patients died but data from autopsy were included **<u>Group 2</u>** **No. randomised:** 13 **No. of dropouts:** 0	**Group 1** Intermittent pneumatic calf compression with Flowtron legging at 40 mmHg to both lesg, each cycle lasts 4 mins. Treatment continuous for 24 hours then for periods of 3 hours, 3/day for next 9 days. **Duration:** 10 days **Group 2** No intervention **Additional non-comparative prophylaxis:** Not Applicable	**DVT, asymptomatic or symptomatic** (screened for by daily FUT scanning)	**Group1:** 6/13 **Group 2:** 6/13 **P value:** NR	**Funding:** Not reported **Limitations:** • Randomisation method not explained • Allocation concealment not mentioned • Blinding of investigators not mentioned **Outcomes not reported:** All cause mortality Fatal PE Symptomatic PE Symptomatic or asymptomatic PE Symptomatic DVT Thigh DVT, Calf DVT Fatal bleeding, Major bleeding, Neurological bleeding, Upper GI bleeding, Minor bleeding HIT, Post thrombotic syndrome, Pulmonary hypertension Quality of life, Length of Stay

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Roderick et al., 2005[557] 18 RCTs [27,65,89,90,112,114,117,119,185,207,279,291,296,353,607,646,647,683] All of these studies were included in the guideline review.	Systematic Review	1+	**Total:** 2181 Some studies do not report numbers randomised for each arm.	**Type of surgery:** Gynaecology: 2 studies Orthopaedic: 5 studies General: 4 studies Neurosurgery: 5 studies Urology: 1 study	IPCD **Timing:** Start time varied from pre-op to time of anaesthesia to post-op. End time varied from 17-24 hours to 17 days postop or until ambulation or discharge.	Noprophylaxis **Additional non-comparative prophylaxis:** Not reported	Not stated	**DVT** confirmed by Doppler US, FUT or impedence phlethysomograph	**Int:** 112/989 **Cont:** 263/1001 **p value:** 0.0000	**Not reported:** QoL, major bleeds, LoS, PTS.
								PE by angiography, PE's identified at post-mortem and no systematic assessment of PE (post-mortem only)	**Int:** 14/564 **Cont:** 18/579 **p value:** 0.5924	
								Proximal DVT	**Int:** 45/663 **Cont:** 85/678 **p value:** 0.0013	

IPCD or FID vs no prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Roderick et al., 2005[557] 2 RCTs included [594,697] All of these studies were included in the guideline review	Systematic Review	1+	2 studies **Total:** 126 **Int:** 61 **Cont:** 65	**Type of surgery:** General:: 1 study Orthopaedic: 1 study **Timing:** One study was periop. The other study was postop to day 9-10.	Foot pump **Additional non-comparative prophylaxis:** Not reported	Nil **Additional non-comparative prophylaxis:** Not reported	One study on day 9 or 10 post op. Other study on day 1,2,3,5,7 postop.	**DVT** confirmed by venography or FUT	**Int:** 11/61 **Cont:** 34/65 **p value:** 0.0001	**Not reported:** LoS, QoL, PTS, and major bleeds.
								PE confirmed by scan	**Int:** 0/28 **Cont:** 0/32 (reported in 1 study) **p value:** N/A	
								Proximal DVT	**Int:** 0/28 **Cont:** 6/32 (1 study reported) **p value:** 0.0345	

IPCD or FID vs no prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Turpie et al., 1977[647] **Country of study:** CANADA **Study design:** RCT **List who was masked to interventions:** None - unblinded **Evidence level:** 1+ **Duration of follow-up:** 14 days	**Patient group:** Intracranial disease including brain tumour, Subarachnoid haemorrhage (SAH), Subdural haemorrhage or head injury **Setting:** Regional Centre for Clinical Neurosciences **Inclusion criteria:** Admission to Clinical Neurosciences centre **Exclusion criteria:** • History of previous VTE within 12 mths • Iodine allergy • Peripheral arterial disease **<u>All patients</u>** **N:** 161 (128 analysed0 **Age (mean):** Group 1: 51 (range 18-31) Group 2: 48 (range 19-80) **M/F:** 64/64 **Additional risk factors:** NR **<u>Group 1</u>** **No. randomised:** 82 (65 analysed) **No. of dropouts:** 17 (21%) **Brain tumour:** 25 **SAH:** 28 **Subdural Haemorrhage/Head injury:** 12 **Craniotomy:** 53 **Non-operated:** 12 **<u>Group 2</u>** **No. randomised:** 79 (63 analysed) **No. of dropouts:** 16 (20%) **Brain tumour:** 27 **SAH:** 20 **Subdural Haemorrhage/Head injury:** 16 **Craniotomy:** 49 **Non-operated:** 14	**Group 1** IPCD Inflatable knee-length plastic boots (Lyne-Nicholson, Inc.) Inflated to 40 mmHg for 12 sec per minute. Start time: Immediately postoperatively or as soon as possible after admission in non-operated group Duration: 5 days **Group 2** No intervention other than routine physiotherapy **Additional non-comparative prophylaxis:** Not applicable	**All cause mortality** (confirmed by:)	**Group1:** 9/82 **Group 2:** 7/79 **P value:** NR	**Funding:** Lyne-Nicholson, Inc. Manufacturers of IPCD device **Limitations:** Includes an overall craniotomy rate of 80% though procedure was evenly distributed between groups. Quite large dropout due to failed imaging. **Outcomes not reported:** Fatal, symptomatic or asymptomatic PE; symptomatic DVT; fatal, major, neurological, upper GI or minor bleeding; HIT; post thrombotic syndrome; pulmonary hypertension; quality of life; length of stay **Additional outcomes reported:** After prophylaxis discontinued non-ambulatory patients scanned for further 9 days. DVT incidence was Group1: 7 Group 2: 3 **Notes:**
			DVT, asymptomatic or symptomatic (confirmed by: FUT leg scan) at 5 days	**Group1:** 1/65 **Group 2:** 12/63 **P value:** 0.00082	
			Thigh DVT (confirmed by: FUT leg scan) at 5 days	**Group1:** 0/65 **Group 2:** 2/63 **P value:** NR	
			Calf DVT (confirmed by: FUT leg scan) at 5 days	**Group1:** 1/65 **Group 2:** 10/63 **P value:** NR P = 0.042 *2-sided Fisher's exact test calculated by NCC-AC using ITT original numbers randomised*	

IPCD or FID vs no prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Turpie et al., 1979[646] **Country of study:** CANADA **Study design:** RCT **List who was masked to interventions:** None - unblinded **Evidence level:** 1+ **Duration of follow-up:** 3-4 months	**Patient group:** Intracranial disease including brain tumour, Subarachnoid haemorrhage (SAH), head or spinal injury and stroke **Setting:** Regional Centre for Clinical Neurosciences **Inclusion criteria:** • Admission to Clinical Neurosciences centre • ≥ 16 years old **Exclusion criteria:** • History of previous VTE within 12 mths • Iodine allergy • Peripheral arterial disease • Multiple trauma • Likely to be discharged after 24 hours **<u>All patients</u>** **N:** 218 (199 analysed) **Age (mean):** Group 1: 52.2 (range 16-90) Group 2: 48.7 (range 16-83) **M/F:** 119/80 **Additional risk factors:** NR **<u>Group 1</u>** **No. randomised:** 112 (103 analysed) **No. of dropouts:** 9 (8%) **Brain tumour:** 25 **SAH:** 27 **Head or spinal injury:** 30 **Stroke:** 21 **Craniotomy:** 65 **Non-operated:** 38 **<u>Group 2</u>** **No. randomised:** 106 (96 analysed) **No. of dropouts:** 10 (9%) **Brain tumour:** 26 **SAH:** 27 **Head or spinal injury:** 24 **Stroke:** 19	**Group 1** IPCD Inflatable knee-length plastic cuffs with 4 compression compartments inflated sequentially from ankle to knee (Gaymar Industries, Inc) Inflated to 50 mmHg with 5 second inflation time for each compartment and whole compartment inflated for further 5 seconds then rapidly deflated. Relaxation phase for 60 seconds. Start time: Immediately postoperatively or as soon as possible after admission in non-operated group Duration: **14 days** or until fully ambulant or discharged. **Group 2** No intervention other than routine physiotherapy **Additional non-comparative prophylaxis:** Not applicable	**Fatal pulmonary embolism** at 14 days (confirmed by autopsy:)	**Group1:** 0/103 **Group 2:** 1/96 **P value:**	**Funding:** Gaymar Industries, Inc manufacturers of IPCD device **Limitations:** Includes an overall craniotomy rate of 65% though procedure was evenly distributed between groups **Outcomes not reported:** All cause mortality (only overall figures reported: 52/190 died at 3.8 months), Symptomatic PE, Symptomatic or asymptomatic PE, Symptomatic DVT, Calf DVT, Thigh DVT, Fatal bleeding, major bleeding, neurological bleeding, upper GI bleeding, minor bleeding, HIT, post thrombotic syndrome, pulmonary hypertension, Quality of Life, Length of stay **Additional outcomes reported:** **Notes:**
			DVT, asymptomatic or symptomatic at 14 days (screened for by: positive FUT leg scan or abnormal Impedance Plethysmography) Where possible confirmation by venography	**Group1:** 8/103 **Group 2:** 20/96 **P value:** 0.01	
			Proximal DVT, asymptomatic or symptomatic at 14 days (screened for by: positive FUT leg scan or abnormal Impedance Plethysmography) Where possible confirmation by venography	**Group1:** 3/103 **Group 2:** 8/96 **P value:**	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Craniotomy: 64 **Non-operated:** 32				

Evidence Table 25: Fondaparinux vs no prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Cohen et al., 2006[121] **Country of study:** 35 centres in 8 contries **Study design:** RCT **List who was masked to interventions:** Patient, clinician, outcome adjudicators **Evidence level:** 1+ **Duration of follow-up:** Asymptomatic events: 15 days Symptomatic events: 1 month	**Patient group:** Older acute medical patients Congestive heart failure (212/849) Acute respiratory distress (167/849) Acute infectious or inflammatory disease (214/849) **Setting:** Not stated **Inclusion criteria:** Patients aged ≥60 years and expected to remain in bed for at least 4 days and with acute illness: Congestive heart failure class III/IV, acute respiratory illness in the presence of chronic lung disease or clinically diagnosed acute infections or inflammatory disorders such as arthritis, connective tissue diseases, or inflammatory bowel disease. **Exclusion criteria:** High risk for bleeding, acute bacterial endocarditis, cerebral metastasis, recent haemorrhagic or ischaemic stroke, brain, spinal or ophthalmological surgery, an indwelling intrathecal or epidural catheter, a serum creatinine level >180 µmol/l in a well hydrated patient, documented hypersensitivity to contras media, anticipated intubation for more than 24 hours, use of antithrombotics within 48 hours before randomisation, an indication for anticoagulant prophylaxis or therapy, or life expectancy of less than one month. **<u>All patients</u>** **N:** 849 **M/F:** 360/489 **Additional risk factors:** <u>Gp1</u> <u>Gp2</u> Age ≥ 75 233 216	**Group 1** Fondaparinux (Atrixa) Start time: within 48 hours of admission End time: 1-13 days (median 7 days) 2.5mg in 0.5ml saline subcutaneously once per day. **Group 2** Placebo Start time: with 48 hours of admission End time: 1-15 days (median 7 days) 0.5 ml isotonic saline subcutaneously once per day. **Additional non-comparative prophylaxis:** Aspirin and NSAIDs discouraged. Graduated compression stockings and physiotherapy were allowed (no information re: how many used this)	**All cause mortality** Follow up: 1 month **Fatal pulmonary embolism** (confirmed by: autopsy or no other explainable reason) Follow up: 1 month **Symptomatic pulmonary embolism** (confirmed by: high probability lung scan, pulmonary angiography or helical computed tomography) Follow up: 1 month **Symptomatic DVT** (confirmed by: bilateral venography) Follow up: 1 month **DVT, asymptomatic or symptomatic** (confirmed by venography) Follow up: 15 days **Thigh DVT** (confirmed by: bilateral venography) Follow up: 15 days **Calf DVT** (confirmed by: bilateral venography) Follow up: 15 days **Fatal bleeding** Follow up: 1 month **Major bleeding** (description: bleeding in a critical location, bleeding leading to surgical intervention, overt bleeding associated with a drop in haemoglobin concentration of ≥20 g/l or leading to transfusion of 2 or more units of red blood cells.)	**Group1:** 14/425 **Group 2:** 25/414 **P value:** 0.071* **Group1:** 3/425 **Group 2:** 7/414 **P value:** 0.218* **Group1:** 4/425 **Group 2:** 11/414 **P value**0.212* (Includes fatal PE) **Group1:** 0/429 **Group 2:** 0/420 **P value:** NS **Group1:** 18/321 **Group 2:** 29/323 **P value:** 0.129* **Group1:** 5/321 **Group 2:** 7/323 **P value:** 0.772* **Group1:** 13/321 **Group 2:** 22/323 **P value:** 0.164* **Group1:** 2/425 **Group 2:** 1/414 **P value:** 1.00* **Group1:** 1/425 **Group 2:** 1/414 **P value:** 1.00*	**Funding:** Sanofi-Synthelabo and NV Organon sponsored the study and carried out on-site monitoring of all participants. The sponsors had an opportunity to comment on the manuscripts before submission. Fondaparinux is manufactured by GlaxoSmithKline **Limitations:** Diagnosis for fatal PE includes where death was sudden and where no other explainable reason was found. Relatively high number of patients for whom the primary outcome could not be evaluated (195/849) due to either no venography completed or venogram not evaluable. **Outcomes not reported:** LoS, QoL, pulmonary hypertension, post thrombotic syndrome, HIT, Neurological bleeding, upper GI bleeding. **Additional outcomes**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	History of VTE 18 21 Cancer 62 69 **<u>Group 1</u>** **No. randomised:** 429 **No. of dropouts:** 108 **Mean Age (SD):** 75.0 (8.3) **<u>Group 2</u>** **No. randomised:** 420 **No. of dropouts:** 97 **Mean Age (SD):** 74.4 (8.3)		Follow up: 15 days **Minor bleeding** (description: Clinically relevant overt bleeding not meeting the criteria for major bleeding.) Follow up: 15 days	**Group1:** 11/424 **Group 2:** 4/414 **P value:** 0.116*	**reported:** None **Notes:** Many of the authors participators, consultants or both for NV Organon and Sanofi-Synthelabo 2 authors were employees of Organon. Outcomes reported from the number analysed not number randomised. * p values calculated by NCC-AC using Fisher Exact test

Evidence Table 26: LMWH vs no prophylaxis and LMWH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Dahan et al., 1986[141] **Country of study:** France **Study design:** RCT **List who was masked to interventions:** patients **Evidence level:** 1+ **Duration of follow-up:** 10 days	**Patient group:** Elderly medical patients (conditions: heart failure 49, respiratory diseases 57, ischemic stroke 46, malignant diseases 35, diabetes 12, depression 10, syncope 13, infection 11, neurologic diseases 7, joint diseases 7, hepatic or biliary diseases 4, miscellaneous 8). **Setting:** hospital **Inclusion criteria:** • age >65 **Exclusion criteria:** • surgical patients • ongoing anticoagulant/platelet inhibitor therapy • need for full anticoagulation • presence of active bleeding • presence of coagulation disorder • predictable short-term hospitalisation (<7 days) **All patients** **N:** 270 **No. of dropouts:** 7 **Risk Factors:** **Gp1** **Gp2** Obseity (>10% ideal weight for age, sex and height) 13 12 Arrhythmia 23 29 Varicose veins 30 34 Previous history of VTE 6 6 Immobilisation 43 42 Dehydration 28 38 **Group I** **No. randomised:** 135 **No. of dropouts:** 3 **Age (mean):** 79.9 ±6.8 **M/F:** 84/51	**Group I** LMWH 10169 (*renamed enoxaparin*) 60mg in a vol of 0.3ml started on admission and continued for 10 days **Group II** placebo **Additional non-comparative prophylaxis:** None Non-steroidal anti-inflammatory drugs, aspirin or platelet inhibitor therapy forbidden.	**All cause mortality**	**Group 1:** 6/135 **Group 2:** 6/135 **P value:** ns	**Funding:** not reported **Limitations:** Only patients appear to be masked to treatment. The study is over 20 years old, not reported if allocation to interventions was concealed from patients and participants **Outcomes not reported:** pulmonary embolism, proximal and distal DVT, major and minor bleeding, heparin induced thrombocytopenia, post-thrombotic syndrome, quality of life, length of stay **Additional outcomes reported:** measurements for hemoglobin, platelets and activated partial antithrombin time **Notes:** Mean red cell count significantly lower in LMWH group (4.42 ±0.63 $10^6/mm^3$) compared to placebo
			DVT, asymptomatic or symptomatic (diagnosed by fibrinogen uptake test)	**Group 1:** 4/132 **Group 2:** 12/131 **P value:** 0.03	
			Fatal pulmonary embolism (diagnosed by autopsy)	**Group 1:** 1/132 **Group 2:** 3/131 **P value:** ns	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Additional risk factors: **Other factors:** **<u>Group II</u>** **No. randomised:** 135 **No. of dropouts:** 4 **Age (mean):** 80.1 ±6.9 **M/F:** 83/52 **Additional risk factors:** **Other factors:**				

LMWH vs no prophylaxis and LMWH adjuvant studies

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Dickinson et al., 1998[164]	RCT	1+	**Total:** 66 Int1: n= 21 Int 2: n=23 Control: n=22	**Type of surgery:** Neurosurgery for intracranial neoplasms **Intervention 1:** Mean age: 43 (28-61) yrs **Intervention 2:** Mean age: 50 (29-72) yrs **Control:** Mean age: 49 (20-72) **M/F numbers not reported** **Pre-existing Risk Factors:** Not reported **Ecluded patients:** history of DVT or PE, allergy to heparin or other anticoagulant agents, history of surgery or major trauma to the lower extremities, concurrent condition requiring anticoagulation therapy; cranial base neoplasms and pituitary adenomas	**Int 1:** LWMH (Enoxaparin) **Dose:** administered subcutaneously at a dose of 30mg in the anaesthesia holding room. He dose was continued at a dose of 30mg every 12 hours **Int 2:** Combination of Enoxaparin and SCD **Dose:** as before **Timing:** started before induction of anaesthesia until discharge from Neurosurgery Service. **Additional non-comparative prophylaxis:** antiembolic stockings on lower extremities at time of admission to the hospital **Int 2:** Combination of LMWH and thigh high sequential compression device.	**Type:** Thigh high sequential compression device **Timing:** started before induction of anesthesia and continued postoperatively until patient was walking without assistance **Additional non-comparative prophylaxis:** antiembolic stockings on lower extremities at time of admission to the hospital	1 month	**DVT** Confirmed by: duplex imaging (on four occasions in the first 1 month after surgery)	**Int 1:** 1/21 **Control:** 3/22 **p value = 0.53** **Int 2:** 4/23 **Comp:** 3/22 **P**=0.90	**Comments:** Study terminated early when it was determined that the enoxaparin treated groups exhibited a greater incidence of postoperative neurological deficits secondary to intracranial haemorrhage. **Not reported:** Post thrombotic leg, length of stay. **Funding:** NR
								Symptomatic PE	**Int 1:** 0/21 **Int 2:** 0/23 **Comp:** 022	
								Bleeding related complications (intracerebral hemorrhage or epidural haematoma)	**Int 1:** 2/21 **Int 2:** 3/23 **Comp:** 0/22	
								Mortality	**Int 1:** 0/21 **Int 2:** 1/23 **Comp:** 122	

LMWH vs no prophylaxis and LMWH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Fraisse et al., 2000[191] **Country of study:** France **Study design:** Multicentre RCT **List who was masked to interventions:** Investigators of VTE diagnosis, possibly patients **Evidence level:** 1+ **Duration of follow-up:** 21 days	**Patient group:** Acute respiratory decompensated COPD requiring mechanical ventilation **Setting:** 34 medical intensive care centres **Inclusion criteria:** • 40-80 years old • weight 45-110kg **Exclusion criteria:** • history of confirmed DVT in last 6 months • presence of DVT on doppler ultrasound • organic lesion that could bleed (i.e. gastroduodenal ulcer, recent hemorrhagic cerebrovascular accident • severe liver failure leading to a decrease of the prothombin time time to <50% • severe renal impairment • confirmed or uncontrolled hypertension • congenital or acquired coagulation disorder • history of hypersensitivity or thrombocytopenia to any heparin • contraindicated to anticoagulant therapy, venography or angiography • receiving any form of acetylsalicylic acid, ticlopidine or oral anticoagulants **All patients** **N:** 223 **No. of dropouts:** 54 **Group I** **No. randomised:** 108 **No. of dropouts:** 25* **Age (mean):** 69.4 ±7.7 **M/F:** 87/22 **Additional risk factors:** previous DVT (n=5), venous insufficiency (n=15), CHF (n=35),	**Group I** LMWH (nadroparin: dose based on body weight: • 3,800 AXa IU – 0.4ml for 45-70kg • 5700 Axa – 0.6ml for 70-110kg) in disposable syringes Started within 24 hours of being placed on mechanical ventilation and continued until removed from mechanical ventilation **Group II** Placebo (0.9% physiological saline) in disposable syringes **Additional non-comparative prophylaxis:** None	**All cause mortality**	**Group 1:** 8/108 **Group 2:** 8/113 **P value:** ns	**Funding:** Sanofi **Limitations:** Not everyone screened for DVT. Double blinded placebo controlled RCT but not clear if both patients and clinicians treating patients were masked to treatment, not reported if allocation to interventions was concealed from patients and participants **Outcomes not reported:** pulmonary embolism, HIT, post-thrombotic syndrome, infection, pulmonary hypertension, quality of life, length of stay **Additional outcomes reported:** Total adverse events, segmental localisation of DVT, adverse events resulting in early permanent discontinuation, thrombocytopaenia (not stated if heparin induced thrombocytopenia) **Notes:** Multicentre RCT * reported as early permanent
			DVT, asymptomatic or symptomatic (screened for by venography)	**Group 1:** 13/84 **Group 2:** 24/85 **P value:** 0.045	
			Proximal DVT, asymptomatic or symptomatic (screened for by venography)	**Group 1:** 3/84 **Group 2:** 7/85 **P value:** 0.045	
			Distal DVT, asymptomatic or symptomatic (screened for by venography)	**Group 1:** 10/84 **Group 2:** 17/85 **P value:** >0.05	
			Major haemorrhage (overt & associated with a decrease in hemoglogin concentration of 2g/dl or more, required transfusion of 2 or more units of packed red cells, retroperitoneal or intracranial or when investigator decided to end heparin because of benefit/risk ratio)	**Group 1:** 6/108 **Group 2:** 3/113 **P value:** 0.28	
			Minor bleeding	**Group 1:** 19/108 **Group 2:** 15/113 **P value:** NS	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	obesity (n=28), cancer (n=3) **Other factors:** **<u>Group II</u>** **No. randomised:** 113 **No. of dropouts:** 29* **Age (mean):** 66.8 ±8.2 **M/F:** **Additional risk factors:** previous DVT (n=4), venous insufficiency (n=13), CHF (n=29), obesity (n=24), cancer (n=8) **Other factors:**				discontinuation of treatment due to lack of efficacy, serious adverse event, patient decision, intercurrent event presenting a potential risk for the patient or a major protocol violation.

LMWH vs no prophylaxis and LMWH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Fuji et al., 2008[202] **Country of study:** Japan **Study design:** RCT **List who was masked to interventions:** Paper states that study is double blind (see limitations) and that the endpoint assessors were blinded. **Evidence level:** 1+ **Duration of follow-up:** 90 days	**Patient group:** Study 1: Total knee replacement (TKR) Study 2: Total hip replacement (THR) **Setting:** Department of Orthopaedic Surgery **Inclusion criteria:** Patients aged ≥ 20 years (no upper age limit was applied) undergoing elective primary THR or TKR. **Exclusion criteria:** • Patients requiring revision TKR or revision THR • Contraindication to heparin therapy • Positive clinical evidence of chronic (post-phlebitic syndrome) or acute DVT within 12 months of the study drug treatment • Documented allergy to iodine or contrast medium • impaired renal function (creatinine clearance <30ml/min or plasma creatinine level >1.5mg/dl) • Severe hepatic disease • Uncontrolled hypertension • Illicit drug use or alcohol abuse • Treatment with other investigational agents within 3 months of surgery • Failure to achieve postoperative haemostasis • Female subjects if pregnant or breast-feeding. **Study 1 (TKR)** **All patients** **N:** 396 **No. of dropouts:** 32 (8.1%) **Group 1** **No. analysed:** 78	**Study 1 (TKR)** **Group 1** LMWH (Enoxaparin) Start time: 24-36 hrs after surgery Duration: 14 days Daily 20mg subcutaneous injection **Group 2** LMWH (Enoxaparin) Start time: 24-36 hrs after surgery Duration: 14 days Daily 40 mg subcutaneous injection **Group 3** LMWH (Enoxaparin) Start time: 24-36 hrs after surgery Duration: 14 days Twice daily 20mg subcutaneous injections **Group 4** Placebo (saline) Start time: 24-36 hrs after surgery Duration: 14 days Subcutaneous injections (no frequency stated) **Additional non-comparative prophylaxis:** More than 50% of patients received	**Symptomatic pulmonary Embolism** (description: ventilation perfusion lung scans or pulmonary angiography at 90 days)	**Study 1 (TKR)** **Group 1:** 1/78 **Group 2:** 1/74 **Group 3:** 0/84 **Group 4:** 1/79 **p value:** Not significant **Study 2 (THR)** **Group 5:** 0/81 **Group 6:** 1/80 **Group 7:** 0/90 **Group 8:** 0/86 **p value:** Not significant	**Funding:** Sanofi-Aventis **Limitations:** Method of randomisation not given. No details provided on allocation concealment. Study reports that it was blinded but no information provided and some of the injection regimens were once daily whilst others were twice daily. **Outcomes not reported:** All cause mortality, fatal bleeding, fatal PE, heparin induced thrombocytopenia, post thrombotic syndrome, pulmonary hypertension, quality of life, length of stay **Additional outcomes reported:** The total number of adverse events were recorded. The authors concluded that most of these were not related to the treatment under investigation. **Notes:** * calculated by NCC using fishers exact test.
			DVT, asymptomatic or symptomatic (screened for by: Doppler ultrasound at 14 days)	**Study 1 (TKR)** **Group 1:** 34/78 **Group 2:** 26/74 **Group 3:** 25/84 **Group 4:** 48/79 **p value:** All groups receiving LMWH (gp 1,2 & 3) had significantly less DVT than the placebo group (gp 4). Group 1 vs. Group 4 = 0.038* Group 2 vs. Group 4 = 0.002* Group 3 vs. Group 4 = <0.001* No other significant differences between groups were found. **Study 2 (THR)** **Group 5:** 21/81 **Group 6:** 27/80 **Group 7:** 18/90 **Group 8:** 36/86 **p value:** The group receiving twice daily injections of 20mg LMWH (gp 7) had signficantly less DVT than the placebo group (gp 8) p = 0.003* No other significant differences between groups were found	
			Thigh DVT (description: screened for by: Doppler ultrasound at 14 days)	**Study 1 (TKR)** **Group 1:** 6/78 **Group 2:** 3/74 **Group 3:** 0/84 **Group 4:** 6/79	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Age (mean): 68.8 (sd = 9.0) **M/F:** 15:63 **Additional risk factors:** BMI ≥ 25 kg/m² = 40 (51.3%) **Group 2** **No. analysed:** 74 **Age (mean):** 70.0 (sd = 9.4) **M/F:** 11:63 **Additional risk factors:** BMI ≥ 25 kg/m² = 44 (59.4%) **Group 3** **No. analysed:** 84 **Age (mean):** 68.3 (sd = 8.7) **M/F:** 5:79 **Additional risk factors:** BMI ≥ 25 kg/m² = 35 (41.7%) **Group 4** **No. analysed:** 79 **Age (mean):** 68.7 (sd =9.5) **M/F:** 15: 64 **Additional risk factors:** BMI ≥ 25 kg/m² = 40 (50.6%) **Study 2 (THR)** **All patients** **N:** 436 **No. of dropouts:** 29 (6.7%) **Group 5** **No. analysed:** 81 **Age (mean):** 63.3 (sd = 10.4) **M/F:** 10: 71 **Additional risk factors:** BMI ≥ 25 kg/m² = 23 (28.4%) **Group 6** **No. analysed:** 80 **Age (mean):** 60.6 (sd = 9.9) **M/F:** 6:74 **Additional risk factors:** BMI ≥ 25 kg/m² = 26 (35.2%)	elastic stockings /bandages for part of the study. No other prophylaxis was used. **Study 2 (THR)** **Group 5** LMWH (Enoxaparin) Start time: 24-36 hrs after surgery Duration: 14 days Daily 20mg subcutaneous injections **Group 6** LMWH (Enoxaparin) Start time: 24-36 hrs after surgery Duration: 14 days Daily 40 mg subcutaneous injections **Group 7** LMWH (Enoxaparin) Start time: 24-36 hrs after surgery Duration: 14 days Twice daily 20mg subcutaneous injections **Group 8** Placebo (saline) Start time: 24-36 hrs after surgery Duration: 14 days Subcutaneous injections (no frequency stated)		**p value:** There were significantly fewer events in the twice daily 20mg LMWH group (gp3) vs the once daily 20mg LMWH group (gp 1) (p = 0.011*). There were significantly fewer events in the twice daily 20mg LMWh group (gp3) vs. the placebo group (gp 4) (p = 0.012*) **Study 2 (THR)** **Group 5:** 3/81 **Group 6:** 6/80 **Group 7:** 3/90 **Group 8:** 9/86 **p value:** No significant difference	
			Major bleeding (description: bleeding episode that was retroperitoneal, intracranial, or intraocular o if it was associated with: death; transfusion of ≥2 units of packed red blood cells or whole blood (except autologous); a reduction of ≥2 g/d; or a serious or life threatening clinical events that required medical intervention.)	**Study 1 (TKR)** **Group 1:** 0/89 **Group 2:** 1/91 **Group 3:** 3/95 **Group 4:** 4/89 **p value:** Not significant **Study 2 (THR)** **Group 5:** 1/100 **Group 6:** 2/102 **Group 7:** 3/104 **Group 8:** 0/101 **p value:** Not significant	
			Minor bleeding (description: at least one of the following features: epistaxis lasting >5 minutes or requiring intervention; ecchymosis or hematoma with a maximum size of >5 cm; haematuria not associated with urinary catheter trauma; gastrointestinal haemorrhage not related to intubation or a nasogastric tube; wound haematoma or haemorrhagic wound complications not associated with major haemorrhage; or subconjunctival haemorrhage requiring cessation of	**Study 1 (TKR)** **Group 1:** 5/89 **Group 2:** 6/91 **Group 3:** 10/95 **Group 4:** 4/89 **p value:** Not significant **Study 2 (THR)** **Group 5:** 1/100 **Group 6:** 7/102 **Group 7:** 4/104 **Group 8:** 2/101 **p value:** Not significant	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 7 **No. analysed:** 90 **Age (mean):** 63.0 (sd = 9.3) **M/F:** 15:75 **Additional risk factors:** BMI ≥ 25 kg/m^2 = 31 (34.4%) **Group 8** **No. analysed:** 86 **Age (mean):** 62.0 (sd =10.3) **M/F:** 11: 75 **Additional risk factors:** BMI ≥ 25 kg/m^2 = 34 (39.5%)	**Additional non-comparative prophylaxis:** More than 50% of patients received elastic stockings /bandages for part of the study. No other prophylaxis was used.	medication)		

LMWH vs no prophylaxis and LMWH adjuvant studies

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Iorio et al., 2000[304] 3 RCT studies [11,441,495] All of these studies were included in the guideline review. }	Systematic Review	1+	**Total:** 922 **Intervention:**461 **Control:**461	**Type of surgery:** Neurosurgery	**LWMH** **Doses:** Enoxaparin: 40mg/day (1 study) and 20mg/day (1 study) Nadroparin 7500 anti-Xa units/d (1 study) **Timing**: Started within 24 hours postoperatively and given daily for ≥7 days (in one study) to 10 days (in two studies). **Background prophylaxis:** GCS 2 studies **Additional non-comparative prophylaxis:** Not reported	**Placebo** **Background prophylaxis:** GCS 2 studies	Follow up 30 days for one study and 56 days for the second study. The third study did not report follow up period.	**DVT** confirmed by venography	**Int:** 63/360 **Cont:** 104/367 [OR: 0.54 (95% CI 0.38-0.77); **p value:** <0.001	**Not reported:** QoL, LoS, PTS and funding.
								Proximal DVT	**Int:** 19/304 **Cont:** 39/312 [OR=0.48 (95% CI 0.28-0.83); **p value:** 0.008	
								Major bleeding	**Int:** 10/461 **Cont:** 6/461 [OR=1.68 (95% CI 0.62-4.52); **p value:** 0.30	
								Fatal PE	**Int:** 1/371 **Cont:** 3/374 **p value:** 0.6240	

LMWH vs no prophylaxis and LMWH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Jorgensen et al., 2002[317] **Country of study:** Denmark **Study design:** RCT **List who was masked to interventions:** assessors of venograms **Evidence level:** 1+ **Duration of follow-up:** while wearing plaster cast (mean duration 5.5 weeks)	**Patient group:** Patients wearing below knee plaster casts on lower extremity (reasons for plaster cast: fracture (n=220); tendon ruptures (n=61); other (n=19) **Setting:** Outpatients **Inclusion criteria:** • age >18 • planned lower limb plaster cast of at least 3 weeks **Exclusion criteria:** • pregnancy • allergy to heparin or contrast media • known liver or renal impairment • uncontrolled hypertension • bleeding disorders • cerebral insults due to bleeding • recent gastrointestinal bleeding • inability to self inject **All patients** **N:** 300 **No. of dropouts:** 95 **Group I** **No. randomised:** 148 **No. of dropouts:** 49 **Age (mean):** 49 **M/F:** 69/79 **BMI:** 25 **Additional risk factors:** smokers 67; oral contraceptives 7; previous DVT 3; varicose veins 5; cardiac diseases 1 **Other factors:** no. having an operation 86 (58%) **Group II** **No. randomised:** 152 **No. of dropouts:** 46	**Group I** LMWH tinzaparin (Innohep) 3500 IU self injected into abdominal wall once daily until plaster cast removed **Group II** no LMWH **Additional non-comparative prophylaxis:** None	**DVT, asymptomatic or symptomatic** (diagnosed by ascending **unilateral** venography when plaster cast removed)	**Group 1:** 10/99 **Group 2:** 18/106 **P value:** 0.15	**Funding:** not reported **Limitations** Only assess one leg for DVT; patients and clinicians not masked to treatment; the reasons for two thirds of patients not reaching an endpoint are not clear for all patients **Outcomes not reported:** major and minor bleeding, heparin induced thrombocytopenia, post-thrombotic syndrome, quality of life **Additional outcomes reported:** ▪ Bleeding-4 hematomas (uncertain which arm) and 1 metroharrgia in LMWH arm. ▪ No. of DVTs by type of injury , no. of DVTs in those having surgery; about 60% reported no difficulty with self injection; mean pre-and post study platelet count; mean aspartate and alanine amino transferase, mean alkaline phosphatise ▪ Main reasons for not reaching an endpoint: discomfort with self-
			DVT, asymptomatic or symptomaticby diagnosis (diagnosed by ascending **unilateral** venography when plaster cast removed)	**Fractured patients** **Group 1:** 8/73 **Group 2:** 10/77 **P value:** 0.70 **Tendon ruptured patients** **Group 1:** 2/20 **Group 2:** 6/21 **P value:** 0.24 **Patients operated on** **Group 1:** 9/86 **Group 2:** 16/89 **P value:** 0.16	
			Above knee DVT (diagnosed by ascending **unilateral** venography when plaster cast removed)	**Group 1:** 0/99 **Group 2:** 1/106 **P value:** not significant	
			Symptomatic DVT (confirmed by ascending **unilateral** venography when plaster cast removed)	**Group 1:** 0/99 **Group 2:** 1/106 **P value:** not significant	
			Symptomatic pulmonary embolism	**Group 1:** 0/99 **Group 2:** 0/106 **P value:** not significant	
			Wound infection	**Group 1:** 4/99 **Group 2:** 1/106 **P value:** not significant	
			Discomfort with self injection – stopped study	**Group 1:** 18/148 Group 2: Not applicable 18/95 of total drop outs due to discomfort in self injection	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Age (mean): 46 **M/F:** 59/93 **BMI:** 25 **Additional risk factors**: smokers 73; oral contraceptives 6; previous DVT 3; varicose veins 15; cardiac diseases 3 **Other factors**: no. having an operation 89 (59%)				injection 18/95, metrorrhagia 1/95, refuse phlebography 12/95, venograph not possible or refused 26/95, miscellaneous 38/95 **Notes:** Bleeding data – excluded due to ambiguity in reporting and definition after discussions between reviewers.

LMWH vs no prophylaxis and LMWH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Kock et al., 1995[356] **Country of study:** Germany **Study design:** RCT **List who was masked to interventions:** nobody **Evidence level:** 1+ **Duration of follow-up:** until plaster cast removed	**Patient group:** Patients with leg injury for which conservative treatment without admission to hospital was indicated. Below knee cast (n=366) or above knee casts (n=62). Reasons for plaster cast: Grade II sprains and bruises (n=122); Grade III sprains (n=130); fractures (n=72); other (n=15) **Setting:** Outpatients **Inclusion criteria:** • age 18-65 **Exclusion criteria:** • previous DVT • pregnancy • clotting disorders or anticoagulant medication • bleeding sources • contraindications to heparin • chronic venous insufficiency • plaster cast after surgery **All patients** **N:** 428 **No. of dropouts:** 89 **Group I** **No. randomised:** NR **No. of dropouts:** NR **Age (mean):** 34.1 (18-63) **M/F:** 104/72 **Weight (mean):** 78.4 ±13 kg **Additional risk factors:** age >40 (n=53); obesity (Broca index >1.2) (n=40); cigarette smoking (n=83); varicose veins (n=23); oral contraceptives (n=18); **Group II**	**Group I** LMWH (Mono-Embolex NM (Sandoz) 0.3ml per syringe with an activated partial thrombo-plastin time activity of 1500 units & anit-Xa activity of 3000 units. Not reported when started, self injected until plaster cast removed **Group II** no LMWH **Additional non-comparative prophylaxis:** None	**DVT, asymptomatic or symptomatic** (* confirmed by venography when plaster cast removed)	**Group 1:** 0/176 **Group 2:** 7/163 **P value:** 0.06	**Funding:** not reported **Limitations** Nobody masked to treatment. Does not report initial numbers randomised to each group **Outcomes not reported:** mortality, pulmonary embolism, minor bleeding, heparin induced thrombocytopenia, post-thrombotic syndrome, quality of life **Additional outcomes reported:** DVT subgrouped by risk factor **Notes:** * DVT checked by clinical examination, measurement of leg circumference, venous occlusion plethysmography, B-mode compression ultrasonography and duplex scanning and confirmed by venography
			Proximal DVT (as above)	**Group 1:** 0/176 **Group 2:** 3/163 **P value:** NS	
			Calf DVT (as above)	**Group 1:** 0/176 **Group 2:** 4/163 **P value:** NS	
			Mean (±SD) duration of plaster-cast immobilisation (days)	**Group 1:** 15.2 ±12 (n=176) **Group 2:** 18.8 ±13 (n=163) **P value:** 0.008	
			Mean (±SD) duration of plaster-cast immobilisation (days)	**Patients with DVT:** 11.4 ±10 (n=7) **Patients without DVT:** 17.2 ±13 (n=332) **P value:** 0.13	
			Major bleeding (not defined)	**Group 1:** 0/176 **Group 2:** 0/163 **P value:** n/a	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No. randomised: NR **No. of dropouts:** NR **Age (mean):** 33 (18-63) **M/F:** 104/59 **Weight (mean):** 75.0 ±14 kg **Additional risk factors:** age >40 (n=44); obesity (Broca index >1.2) (n=34); cigarrette smoking (n=70); varicose veins (n=31); oral contraceptives (n=25)				

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Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Kujath et al., 1993[367] **Country of study:** Germany **Study design:** RCT **List who was masked to interventions:** no one **Evidence level:** 1+ **Duration of follow-up:** until plaster cast removed	**Patient group:** Outpatients with leg injury treated conservatively and immobilisation by plaster cast. Type of injury: soft tissue (n=176); fractures (n=77) **Setting:** Outpatients **Inclusion criteria:** • age >16 • immobilisation by plaster cast for at least 7 days **Exclusion criteria:** • known thrombopathy • oral anticoagulation • fresh brain or gastrointestinal bleeding • acute pancreatitis • inflammatory heart disease **All patients** **N:** 306 **No. of dropouts:** 53 **Group I** **No. randomised:** 126 **No. of dropouts:** NR **Age (mean):** 32.9 ±13.8 **M/F:** 69/57 **Weight (mean):** 73.7 ±14.2 kg **Additional risk factors:** history of thrombosis or embolism (n=9); age >40 (n=31); overweight (n=34); smoking (n=48); varicose veins (n=18); oral contraceptives (n=8); **Group II** **No. randomised:** 127 **No. of dropouts:** NR **Age (mean):** 35.6 ±14.6	**Group I** LMWH (Fraxiparin) 0.3ml daily [36mg heparin fraction calcium, molecular mass 4000-5000. Started on first day of treatment, continued until plaster cast removed **Group II** no LMWH **Additional non-comparative prophylaxis:** None	**DVT, asymptomatic or symptomatic** (diagnosed by ultrasound confirmed by venography) **Mean (±SD) duration of plaster-cast** (days)	**Group 1:** 6/126 **Group 2:** 21/127 **P value:** <0.01 **Group 1:** 15.6 ±6.8 (n=126) **Group 2:** 15.8 ±9.6 (n=127) **P value:** 0.85	**Funding:** not reported **Limitations** Nobody masked to treatment. **Outcomes not reported:** mortality, pulmonary embolism, minor bleeding, heparin induced thrombocytopenia, post-thrombotic syndrome, quality of life **Additional outcomes reported:** DVT subgrouped by risk factor; total no. of symptomatic DVTs 9/27 (not given by group) **Notes:**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	M/F: 77/50 **Weight (mean):** 74.4 ±13.6 kg **Additional risk factors**: history of thrombosis or embolism (n=6); age >40 (n=44); overweight (n=36); smoking (n=45); varicose veins (n=15); oral contraceptives (n=13);				

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Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Lapidus, 2007[375] **Country of study:** Sweden **Study design:** Double blinded RCT **List who was masked to interventions:** All **Evidence level:** 1+ **Duration of follow-up:** Up to 6 weeks	**Patient group:** Acute ankle fracture, all received surgery A majority of patient used plaster casts, 18% used orthosis **Setting:** Stockholm Soder Hospital (May2000-March2004) **Inclusion criteria:** - 18-75 years old - Admitted because of acute ankle (0-72h) fracture accepted for surgery **Exclusion criteria:** - Inability or refusal to sign informed consent form - Ongoing treatment with anticoagulant therapy - Known allergy to contrast media - Planned follow up at another hospital - Recent surgery - Known malignancy - Current bleeding disorder - Pregnancy - Treatment with high doses of acetyl salicylic acid (≥325 mg) or other platelet inhibitors - Multi-trauma (injuries involving >1 organ system in addition to the musculoskeletal system or multiple fractures) **All patients** **N:** 272 **Age (mean):** 48 (18-76) years **M/F:** 124/148 **Group 1** **No. randomised:** 136 **No. of dropouts (non-evaluable):** 35 M/F: 62/74	**Group 1** LMWH Dalteparin 5000U, once daily Subcutaneous injection **Group 2** Placebo(9%w/v sodium chloride), 0.2 ml in identical syringes to dalteparin. Start time: 7 days post surgery End time: until plaster cast removed (mean 44 days±2) Duration: up to 6 week after surgery **Additional non-comparative prophylaxis:** Both groups received 5000Uof s/c dalteparin once daily for 7 days, starting on evening after surgery. All received 1000mL Dextran 60 on admission	**All cause mortality** (confirmed by: No death was reported)	**Group1:** 0/136 **Group 2:** 0/136 **P value:** 1.0	**Funding:** Pfizer/Pharmacia and Karolinska Institute provided grants **Limitations:** - Randomisation method and concealment not described. - Only the affected leg was scanned. - Baseline risk factors and comorbidities not reported **Outcomes not reported:** Calf DVT, minor bleeding, heparin induced thrombocytopenia, post thrombotic syndrome, pulmonary hypertension, quality of life, length of stay **Additional outcomes reported:** - Details/reasons for patients to be non-evaluable - Compliance, duration of immobilisation, subgroup analysis of orthosis and casts - Average age of patients who used an orthosis was 45 years p=0.03 compared to plaster cast patients **Notes:** - All subjects were trained in self-injection by as study nurse before leaving hospital. - All ankle fracture patients admitted to hospital who
			Fatal pulmonary embolism (confirmed by: None reported)	**Group1:** 0/136 **Group 2:** 0/136 **P value:** 1.0	
			Symptomatic pulmonary embolism (confirmed by: ventilation perfusion scan or spiral CT if suspected)	**Group1:** 0/136 **Group 2:** 0/136 **P value:** 1.0	
			Symptomatic DVT (confirmed by: phlebography or CDS whenever indicated) One of the 8 events is a calf muscle vein thrombosis, not specified which arm	**Group1:** 2/136 **Group 2:** 6/136 **P value:** 0.28 **Plaster cast subgroup:** **Group 1:** 2/114 **Group 2:** 6/108 **P value:** 0. 16 *[value calculated by NCC-AC team using Fishers' exact test]*	
			DVT, asymptomatic or symptomatic (screened for by: unilateral ascending phlebography of the affected legs, or colour duplex sonography (CDS) when phlebography fails at 2nd and 6th week, on the last day of the dose (or a day after), and when thrombosis is suspected, whichever earlier.	Up to Week 6 (by phlebography) ITT analysis **Group1:** 21/101 (21%) **Group 2:** 27/96 (28%) **P value:**0.2 Up to Week 6 (by phlebography), per protocol **Group1:** 13/75 **Group 2:** 17/65 **P value:**0.2 Up to Week 6 (by phlebography or CDS, ITT analysis) **Group1:** 24/117 **Group 2:**34/109 **P value:**0.07 **Plaster cast subgroup** Up to Week 6 (by phlebography) ITT analysis **Group1:** 18/86 **Group 2:** 27/75 **P value:** 0.04	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Age (years): 49±14 Weight (kg): 80±16 BMI (kg/m²): 27±4 Time in surgery (min): 65±28 Tourniquet time (min): 70±28 Fracture type: - Unimalleolar: 59/136 (43%) - Bimalleolar: 42/136 (31%) - Trimalleolar: 35/136 (26%) Used plaster cast: 114/136 **Group 2** **No. randomised:** 136 **No. of dropouts (non-evaluable):** 40 M/F: 62/74 Age (years): 48±14 Weight (kg): 78±13 BMI (kg/m²): 26±3 Time in surgery (min): 63±28 Torniquet time (min): 68±30 Fracture type: - Unimalleolar: 44/136 (32) - Bimalleolar: 53/136 (39) - Trimalleolar: 39/136 (29) Used plaster cast: 108/136			Up to Week 6 (by phlebography), per protocol **Group1:** 21/99 **Group 2:** 33/86 **P value:** 0.02	required surgery was assessed for eligibility (n=1072). Details of reason for exclusion provided
			Thigh DVT (screened for by: as above, defined as affecting popliteal vein or any other more proximal vein, with or without involvement of the calf veins)	**Group1:** 4/101 **Group 2:** 3/96 **P value:** 0.2	
			Fatal bleeding (description: no death or major bleeding reported)	**Group1:** 0/136 **Group 2:** 0/136 **P value:** 1.0	
			Major bleeding (description: requiring blood transfusion/ surgery, or at a critical site such as intracranial, intraocular, intraspinal, or retroperitoneal)	**Group1:** 0/136 **Group 2:** 0/ 136 **P value:** 1.0 **Plaster cast subgroup:** **Group 1:** 0/114 **Group 2:** 0/108	
			Minor bleeding (description: All local bleedings not classified as "major bleeding")	**Group1:** 1/ 136 **Group 2:** 1/136 **P value:** 1.0	

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Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Lapidus, 2007{LAPIDUS2007A) **Country of study:** Sweden **Study design:** Single centre, double blinded RCT **List who was masked to interventions:** Investigators, patients, radiologist who carried out standardised final evaluation **Evidence level:** 1+ **Duration of follow-up:** Up to 6 weeks	**Patient group:** Achilles tendon rupture, all received surgery. **Setting:** Stockholm Soder Hospital (Nov2001-May2004) **Inclusion criteria:** - Consecutive patients - 18-75 years old - Admitted because of Achilles tendon rupture (0-72h) and accepted for surgery **Exclusion criteria:** - Inability or refusal to sign informed consent form - Ongoing treatment with anticoagulant - Known allergy to contrast media - Planned follow up at another hospital - Recent surgery or thromboembolic event (during the proceeding 3 months) - Known malignancy - Current bleeding disorder - Pregnancy - Treatment with high doses of acetyl salicylic acid (≥325 mg) or other platelet inhibitors - Other injuries **<u>All patients</u>** **N:** 105 **Age (mean):** 40 years **M/F:** 83/22 **Time to surgery (mean):** 2days **VTE history :** 0/105 **Surgery method:** Usually short skin incision placed medially over the rupture, end to end suture most commonly with modified Kessler technique. **Plaster cast:** Below knee plaster cast with ankle in the equinus position. At 3rd week, this was replaced by another plaster cast or orthoses at neutral position. **Anaesthesia:** spinal or local	**Group 1** LMWH Dalteparin 5000U **Group 2** Placebo (9%w/v sodium chloride), 0.2 ml in identical syringes to dalteparin. <u>Frequency:</u> once daily <u>Route:</u> subcutaneous injection <u>Start time:</u> Within hours post surgery <u>End time:</u> up to 6th week, or mobilisation <u>Duration:</u> up to 6 weeks after surgery All patients given 45 syringes. **Additional non-comparative prophylaxis:** Not mentioned	**All cause mortality** (confirmed by: No death was reported)	**Group1:** 0/52 **Group 2:** 0/53 **P value:** 1.0	**Funding:** Pfizer/Pharmacia and Karolinska Institute provided grants. Dalteparin provided by Pharmacia/ Pfizer **Limitations:** - Positive events detected by CDS, but not confirmed by phlebography (either not performed or not interpretable) had not been included in the primary and secondary analysis of efficacy - Only the affected leg was scanned routine scanning **Outcomes not reported:** Symptomatic DVT, Thigh DVT; Fatal or neurological or upper GI bleeding, Heparin induced thrombocytopaenia, Post thrombotic syndrome, Pulmonary hypertension, Quality of life, Length of stay **Additional outcomes reported:** - Details/reasons for patients to be non-evaluable. - Compliance with extended LMWH injections, duration of immobilisation, mean time to DVT diagnosis - Number of patients treated for DVT was reported as 20/49 (40%) in the treatment and 23/47(43%) in the placebo arms respectively. An additional 1 patient from
			Fatal pulmonary embolism (confirmed by: None reported)	**Group1:** 0/52 **Group 2:** 0/53 **P value:** 1.0	
			Symptomatic pulmonary embolism (confirmed by: ventilation perfusion scan or spiral CT if suspected)	**Group1:** 0/52 **Group 2:** 0/53 **P value:** 1.0	
			DVT, asymptomatic or symptomatic (screened for by: unilateral ascending phlebography of the affected legs, or colour duplex sonography (CDS) when phlebography fails at the 3rd week and 6th week, on the last day of the dose (or a day after), and when thrombosis is suspected, whichever earlier.	**<u>(As reported)</u>** <u>Up to Week 6 (by phlebography) ITT analysis</u> **Group1:** 16/47 (34%) **Group 2:** 16/44 (36%) **P value:**0.8 <u>Up to Week 6 (by phlebography or CDS), ITT analysis</u> **Group1:** 18/49 (37%) **Group 2:** 19/47(40%) **P value:** 0.8 Note: 24 (65% diagnosed at week 3, the rest at the end of study) *[value calculated by NCC-AC team using Fishers' exact test]*	
			Thigh DVT (screened for by: as above, defined as affecting popliteal vein or any other more proximal vein, with or without involvement of the calf veins)	**Group1:** 1/49 **Group 2:** 3/47 **P value:** 0.6	
			Fatal bleeding (description: no death or major bleeding reported)	**Group1:** 0/52 **Group 2:** 0/53 **P value:** 1.0	
			Major bleeding (description: requiring blood transfusion/ surgery, or at a critical site such as intracranial,	**Group1:** 0/52 **Group 2:** 0/53 **P value:** 1.0	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 **No. randomised:** 52 **No. of dropouts:** 2 **M/F:** 41/11 Age (years): 37±8 Weight (kg): 80±12 BMI (kg/m²): 26±3 Time in surgery (min): 44±18 Torniquet used, time (min): 6/52, 34±14 Local/spinal anaesthesia:48/4 Smokers:9/52, 8/53 Hormonal contraceptives: 0/11, 1/11 Diabetes: 0/52, 2/53 Varicose veins: 3/52, 6/53 Orthosis used:12/52 **Group 2** **No. randomised:** 53 **No. of dropouts :** 2 **M/F:** 42/11 Age (years): 42±9 Weight (kg): 81±11 BMI (kg/m²): 26±3 Time in surgery (min): 45±18 Torniquet used, time (min): 6/53, 39±17 Local/spinal anaesthesia:48/5 Smokers:8/53 Hormonal contraceptives: 1/11 Diabetes: 2/53 Varicose veins: 6/53 Orthosis used : 15/53		intraocular, intraspinal, or retroperitoneal) **Minor bleeding** (description: A nose bleed)	 **Group1:** 1/ 52 **Group 2:** 0/53 **P value:** 1.0	each arm was treated but not included in the ITT analysis. **Notes:** - All admitted Achilles tendon rupture patients I who required surgery was assessed for eligibility (n=285), and 257 fulfilled criteria. - Patients with asymptomatic DVT detected by CDS but not verified by phlebography were excluded (n=5, 4 in placebo) - Subjects were trained in self-injection by study nurse in hospital. - Patients were followed up at 3 weeks after surgery, where plaster casts were changed and screening for DVT was done, and screened again at the end of study

LMWH vs no prophylaxis and LMWH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Lassen et al., 2002[382] **Country of study:** Denmark **Study design:** RCT **List who was masked to interventions:** Patients and investigators of venography **Evidence level:** 1+ **Duration of follow-up:** until plaster cast removed	**Patient group:** Outpatients with fracture of the leg or rupture of the Achilles tendon requiring at least five weeks immobilisation in plaster cast or brace within 4 days of injury. **Setting:** Outpatients **Inclusion criteria:** • age >18 • requiring lower limb cast >5 weeks **Exclusion criteria:** • weight <35kg • pre-existing venous thromboembolism • systolic blood pressure >200mmHg • diastolic blood pressure >110mmHg • cerebral vascular aneurysm • cerebral vascular accident within preceding 3 weeks • active gastroduodenal ulcer • hemorrhagic diathesis • bacterial endocarditis • platelet count <100,000 per mm^3 • previous treatment with heparin lasting >4 days • previous treatment with fibrinolytic agents or oral anticoagulants • immobilisation for >4 days before enrolment • known hypersensitivity to heparin or contrast medium • contraindications to venography • myocardial infarction in previous 3 months • multiple myeloma • current pregnancy or lactation • current treatment with any investigational drug or such treatment within preceding 4 weeks • history of drug or alcohol abuse	**Group I** LMWH (Reviparin, 1750 anti-Xa units self injected daily Started not more than more 4 days after fractures and continued throughout immobilisation. **Group II** Placebo **Additional non-comparative prophylaxis:** Patients who underwent surgery were permitted to have had heparin treatment lasting up to 4 days **before** randomisation. Numbers treated **Group I:** 65 **Group II:** 71	**DVT, asymptomatic or symptomatic** (diagnosed by unilateral venography within a week of plaster cast removal)	**Group 1:** 17/183 **Group 2:** 35/188 **P value:** 0.01	**Funding:** supported by grant from Knoll **Limitations** Appears a fairly well conducted study **Outcomes not reported:** mortality, pulmonary embolism, minor bleeding, heparin induced thrombocytopenia, post-thrombotic syndrome, quality of life **Notes:** Discussed between reviewers: Major bleeding included "minor bleeding" cases where treatment was discontinued, based on author's definition. Denominator for Group 1 set as 217 – the number randomised to be consistent as ITT. Paper reported safety population based on 438, but unclear which were the patients excluded.
			Symptomatic DVT (confirmed by unilateral venography)	**Group 1:** 0/217 **Group 2:** 4/221 **P value:**	
			Proximal DVT (diagnosed by unilateral venography within a week of plaster cast removal)	**Group 1:** 3/183 **Group 2:** 10/188 **P value:** 0.09	
			Distal DVT (diagnosed by unilateral venography within a week of plaster cast removal)	**Group 1:** 14/183 **Group 2:** 25/188 **P value:** 0.09	
			Symptomatic pulmonary embolism (confirmed by ventilation perfusion scanning)	**Group 1:** 0/217 **Group 2:** 2/221 **P value:** NS	
			Major bleeding (defined as clinically apparent bleeding associated with a decrease of at least 2.0g per deciliter in the hemoglobin level, requirement for transfusion of at least 2 units of packed red cells, or retroperitoneal or intracranial bleeding or other bleeding that investigators decided required permanent discontinuation of treatment)	**Group 1:** 2/217 **Group 2:** 1/221 **P value:** NS	
			Minor bleeding (defined as bleeding not meeting definition for major bleeding)	**Group 1:** 12/217 **Group 2:** 11/221 **P value:** NS	
			Mean (±SD) duration of immobilisation (days)	**Group 1:** 43 (n=126) **Group 2:** 44 (n=127) **P value:** NS	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	All patients **N:** 440 **No. of dropouts:** 69 **Group I** **No. randomised:** 217 **No. of dropouts:** 34 (reasons: withdrew consent 2; adverse events 1; venograms not evaluable 31) **Age (median, interquartile range):** 47 (37-55) **M/F:** 112/105 **BMI (median, interquartile range):** 25 (23-28) kg/m^2 **Additional risk factors**: previous thromboembolism (n=5); varicose veins (n=20); hypertension (n=13); hypercholesterolmia (n=14); oral contraceptives (n=14); current hormone replacement therapy (n=8); diabetes mellitus (n=5); smoking (n=79) **Type of injury**: tibial fracture (n=18), patellar fracture (n=7); malleolar fracture (n=127); fracture in the foot (n=15); rupture of Achilles tendon (n=52) **Surgical treatment**: 118 **Group II** **No. randomised:** 223 **No. of dropouts:** 35 (reasons: no injections 2; adverse events 3; venograms not evaluable 30) **Age (median, interquartile range):** 47 (37-56) **M/F:** 114/109 **BMI (median, interquartile range):** 26 (24-28) kg/m^2 **Additional risk factors**: previous thromboembolism (n=5); varicose veins (n=21); hypertension (n=22); hypercholesterolmia (n=15); oral contraceptives (n=11); current hormone replacement therapy (n=9); diabetes mellitus (n=5); smoking (n=105) **Type of injury**: tibial fracture (n=10),				

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	patellar fracture (n=8); malleolar fracture (n=155); fracture in the foot (n=13); rupture of Achilles tendon (n=36) **Surgical treatment:** 126				

LMWH vs no prophylaxis and LMWH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Lederle et al., 2006[390] **Country of study:** US **Study design:** RCT **List who was masked to interventions:** Double blind: patient, clinician and researcher **Evidence level:** 1+ **Duration of follow-up:** 90 days (although number of deaths at 1 year is reported)	**Patient group:** Hospitalised general medical patients age 60 or over **Setting:** Medical ward, intensive care units or intermediate care **Inclusion criteria:** • Admitted or transferred (from home or another hospital, institution,or service) to the medical service (medical wards or intensive care units or intermediate care) of the participating Veterans Affairs medical centre on the day of randomisation or the previous day. • Age 60 years or older • expected to by at the medical centre for at least 3 days from the time of randomisation • able and willing to give informed consent. **Exclusion criteria:** • Already receiving or requiring anticoagulation for reasons other than VTE phrophylaxis • known thrombocytopenia (platelet count < 100000/mm^3) • systolic blood pressure higher than 220 mm Hg • diastolic blood pressure higher than 110 mm Hg • other contraindication to low-dose heparin in the opinion of the patient's physicians • previous randomisation into the study, • "supportive/palliative care only" status • occurrence within the past 30 days of myocardial infarction, stroke, major surgery (defined as requiring general, spinal, or epidural anesthesia and lasting >30 minutes), or any eye surgery. **<u>All patients</u>** **N:** 280 **<u>Enoxaparin Group</u>**	**LMWH** Enoxaparin 40 mg syringes. Subcutaneous daily injections. First injection given immediately after randomisation. **Placebo Group** Identical syringes containing placebo. Treatment was withheld if the patient developed any of the following: need for anticoagulation or thrombolytic therapy, decrease in platelet count of 50%, systolic pressure higher than 220 mm Hg or diastolic pressure more than 110 mm Hg, other contraindication to low-dose heparin in the opinion of the attending physicians, change of status to supportive/palliative care only, of if more than 90 days had elapsed since randomisation. **Additional non-comparative prophylaxis:** Not reported	**All cause mortality at 90 days**	**Enoxaparin:** 13/140 **Placebo:** 14/140 **P value:** Not reported. RR (95% CI): 0.93 (0.26-1.59)	**Funding:** Supported by the Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development. Enoxaparin and matching placebo syringes were provided by Rhone-Poulene Rorer Pharmaceuticals. **Limitations:** Very small sample size. This pilot study aimed to recruit 1000 patients and only 280 patients (140 in each group) were recruited. The pilot study was not large enough to answer the study question. 32 (23%) patients in enoxaparin group and 25 (18%) in the placebo group had study drug discontinued. **Outcomes not reported:** fatal pulmonary embolism; thigh & calf DVT; fatal, neurological, upper GI or minor bleeding; post thrombotic syndrome; pulmonary hypertension; quality of life **Additional outcomes reported**
			All cause mortality at 1 year	**Enoxaparin:** 36/140 **Placebo:** 32/140 **P value:** Not reported. RR (95% CI): 1.13 (0.66-1.60)	
			Symptomatic pulmonary embolism at 90 days (ventilation perfusion scan, pulmonary angiogram or autopsy)	Reported as "Pulmonary embolism" in table **Enoxaparin Group:** 1/140 **Placebo Group:** 3/140 **P value:** Not reported. Difference was NS	
			Major bleeding (description: No details provided)	**Enoxaparin Group:** 2/140 **Placebo Group:** 5/140 **P value:** Not reported. Difference was NS	
			Heparin induced thrombocytopaenia	**Enoxaparin Group:** 1/140 **Placebo Group:** 3/140 **P value:** Not reported. Difference was NS	
			Length of stay (mean total hospital days, initial and readmissions)	**Enoxaparin Group:** 13.4 **Placebo Group:** 11.1 **P value:** Not reported. Difference was NS	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No. randomised: 140 **No. of dropouts:** 2 **Age (mean):** 71.3 **M/F:** 99.3 % men **Additional risk factors:** Weight (kg): 85.1 (units not reported) White race: 83.2 % Current pneumonia: 15 % Current smoker: 17.9 % History of: Thromboembolism: 5.7 % Heparin: 9.3 % Cancer: 5.0 % Cerebrovascular disease 8.6% Chronic obstructive lung disease 47.1 % Diabetes: 27.9 % Congestive Heart Failure: 22.1 % Myocardial infarction: 25.7 % Peripheral vascular disease: 22.0 Surgery in the past 6 months: 2.9 % Charlson Comobidity Index (score): 2.49 % Self reported general health: Excellent: 2.3% Good: 16.2 % Fair: 68.5% Poor: 13.1 % **Placebo Group** **No. randomised:** 140 **No. of dropouts:** 1 **Age (mean):** 72.1 **M/F:** 97.8% men **Additional risk factors:** Weight (kg): 85.5 (units not reported) White race: 75.2 % Current pneumonia: 19.3 % Current smoker: 15.0 % History of: Thromboembolism: 3.6 % Heparin: 8.6 % Cancer: 4.3 % Cerebrovascular disease 11.4% Chronic obstructive lung disease 40.0 %				stroke, myocardial infarction, no. patients readmitted, DVT but not clear how diagnosed **Notes:** Authors do not provide detailed information on how outcomes were measured. Causes of deaths and drug discontinuation are not described.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Diabetes: 28.6 % Congestive Heart Failure: 27.1 % Myocardial infarction: 22.9 % Peripheral vascular disease: 10.0 p= 0.02 Surgery in the past 6 months: 2.9 % Charlson Comobidity Index (score): 2.47 % Self reported general health: Excellent: 3.0% Good: 21.1 % Fair: 56.4% Poor: 19.5 %				

LMWH vs no prophylaxis and LMWH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Leizorovicz et al., 2004[394] Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE (The PREVENT Study) **Country of study:** Multi-national **Study design:** RCT **List who was masked to interventions:** Subjects and investigators of VTE assessment **Evidence level:** 1+ **Duration of follow-up:** 14 days treatment, 90 days follow-up	**Patient group:** Acutely ill medical patients with on of: • acute congestive heart failure • acute respiratory failure not requiring mechanical ventilation Or one of following with ≥1 risk factors listed in last point: • acute infection without septic shock • episode of inflammatory bowel disease • acute rehumatic disorders • acute lumbar pain, sciatica or vertebral compression • acute arthritis of the legs or acute episode of rheumatoid arthritis in the legs • risk factors: age ≥75, cancer, previous VTE, obesity, varicose veins, chronic venous insufficiency, hormone therapy, chronic heart or respiratory failure or myeloproliferative disorder **Setting:** hospital **Inclusion criteria:** • immobilised but have been for <3 days • projected hospital stay of >4 days • ≥40 years old **Exclusion criteria:** • acute coronary syndrome within previous month • major surgical or invasive procedure within previous month or to be undertaken within next 2 weeks • bacterial endocarditis • immobilised lower limb due to cast or fracture	**Group I** LMWH dalteparin 5000 IU 1x/day for 14 days **Group II** placebo 1x/day for 14 days **Additional non-comparative prophylaxis:** Low dose aspirin (up to 325mg/day), ticlopidine and clopidogrel permitted; "Chronic use" non-steroidal anti-inflammatory drugs discourage but not forbidden. Other antithrombotic agents not permitted, anyone given one of these withdrawn from the study Numbers not given for any of the above	**All cause mortality at day 14**	**Group 1**: 8/1846 **Group 2**: 7/1831 **Relative risk**: 1.13 (0.41, 3.12)	**Funding:** Pharmacia **Limitations:** Not clear if clinicians treating patients were masked to treatment, not reported if allocation to interventions was concealed from patients and participants **Outcomes not reported:** post-thrombotic syndrome, quality of life, length of stay **Additional outcomes reported:** thrombocytopenia (not stated if heparin induced thrombocytopenia), **Notes:** * pulmonary embolism diagnosed by ventilation-perfusion scanning, pulmonary angiography, spiral CT scan or MRI $ DVT diagnosed by compression ultrasonography or venography £ major bleeding defined as: intraocular,
			All cause mortality at day 21	**Group 1**: 43/1829 **Group 2**: 42/1807 **Relative risk**: 1.01 (0.66, 1.54)	
			All cause mortality at 90 days	**Group 1**: 107/1747 **Group 2**: 103/1715 **Relative risk**: 1.02 (0.78, 1.33)	
			Fatal pulmonary embolism at day 21 (confirmed by autopsy)	**Group 1**: 0/1829 **Group 2**: 2/1807 **Relative risk**: 0.00	
			Symptomatic pulmonary embolism at day 21 *	**Group 1**: 5/1759 **Group 2**: 4/1740 **Relative risk**: 1.22	
			Symptomatic pulmonary embolism at day 90 *	**Group 1**: 5/1615 **Group 2**: 6/1583 **Relative risk**: 0.82 (0.25, 2.67)	
			Symptomatic distal DVT at day 21 $	**Group 1**: 3/1759 **Group 2**: 4/1739 **Relative risk**: 1.22	
			Symptomatic proximal DVT at day 21 $	**Group 1**: 2/1759 **Group 2**: 7/1739 **Relative risk**: 0.28 ()	
			Asymptomatic proximal DVT at day 21 $	**Group 1**: 27/1507 **Group 2**: 53/1453 **Relative risk**: 0.48 (0.31, 0.77)	
			DVT: any proximal and symptomatic distal at day 21	**Group 1**: 32/1508 **Group 2**: 64/1464 **Relative risk**: 0.49 (0.32, 0.74)	
			Symptomatic VTE at 90 days	**Group 1**: 15/1615 **Group 2**: 21/1583 **Relative risk**: 0.70 (0.36, 1.35)	
			All symptomatic DVT at 90 days	**Group 1**: 10/1614 **Group 2**: 15/1579 **Relative risk**: 0.65 (0.29, 1.45)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	• stroke within previous 3 months • high risk of bleeding • platelet count <100x10⁹/L • heparin or LMWH given for >48 hours before randomisation • contraindication to heparin anticoagulation • creatinine >2.0mg/dL • hepatic insufficiency or active hepatitis • pregnancy or breast feeding • life expectance <1 month **All patients** **N:** 3706 **No. of dropouts:** 25 **Primary Diagnosis Gp1 Gp2** Acute congestive heart failure (NYHA class III or IV) 965 940 Acute respiratory failure 561 560 Infectious disease 673 687 Rheumatological disease 200 198 Inflammatory bowel disease 10 8 **Group I** **No. randomised:** 1848 **No. of dropouts:** 8 **Age (mean):** 68.5 ±11.1 **M/F:** 884/964 **Additional risk factors:** age ≥75 33.1%; cancer 4.6%; previous VTE 3.4%; obesity 30.2%; varicose veins 26.4%; hormone therapy 1.8%; chronic heart failure 50.1%; myeloproliferative syndrome 0.3%, chronic respiratory failure 9.5% **Group II** **No. randomised:** 1833 **No. of dropouts:** 7 **Age (mean):** 68.5 ±11.7		**Major bleeding at day 21 £**	**Group 1:** 9/1759 **Group 2:** 3/1740 **p value:** not significant	spinal/epidural, intracranial or retroperitoneal bleeding; if hemoglobin decreased by ≥2g/dL; if transfusion of ≥2 U of blood or significant medical or surgical intervention required; or it resulted in sudden death.
			Major bleeding at day 14 £	**Group 1:** 8 (unsure of denominator) **Group 2:** 0 (unsure of denominator) **p value:** not significant	
			Fatal bleeding at day 21	**Group 1:** 10/1614 **Group 2:** 15/1579 **Relative risk:** 0.65 (0.29, 1.45)	
			Minor bleeding at day 21	**Group 1:** 19/1759 **Group 2:** 10/1740 **p value:** not significant	
			Minor bleeding at day 14	**Group 1:** 16 (unsure of denominator) **Group 2:** 5 (unsure of denominator) **p value:** not significant	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	M/F: 888/945 **Additional risk factors**: age ≥75 33.6%; cancer 5.7%; previous VTE 4.4%; obesity 30.6%; varicose veins 28.9%; hormone therapy 1.6%; chronic heart failure 51.6%; myeloproliferative syndrome 0.5%, chronic respiratory failure 10%				

LMWH vs no prophylaxis and LMWH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Levi et al., 2007[397] **Country of study:** multicentre- US, Uk, Netherlands etc (20 countries) **Study design:** RCT, equivalence 1:1:2 randomisation of UFH, LMWH, placebo **List who was masked to interventions:** Patients, investigators and all study personnel **Evidence level:** 1+ **Duration of follow-up:** 28 days	**Patient group:** Patient with severe sepsis on drotrecogin alfa (Activated) (Drot AA) **Setting:** Multicentre, inpatient **Inclusion criteria:** 1. Aged ≥18 years old 2. Receiving inpatient treatment for severe sepsis 3. Indicated for DrotAA under an approved label in the country in which the patient enrolled, defined as one or both of the following: - Multiple organ dysfunction (MOD); EMEA label - Patients at higher risk of death (as defined by Acute Physiology Age and Chronic Health Evaluation [APACHE] II scores ≥ 25; US label) **Exclusion criteria:** 1. Contraindicated for treatment with prophylactic LMWH or UFH 2. Required a higher dose of heparin than specified in protocol or concurrent need for other anticoagulant medication 3. Acute or chronic renal failure with estimates creatinine clearance less than 30ml/min 4. Moribund or not expected to survive 28 days 5. Patient or family not committed to aggressive management of severe sepsis **<u>All patients</u>** **N:** 1935 (ITT population. 2002 enrolled, 2 had consent issues, 59 did not receive study drugs) **<u>Group 1 and Group 2</u>** **No. randomised:** 976 **Age (mean):** 59.6±16.1	**Group 1** UFH 5000 U, subcutaneous, every 12 hours **Group 2** LMWH (enoxaparin) 40 mg, subcutaneous, one daily, (a second injection of placebo was administered after 12 hours to maintain blinding of 12 hourly injections. *Group 1 and 2 were combined in many section of the analysis as "heparin"* **Group 3** Placebo Administered twice daily <u>Start:</u> as soon as possible after initiating Drot AA, no more than 12 hours later <u>Stop</u>: Until completion of Drot AA infusion. <u>Duration:</u> 96 hours, during administration of Drot AA. If Drot AA infusion continued beyond Day 4 because of interruptions, study drug injections were continued every 12	**All cause mortality** (for 28 days, cause of death determined by investigator opinion). This was the primary objective of study. 8 patients had unknown 28-day survival status	**Heparin (Group 1 and 2):** 275/972 (28.3) **Group1:**145/495 (29.3%) **Group2:**130/477 (27.3%) **Group3:**305/955 (31.9%) **P value**: (reported) heparin vs placebo=0.08	**Funding:** Eli Lilly (designed and sponsored the study1) **Limitations:** The protocol only covered administration of Drot AA and placebo/heparin in Days 0-6. Any other aspects of care, use of heparin &/or mechanical methods, including the use of heparin after the completion of Drot AA Days 4-6 were at the discretion of the investigators. Subgroup analysis of the study had shown that: among the group of patients who were exposed to heparin at baseline, those randomised to placebo had higher mortality rate than those receiving heparin. **Outcomes not reported:** Fatal PE, Symptomatic PE, PE asymptomatic or symptomatic, symptomatic DVT DVT, asymptomatic or symptomatic Thigh DVT, Calf DVT, Upper GI bleeding, Minor bleeding, post thrombotic syndrome, pulmonary hypertension, Quality of life, Length of stay **Additional outcomes reported:** **Venous thrombotic events:** <u>Days 0-6:</u> **Heparin:** 45/976 **Placebo:** 49/959 **P value:** 0.60
			Fatal bleeding (overt bleeds considered the primary cause of death)	<u>Days 0-6</u> **Heparin:** 1/976 **Placebo:** 3/959 **P value**: 0.31 <u>Days 0-28</u> **Heparin:** 4/976 **Placebo:** 11/959 **P value**: 0.06	
			Major bleeding (described as <u>"serious bleeding events</u>" and included: fatal bleeding &/or non fatal serious bleeding defined as intracranial brain haemorrhage confirmed by brain imaging or autopsy, or bleeding at a critical location [e.g. retinal haemorrhage, major haemorrhage, or spinal haemorrhage] and/or an otherwise life threatening event bleed that did not meet other criteria)	<u>Days 0-6</u> **Heparin:** 22/976 **Placebo:** 24/959 **P value**: 0.72 <u>Days 0-28</u> **Heparin:** 38/976 **Placebo:** 50/959 **P value**: 0.16 Note: Bleeding events which were reported as non serious adverse events that occurred during infusion (Days 0-6) and led to or contributed to the need for transfusion of packed red blood cells were classified as "non serious bleeding events".	
			Neurological bleeding (central nervous system bleeding events)	<u>Days 0-6</u> **Heparin:** 3/976 **Placebo:** 3/959 **P value**: 0.98 <u>Days 0-28</u> **Heparin:** 10/976 **Placebo:** 7/959	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No. of dropouts: **Additional risk factors:** Age ≥65 years: 411/976 Patient history: - Hypertension:378/976 - Recent surgery: 330/976 - COPD: 171/976 - Malignancy: 134/976 - Chronic liver disease: 55/976 - Congestive myopathy 49/976 - Deep vein thrombosis: 32/976 - Pulmonary thromboembolism: 12/976 - APACHE II score: 23.8±7.6 - APACHE≥25: 462/976 **Group 3** **No. randomised:** 959 **Age (mean):** 58.4±16.0 **No. of dropouts:** **Additional risk factors:** Age ≥65 years: 367/959 Patient history: - Hypertension: 356/959 - Recent surgery: 331/959 - COPD: 160/959 - Malignancy: 112 /959 - Chronic liver disease: 52/959 - Congestive myopathy: 46/959 - Deep vein thrombosis: 19/959 - Pulmonary thromboembolism: 13/959 - APACHE II score: 24.0±7.4 - APACHE≥25: 431/959	hours until the infusion was completed. If the 12-hour time point for study drug administration occurred within 2 hours after completion of Drot AA infusion, the final study drug injection was administered then. **Other drugs:** Both groups received Drot AA at 24 microgram/kg/hour for 96 hours, according to local hospital guidelines **Additional non-comparative prophylaxis:** "all other patient care was at the discretion of the investigator, including the use of commercial heparin (commercial use of heparin use during Days 0-6 refers to use in the 1-2 d after Drot AA and study drug administration)". Commercial use of heparin was not statistically significant between treatment arms(data not shown) "The use of		**P value:** 0.49	Days 0-28: **Heparin:** 56/976 **Placebo:** 67/959 **P value:** 0.26 (defined as objectively confirmed non fatal or fatal pulmonary embolism (PE), asymptomatic lower extremity DVT, detected by bilateral compression ultrasonography performed at the end of study drug administration (Study Days 4-6), symptomatic lower extremity DVT confirmed by objective means (ultrasound or other accepted diagnostic modalities) an symptomatic central vein thrombosis, confirmed by objective means) **Ischaemic stroke:** Days 0-6 **Heparin:** 3/976 **Placebo:** 12/959 **P value:** 0.02 Days 0-28 **Heparin:** 5/976 **Placebo:** 17/959 **P value:** 0.01 **Any bleeding event:** Days 0-6 **Heparin:** 105/976 **Placebo:** 78/959 **P value:** 0.049 Days 0-28 **Heparin:** 121/976 **Placebo:** 105/959 **P value:** 0.32 **Notes:** The study was designed to evaluate whether heparin
			Heparin induced thrombocytopaenia	Days 0-6 **Heparin:** 10/976 **Placebo:** 6/959 **P value:** 0.33 Days 0-28 **Heparin:** 12/976 **Placebo:** 11/959 **P value:** 0.87	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
		prophylactic heparin and mechanical methods between Study Days 7-28 were very similar in both groups"- details not reported			interfered with the efficacy of Drot AA in adult patients with severe sepsis at high risk of death. Heparin may have direct therapeutic effects in severe sepsis and disseminated intravascular coagulation independent of their anti thrombotic properties. High doses of heparin lead to higher clearance of DrotAA through increasing the rate of inhibition of activated protein C by protein C inhibitors

LMWH vs no prophylaxis and LMWH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Mahe et al., 2005[418] and Bergmann & Caulin, 1996[44] **Country of study:** France **Study design:** RCT **List who was masked to interventions:** patients **Evidence level:** 1+ **Duration of follow-up:** 21 days or until discharge (mean study period 13.08 (±6.53 days)	**Patient group:** Bedridden medical patients (main conditions at inclusion: acute cardiovascular disease 13%, atrial fibrilation 12%, acute pulmonary disease 22%, cancer 14%, sepsis (not pulmonary) 23%) **Setting:** hospital **Inclusion criteria:** • age >40 • hospitalised for <24 hours before randomisation • immobilised (unable to walk 10m alone **Exclusion criteria:** • conditions that could increase the risk of haemorrhage (systolic blood pressure >240mmHg, active gastroduodenal ulcer, renal failure – creatinine level >300 µmol/1, prothrombin time <50%, platelet level <50,000/mm^3, TCA >control + 10s) • conditions requiring full anticoagulation • stroke or major surgery within previous 30 days • anticoagulant or antiplatelet threapy within last 7 days • pregnancy **All patients** **N:** 2474 **No. of dropouts:** 0 **Group I** **No. randomised:** 1230 **No. of dropouts:** 0 **Age (mean):** 76.1 **M/F:** 42% male **Additional risk factors:** chronic heart failure 26.7%, previous VTE 1.9%, chronic	**Group I** LMWH (nadroparin, 0.3ml (7500 AXa IU)) subcutaneously started within 24 hours of hospitalisation and continued for 21 days or until discharge. **Group II** placebo **Additional non-comparative prophylaxis:** None	**All cause mortality** **Fatal pulmonary embolism by total no. deaths confirmed by autopsy**	**Group 1:** 124/1230 **Group 2:** 128/1244 **P value:** 0.89 **Group 1:** 10/63 **Group 2:** 17/60 **P value:** 0.26	**Funding:** "supported by a grant for Independent Research from Sanofi-Choay" **Limitations:** Only patients appear to be masked to treatment; not reported if allocation to interventions was concealed from patients and participants; only around half of deaths received autopsy **Outcomes not reported:** pulmonary embolism, DVT, major and minor bleeding, heparin induced thrombocytopenia, post-thrombotic syndrome, quality of life, length of stay **Additional outcomes reported:** venous thrombosis diagnosed at autopsy, thrombocytopenia (not stated if heparin induced thrombocytopenia) **Notes:** Study first reported as a letter in 1996 only published as an article in 2005.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	pulmonary disorder 18.5, smoking 15.7%, alcohol abuse 10%, previous stroke 8.5%, recent surgery or trauma (within 1-3 months) 3.7% **Other factors**: **<u>Group II</u>** **No. randomised:** 1244 **No. of dropouts:** 0 **Age (mean):** 76.5 **M/F:** 39% male **Additional risk factors**: chronic heart failure 24.8%, previous VTE 1.9%, chronic pulmonary disorder 17.6, smoking 14.1%, alcohol abuse 8.4%, previous stroke 7.1%, recent surgery or trauma (within 1-3 months) 2.9% **Other factors**:				Study stopped at interim review. Power analysis determine 3000 patients would be needed to show a difference in mortality. However, the investigators concluded that and additional 600 patients to the interim results of 2474 patients would not lead to a difference. Study screened 35,000 patients for inclusion, main reasons for not being included: ability to walk >10m alone (73%), age <40 years (11%), recent anticoagulation (4.5%)

LMWH vs no prophylaxis and LMWH adjuvant studies

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Michot et al., 2002[443]	RCT	1+	Total: 130 Intervention n: 66 Control n: 64	**Type of surgery:** Patients scheduled for diagnostic or therapeutic arthroscopic knee surgery. Surgery was performed expeditiously with a mean duration of 42.3 mins.	**Type, dose and timing:** First dose of subcutaneous LMWH (2500 IU anti-Xa Dalteparin) 60-120 mins before start of procedure. Second weight adapted dose (2500 IU if weight <70 kg, 5000 IU if >70 kg) was given 6 hrs after surgery for up to 30 days post op. **Additional non-comparative prophylaxis**: Not reported	**Type, dose and timing:** No prophylaxis	30 days	**DVT** confirmed by Clinical examination, routine platelet count and bilateral US. If no compression US was available then a venography was performed.	Thromboembolic events **Int:** 1*/66 **Control:** 10/64 **p value:** 0.004	**Pre-existing risk factors:** Family history of VTE/PE: int: 5; Cont: 6. Oestrogen therapy/oral contraceptives: int: 4; Cont: 0. Oral contraceptives smoking : int: 3; Cont: 1. Varicose veins: int: 8; Cont: 9. Preoperative immobility/reduced weight bearing: int: 4; Cont: 4.
				Intervention: Mean age: 42 (SD, 14.7 years) M/F:40/60				**PE** Confirmed by ventilation – perfusion lung scan or a pulmonary angiography.	**Int:** 1*/66 **Control:** 0/64 Same patient with DVT & symptomatic PE	
				Control: Mean age: 46.5 (SD, 13.2 years) M/F:46/54				**Bleeding complications:**	**Int:** 8/66 **Control:** 4/64 **p value:** 0.365	
								Major bleeding	**Int:** 0/66 **Control:** 0/64 **p value:** 0.0559	

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Mismetti et al., 2001[450] 9 studies included [29,53,280,386,423,499,516,517,653] 8 of these studies were included in the guideline review: [29,280,386,423,499,516,517,653]	Systematic review (8 studies)	1+	**Total:** 5520	**Type of surgery:** General (7 studies) Urology (1 study) Not all studies reported on all outcomes.	**Type:** LMWH **Timing:** preoperative 7 studies, post operative 1 study **Duration:** 4-9 days	**Type:** nil or placebo	7 days-9 months	**DVT** (Clinical, confirmed by US or veno/FUT)	**Int:** 9/258 **Cont:** 37/255 **p value:** 0.000	Also reported, wound haematoma, death, but data not given for patient numbers by control/intervention group. Event rates reported here are for all studies as published in the systematic review.
								PE (intervention: both fatalities)	**Int:** 2/2526 **Cont:** 13/2558 **p value:** 0.0073	
								Major Bleeding	**Int:** 75/2710 **Cont:** 337/2746 **p value:** 0.0000	
								Proximal DVT	**Int:** 0/50 **Cont:** 2/50 **p value:** 0.4949	

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Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Osman et al., 2007[504] **Country of study:** Egypt **Study design:** Prospective randomised open label study **List who was masked to interventions:** Open label? **Evidence level:** 1- **Duration of follow-up:** 2 weeks? Not clearly stated	**Patient group:** Non "high risk", isolated, live-donor renal transplantation. **Setting:** Dec 2003 to March 2005. Urology and Nephrology Centre, Mansoura University **Inclusion criteria:** Consecutive, isolated, live-donor renal transplantation operated by the same surgical team **Exclusion criteria:** Categorised as "risky " because - <16 years old - grafts with multiple arteries - a history of thromboembolic disease - artheromatous arteries - collagen vascular disease - intraoperative technical difficulties **All patients** **N:** 75 **M/F:** 52/23 **Group 1 (LMWH)** **No. randomised:** 25 **No. of dropouts:** M/F:14/11 Age (year): 28.3±8 Pre-transplant Hb level: 8.8±2 Ischaemia time (min): 44.7±11 Delayed diuresis: 1/25 Donor gender, M/F:11/14 Donor age (year): 35.9±11 Harvested kidney (right): 10/25 **Group 2 (UFH)**	**Group 1** LMWH Dose: 3500anti-Xa IU in 0.35 ml once daily Duration: 1week **Group 2** UFH Dose: 5000IU, twice daily Duration: 1 week **Group 3** Control Did not receive heparinisation **Additional non-comparative prophylaxis:** Not reported Note: All patients discharged 2 weeks post operatively if no post-operative complications were found	**All cause mortality** (confirmed by: no mortality reported)	**Group1:** 0/25 **Group 2:** 0/25 **Group 3:** 0/25 **P value:** 1.0	**Funding:** None stated **Limitations:** - Open label study - No indication that patients or investigators were blinded – very likely open label study - Method of DVT screening not clearly specified, and frequency of screening not reported. - Duration of follow up not clearly stated **Outcomes not reported:** PE asymptomatic or symptomatic, DVT, asymptomatic or symptomatic, Thigh DVT, Calf DVT, Fatal bleeding, Neurological bleeding, Upper GI bleeding, Minor bleeding, Heparin induced thrombocytopaenia, Post thrombotic syndrome, Pulmonary hypertension, Quality of life, Length of stay
			Fatal pulmonary embolism (confirmed by: screening method and frequency not specified)	**Group1:** 0/25 **Group 2:** 0/25 **Group 3:** 0/25 **P value:** 1.0	
			Symptomatic pulmonary embolism (confirmed by: screening method and frequency not specified)	**Group1:** 0/25 **Group 2:** 0/25 **Group 3:** 0/25 **P value:** 1.0	
			Symptomatic DVT (confirmed by: screening method and frequency not specified)	**Group1:** 0/25 **Group 2:** 0/25 **Group 3:** 0/25 **P value:** 1.0	
			Major bleeding (description: Reoperated. Found to be due to slipped ligature)	**Group1:** 1/25 **Group 2:** 0/25 **Group 3:** 0/25 **P value:** 0.37	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No. randomised: 25 **No. of dropouts:** M/F:19/6 Age (year): 29.4±8 Pre-transplant Hb level: 9.7±1.6 Ischaemia time (min): 46.3±12 Delayed diuresis: 1/25 Donor gender, M/F: 15/25 Donor age (year): 35.3±10 Harvested kidney (right): 10/25 **<u>Group 3 (Control)</u>** **No. randomised:** 25 **No. of dropouts:** M/F:19/6 Age (year): 26±6 Pre-transplant Hb level: 8.6±1.7 Ischaemia time (min): 42.5±8 Delayed diuresis: 2/25 Donor gender, M/F:14/9 Donor age (year): 33±9 Harvested kidney (right): 11/25 Note: The groups were comparable, in all the above variables. However, there was a trend to significance for pretransplant haemoglobin levels, p=0.07				**Additional outcomes reported:** - Graft thrombosis - Number receiving transfusion - Mean transfused units - Haemoglobin drop in non transfused patients - Other transplant related parameters **Notes:**

LMWH vs no prophylaxis and LMWH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Samama et al., 1999[579] MEDENOX study **Country of study:** International: 60 centres in 9 countries **Study design:** RCT **List who was masked to interventions:** Double-blind: Patients and investigators of VTE **Evidence level:** 1+ **Duration of follow-up:** 3 months	**Patient group:** Acutely ill medical patients **Setting:** General medical ward (most patients were not in an intensive care unit) **Inclusion criteria:** Medical patients older than 40 years, whose projected stay in hospital was at least six days and not immobilised for more than three days. Patients had to have congestive heart failure (CHF) (New York Association class III or IV), acute respiratory failure that did not require ventilatory support, or one of the following conditions if it was associated with at least one additional risk factor for VT: acute infection with septic shock, acute rheumatic disorders, acute arthritis of the legs, or an acute episode of rheumatoid arthritis in the legs; or an episode of inflammatory bowel disease. The additional risk factors were age >75 years, cancer, previous VT, obesity (BMI >=30 for men and >=28 for women), varicose veins, hormone therapy (antiandrogen or estrogen, except for postmenopausal hormone-replacement therapy) and chronic heart or respiratory failure. **Exclusion criteria:** Women of childbearing age if pregnant, breast-feeding or not using contraception. Other exclusions were: stroke or major surgery within the previous three months, contraindications to use of iodinated contrast medium; known thrombofilia; a serum creatinine concentration >1.7 mg/dl, intubation, HIV, uncontrolled arterial hypertension, active peptic ulcer, bacterial endocarditis, or other conditions that could increase the risk of hemorrhage; hypersensitivity to heparin or heparin-	**Group 1** LMWH (20 mg Enoxaparin) 20 mg of enoxaparin (Lovenox, Clexane or Klexane, Rhone-Poulenc Rorer, Antony, France) subcutaneously once daily. 20 mg of enoxaparin in 0.2 ml of water for injectable preparations Start time: within 24 after randomisation End time: Treatment scheduled to last 6 to 14 days in the hospital **Group 2** LMWH (40 mg Enoxaparin) 40 mg of enoxaparin (Lovenox, Clexane or Klexane, Rhone-Poulenc Rorer, Antony, France) subcutaneously once daily. 40 mg of enoxaparin in 0.2 ml of water for injectable preparations Start time: within 24 after randomisation End time: Treatment scheduled to last 6 to 14 days in the hospital **Group 3** (Placebo) Placebo (0.2 ml of isotonic water) Start time: within 24 after randomisation End time: Treatment scheduled to last 6 to 14 days in the hospital **Additional non-**	**All cause mortality** (confirmed by:)	**Treatment period (days 1-14)** **Group 1:** 15/351 **Group 2:** 12/360 **Group 3:** 16/362 P: NR **Study period (days 1-110)** **Group 1:** 51/351 **Group 2:** 41/360 **Group 3:** 50/362 **RR (95% CI)** as compared with placebo: Group 1: 1.05 (0.71-1.56) p= 0.80 Group 2: 0.83 (0.56-1.21) p=0.31	**Funding:** Supported by grant from Rhone-Poulenc Rorer (France) **Limitations:** A number of patients were not included in the analyses for primary and secondary outcomes. Reasons below **Outcomes not reported:** pulmonary hypertension, heparin-induced thrombocytopenia; post thrombotic syndrome, quality of life, length of stay **Additional outcomes reported:** Local reaction at injection site (hematoma>5 cm in diameter); any thrombocytopaenia **Notes:** * (description: If bleeding was overt and was associated with the need for transfusion of two or more units of packed red cells or whole blood or with a decrease in the hemoglobin concentration of 2.0 g per decilitre or more from baseline or if bleeding was retroperitoneal, intracranial, or fatal)
			Fatal pulmonary embolism (confirmed by autopsy)	**Primary outcome (VT between days 1-14)** **Group 1:** 0/287 **Group 2:** 0/291 **Group 3** 0/288 P: NR **Secondary outcome (VT between days 1-110)** **Group 1:** 1/263 **Group 2:** 2/272 **Group 3:** 1/263 **P value:** NR	
			Symptomatic pulmonary embolism (confirmed by: not reported)	**Reported in text: by day 14** **Group 1:** 1/287 **Group 2:** 0/291 **Group 3:** 3/288 **P value:** NR	
			Pulmonary embolism, asymptomatic or symptomatic (confirmed by high-probability lung scanning, pulmonary angiography, or helical computed tomography or at autopsy)	**Primary outcome (VT between days 1-14)** **Group 1:** 1/287 **Group 2:** 0/291 **Group 3** 3/288 **P value:** NR **Secondary outcome (VT between days 1-110)** **Group 1:** 1/263 **Group 2:** 0/272 **Group 3:** 3/263 **P value:** NR	
			Symptomatic DVT (confirmed by: not reported)	**Primary outcome (VT between days 1-14)** **Group 1:** 3/287 **Group 2: :** 1/291 **Group 3:** 2/288 **Secondary outcome (VT between days 1-110)** **Group 1:** 6/263	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	induced thrombocytopenia; or platelet count < 100,000/mm^3 a prolonged activated partial-thromboplastin time, a prothrombin ratio of less than 50 percent, or an international normalized ratio of more than 1.2. Patients who required anticoagulant therapy and those who received any type of anticoagulant therapy for more than 48 hours. **<u>All patients</u>** **N:** 1,102 **No. of dropouts:** There were 236 patients not evaluated for the primary outcome (VT defined as DVT, PE, or both between days 1 and 14) and 71 patients were not evaluated for the secondary outcome (VT between days 1 and 110) reasons included in table 1. **<u>Group 1</u>** <u>(20 mg Enoxaparin)</u> **No. randomised:** 364 **No. of dropouts** No. evaluated for primary outcome: Evaluated: 287 (78.8%) Not evaluated: 77 (21.2%) No. evaluated for secondary outcome: Evaluated: 263 (72.3%) Not evaluated: 25 (6.9%) **Age (mean +/- SD):** 72.9 +/- 10.1 **M/F:** 187/176 **Reasons for hospitalisation-no. (%):** NYHA class III CHF: 76 (20.9) NYHA class IV CHF: 44 (12.1) Acute respiratory failure: 192 (52.9) Acute infectious disease: 194 (53.4) Acute rheumatic disorder: 40 (11.0) Inflammatory bowel disease: 1 (0.3) **Additional risk factors- no. (%):** Age>75 yr: 172 (47.4) Cancer (previous or current): 56 (15.4) History of VT: 35 (9.6) Obesity: 79 (21.8) Varicose veins: 88 (24.2)	**comparative prophylaxis:** Elastic bandages or support stockings, and physiotherapy were used according to the usual practice at each centre. Throught the treatment period, intramuscular injections and treatment with nephrotoxic substances, particularly nephrotoxic antibiotics, were not permitted. Centres were advised to avoid giving patients nonsteroidal anti-inflammatory drugs		**Group 2: :** 3/272 **Group 3:** 4/263	Reasons for patients not evaluated for primary outcome, analysis of VTE at 14 days: death 28/236; patient's refusal 62/236, investigator's decision 62/236, venography technically unfeasible 12/236, venogram could not be evaluated 72/236, unknown, venography not performed 10/236 Reasons for patients not evaluated for secondary outcome, analysis of VTE at 110 days: death 61/71; loss to follow up or scheduled visit before 90 days 10/71
			DVT, asymptomatic or symptomatic (confirmed by systematic ascending contract venography of the legs between days 6 and 14, or earlier if thrombosis was clinically suspected. If venography was infeasible venous ultrasonography was performed.)	**Primary outcome (VT between days 1-14)** **Group 1:** 42/287 **Group 2: :** 16/291 **Group 3:** 41/288 **RR (95% CI)** as compared with placebo: Group 1: 1.05 (0.71-1.57) p= 0.81 Group 2: 0.40 (0.23-0.69) p<0.001 **Secondary outcome (VT between days 1-110)** **Group 1:** 44/263 **Group 2: :** 17/272 **Group 3:** 42/263 **RR (95% CI)** as compared with placebo: Group 1: 1.07 (0.73-1.58) p= 0.81 Group 2: 0.40 (0.23-0.69) p<0.001	
			Thigh DVT Reported in table described as proximal deep-vein thrombosis. Confirmed by see above	**Primary outcome (VT between days 1-14)** **Group 1:** 13/287 **Group 2:** 5/291 **Group 3:** 14/288 **RR (95% CI)** as compared with placebo: Group 1: 0.93 (0.45-1.94) p=0 1 Group 2: 0.35 (0.13-0.97) p=0.04 **Secondary outcome (VT between days 1-110)** **Group 1:**14/263 **Group 2:** 6/272 **Group 3:** 17/263 **RR (95% CI)** as compared with placebo: Group 1: 0.83 (0.42-1.64) p= 0.71 Group 2: 0.34 (0.14-0.86) p=0.02	
			Calf DVT Reported in table described as distal deep-vein thrombosis. Confirmed by see above	**Primary outcome (VT between days 1-14)** **Group 1:** 30/287 **Group 2: :** 11/291 **Group 3:** 27/288 G **Secondary outcome (VT between days 1-110)** **Group 1:** 31/263 **Group 2:** 12/272 **Group 3:** 27/263	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Hormone therapy: 8 (2.2) Chronic heart failure: 106 (29.2) Chronic respiratory failure: 197 (54.3) >=2 Risk factors 241 (66.4) **Group 2** (40 mg Enoxaparin) **No. randomised:** 367 **No. of dropouts:** No. evaluated for primary outcome: Evaluated: 291 (79.3) Not evaluated 76 (20.7%) No. evaluated for secondary outcome: Evaluated: 272 (74.1%) Not evaluated: 20 (5.4%) **Age (mean):** 73.1 +/- 10.8 **M/F:** 171/196 **Reasons for hospitalisation-no. (%):** NYHA class III CHF: 103 (28.1) NYHA class IV CHF: 26 (7.1) Acute respiratory failure: 195 (53.1) Acute infectious disease: 197 (53.7) Acute rheumatic disorder: 28 (7.6) Inflammatory bowel disease: 3 (0.8) **Additional risk factors- no. (%):** Age>75 yr: 185 (50.4) Cancer (previous or current): 45 (12.3) History of VT: 30 (8.2) Obesity: 72 (19.6) Varicose veins: 98 (26.7) Hormone therapy: 5 (1.4) Chronic heart failure: 123 (33.5) Chronic respiratory failure: 195 (53.1) >=2 Risk factors: 245 (66.8) **Group 3** (Placebo) **No. randomised:** 371 **No. of dropouts:** No. evaluated for primary outcome: Evaluated: 288 (77.6 %) Not evaluated: 83 (22.4%)		**Fatal bleeding** (description:)	**Treatment period (days 1-14)** **Group 1:** 0/351 **Group 2:** 1/360 **Group 3:** 0/362 P value not reported Study reports NS difference between groups **Study period (days 1-110)** **Group 1:** 1/351 **Group 2: :** 2/360 **Group 3:** 0/362 P value not reported Study reports NS difference between groups	
			Major bleeding *	**Treatment period (days 1-14)** **Group 1:** 1/351 **Group 2:** 6/360 **Group 3:** 4/362 P value not reported Study reports difference NS **Study period (days 1-110)** **Group 1:** 4/351 **Group 2:** 12/360 **Group 3:** 7/362 P value not reported Study reports difference NS	
			Minor bleeding (description: Overt but did not meet the other criteria for major bleeding)	**Treatment period (days 1-14)** **Group 1:** 40/351 **Group 2:** 39/360 **Group 3:** 27/362 P value not reported Study reports difference NS **Study period (days 1-110)** **Group 1:** 57/351 **Group 2:** 51/360 **Group 3:** 45/362 P value not reported Study reports difference NS	
			Venous thromboembolic events (defined as DVT, PE or both)	**Primary outcome (VT between days 1-14)** **Group 1:** 43/287 **Group 2:** 16/291 **Group 3:** 43/288 **RR (95% CI)** as compared with placebo: Group 1: 1.02 (0.70-1.51) p= 0.90 Group 2: 0.37 (0.22-0.63) p<0.001 **Secondary outcome (VT between days 1-110)** **Group 1** (20 mg Enoxaparin):46/263	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No. evaluated for secondary outcome: Evaluated: 263 (70.9%) Not evaluated: 26 (7.0 %) **Age (mean):** 74.1 +/- 10.6 **M/F:** 192/178 **Reasons for hospitalisation-no. (%):** NYHA class III CHF: 95 (25.7) NYHA class IV CHF: 32 (8.6) Acute respiratory failure: 202 (54.6) Acute infectious disease: 193 (52.2) Acute rheumatic disorder: 32 (8.6) Inflammatory bowel disease: 1 (0.3) **Additional risk factors- no. (%):** Age>75 yr: 197 (53.2) Cancer (previous or current): 56 (15.1) History of VT: 39 (10.5) Obesity: 71 (19.2) Varicose veins: 93 (25.1) Hormone therapy: 9 (2.4) Chronic heart failure: 124 (33.5) Chronic respiratory failure: 197 (53.2) >=2 Risk factors: 247 (66.8)			**Group 2:** 19/272 **Group 3:** 45/263 **RR (95% CI)** as compared with placebo: Group 1: 1.02 (0.70-1.49) p= 0.91 Group 2: 0.41 (0.25-0.68) p<0.001	
			DVT and PE	**Primary outcome (VT between days 1-14)** **Group 1:** 1/287 **Group 2:** 0/291 **Group 3** (Placebo): 1/288 **Secondary outcome (VT between days 1-110)** **Group 1:** 1/263 **Group 2:** 0/272 **Group 3:** 1/263	
			Thrombocytopaenia (Thrombocytopenia was defined as a decrease in the platelet count of less than 100,000/mm^3. Thrombocytopenia was considered severe if the platelet count was less than 50,000/mm^3	**Treatment period (days 1-14)** **Group 1:** 10/351 (4 related to treatment) **Group 2:** 8/360 (2 related to treatment) **Group 3:** 3/362 (8 related to treatment) P value not reported Study reports NS difference **Severe thrombocytopenia:** **Group 1:** 0/351 **Group 2:** 0/360 **Group 3:** 3/362 **Study period (days 1-110)** **Thrombocyotpenia:** **Group 1:** 10/351 **Group 2:** 8/360 **Group 3:** 13/362 **Severe thrombocytopenia:** **Group 1:** 0/351 **Group 2:** 0/360 **Group 3:** 3/362 P value not reported Study reports NS difference	

LMWH vs no prophylaxis and LMWH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Weber et al., 2008[681] **Country of study:** Switzerland **Study design:** RCT **List who was masked to interventions:** No one **Evidence level:** 1+ **Duration of follow-up:** 3 months	**Patient group:** Palliative Care Patients **Setting:** Centre of continuous care **Inclusion criteria:** Consecutive cancer patients admitted to the centre of continuous care with an estimated life expectancy inferior to 6 months **Exclusion criteria:** Patients with absence of judgement ability precluding to sign written informed consent, VTE during the past 6 months, active bleeding, creatinine clearance <20ml/min, thrombocytopenia <50 G/l, past history of heparin thrombocytopedia, partial thromboplastin time (PTT) >45s, prothrombin time (TP) <35% and concomitant anti-coagulation treatment on admission were excluded from this study **<u>All patients</u>** **N:** 20 **Age (mean):** 70.0 **M/F:** 10/10 **Additional risk factors:** Duration of cancer (months): 18 WHO performance Status: 2.5 Functional Independence Measure Score (max 126): 123 Mini Mental State (MMS) score (max 30): 28 **<u>Group 1</u>** **No. randomised:** 10 **No. of dropouts:** 0 **<u>Group 2</u>** **No. randomised:** 10 **No. of dropouts:** 0	**Group 1** LMWH (Nadroparine) Start time: unclear End time: unclear Duration: unclear Dose: 0.3ml (2850 U of anti-Xa) for patients <70kg 0.4ml (3800 U for anti-Xa) for patients >70kg **Group 2** No prophylaxis **Additional non-comparative prophylaxis:** None mentioned	**All Cause Mortality** (at 3 months) **Symptomatic Pulmonary Embolism** (confirmed by: spiral computed tomography) **Symptomatic Deep Vein Thrombosis** (confirmed by: doppler ultrasound) **Major bleeding:** (rectorrhagia) **Minor bleeding:**	**Group 1:** 5/10 **Group 2:** 9/10 **p value =** 0.141 **Group 1:** 1/10 **Group 2:** 0/10 **p value =** 1.00 Group 1: 1/10 Group 2: 0/10 **p value =** 1.00 **Group1:** 1/10 **Group 2:** 0/10 **p value =** 1.00 **Group 1:** 0/10 **Group 2:** 2/10 **P value =** 0.474	**Funding:** Not stated **Limitations:** Open randomised trial No method of randomisation mentioned Power calculation indicated 389 in each group would be required but only 20 were recruited. **Outcomes not reported:** PTS, pulmonary hypertension, QoL, LoS **Additional outcomes reported:** None **Notes:**

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Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Wirth et al., 2001[699]	RCT	1+	**Total:** 239 **Intervention** n: 117 **Control** n: 122	**Type of surgery:** Patients scheduled for arthroscopic knee surgery. Surgery was performed expeditiously with a mean duration of 34 mins (± 38 mins). **Intervention:** Mean age: 37.6 (SD, ±13.0 years) M/F:81/36 **Control:** Mean age: 38.5 (SD, ±11.6 years) M/F:98/24 **Pre-existing risk factors:** No risk factors: **Int:** n = 73 **Control:** n = 77 1 risk factor: **Int:** n = 42 **Control:** n = 39 2 risk factors: **Int:** n = 2 **Control:** n = 6	**Type, dose and timing:** One dose daily of subcutaneous LMWH (1750 IU anti-Xa Reviparin) for 7-10 days after surgery? **Additional non-comparative prophylaxis:** Not reported	**Type, dose and timing:** No prophylaxis	7 - 10 days	**DVT** confirmed by compression colour - coded US.	**Int:** 1/117 **Control:** 5/122 **p value:** 0.2134	
								PE Confirmed by ?	**Int:** 0/117 **Control:** 0/122 **p value:** N/A	
								Major bleeding	**Int:** 0/117 **Control:** 0/122 **p value:** N/A	
								Minor bleeding	**Int:** 3/117 **Control:** 1/122 **p value:** 0.3616	
								Hospital stay:	**Int:** 1.5/117; SD ±1.9 **Control:** 1.3/122; SD ±2.8 **p value:** 0.7326	

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Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Zuffrey et al., 2003[719] 13 studies 316,330,379-381,388,399,573,613,638,650,673,705 9 of these studies were included in the guideline review: 316,330,380,381,388,613,638,650,705	Systematic Review	1+	**Total:** 1925 Int:928 Cont:940 **Note:** 2 studies did not give total distribution of randomised patients and only gave number for those that had detection test.	**Type of surgery:** Hip fracture: 3 studies Knee surgery: 2 studies Hip replacement 8 studies	**LMWH:** (Enoxaparin, certoparin, tinzaparin, dalteparin, nadroparin, ardeparin) **Doses:** Ranged from 3000 anti-Xa IU to over 6000 anti-Xa IU. **Timing:** Treatment started preoperatively in 9 studies and postoperatively in 4 studies. The treatment varied from 3 to 14 days **Additional non-comparative prophylaxis:** Not reported	**Placebo** (11 studies) or **No treatment** (2 studies) **background:** GCS in 4 studies. electrical stimulation 2 studies	Studies ranged from 6 to 14 days follow-up.	**DVT** confirmed by fibrinogen or plasminogen uptake test, duplex US or venography.	**Int:** 199/823 **Cont:** 416/835 RR=0.51, 95% CI 0.45-0.59; **p value:** <0.001	**Not reported:** QoL, LoS, PTS and funding. **Note:** RR and CI reported by SR authors. Event rates reported here are for all studies as published in the systematic review.
								Proximal DVT	**Int:** 66/779 **Cont:** 163/760 RR=0.35, 95% CI 0.21 – 0.57; **p value:** <0.001 (reported from 11 studies)	
								Major bleeds (defined as major haemorrhage)	**Int:** 7/550 **Cont:** 10/555 RR=0.80, 95% CI 0.36-1.79; **p value:** =0.58 (reported from 7 studies)	
								PE	**Int:** 4/344 **Cont:** 8/379 (reported from 5 studies) **p value:** 0.3905	

Evidence Table 27: UFH vs no prophylaxis and UFH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Anon, 1973[2] **Country of study:** US **Study design:** RCT **List who was masked to interventions:** Patients only Outcome assessment **Evidence level:** 1+ **Duration of follow-up:** 28 days	**Patient group:** Myocardial Infarction (MI) **Setting:** Unclear **Inclusion criteria:** Diagnosis of myocardial infarction of was based on a history of chest pain together with the presence of Q waves, S-T segment and T waves changes characteristic of acute MI, or S-T segment and T-wave changes without characteristic Q waves but with changes in serum enzyme values compatible with acute MI. **Exclusion criteria:** • Complicating rheumatic, syphilitic, or congenital heart disease; a tendency to bleed; • severe liver disease; • severe hypertension; • severe renal disease; • ulcerative disease of the gastrointestinal tract; • severe psychiatric or neurological disease; • diabetes mellitus difficult to control or with serious complications; • serious concurrent disease such as malignant neoplasm that might influence prognosis; • immediate postoperative or posttraumatic stroke; • current treatment with anticoagulants • Age of more than 75 years **<u>All patients</u>** **N:** 1037 **No of dropouts:** 38 10 dropped out, 17 had incorrect diagnosis of MI	**Group 1** Unfractionated Heparin (sodium) and warfarin sodium (Coumadin) Dose and frequency: **Heparin:** 10,000U subcutaneously every 8-12 hours Dose adjusted to produce a clotting time twice normal immediately before the following dose. End time: when prothrombin time reached 25 seconds or longer. **Warfarin:** Dose adjusted to maintain a prothrombin time of 25 to 30 seconds. (average daily dose was 9mg) Start time: at the same time as heparin End time: 28 days **Group 2** Placebo resembling heparin and warfarin. No details given about how the placebo was administered. **Additional non-comparative prophylaxis:** No information	**All cause mortality** NB. A breakdown of cause of death is provided but study does not indicate how reasons were determined.	**Group1:** 48/500 **Group 2:** 56/499 **P value:** 0.409*	**Funding:** No information provided. **Limitations:** All study participants are male. Clinician was not blinded to the study Protocol changed to complete lung scans for all rather than just symptomatic patients during the trial which could lead to bias. **Outcomes not reported:** DVT, neurological bleeding, minor bleeding, post thrombotic syndrome, heparin induced thrombocytopaenia, pulmonary hypertension, quality of life, length of stay **Additional outcomes reported:** Recurrent myocardial infarction, Congestive Heart failure, successful cardiac resuscitation, length of stay until death, stroke, renal emboli, Mesenteric embolism, thrombophlebitis **Notes:** * Calculated by the NCC team using
			Fatal pulmonary embolism	**Predominant cause of death results** (no information about how this was assessed) **Group1:** 0/500 **Group 2:** 2/499 **P value:** 0.249* **Autopsy results indicating presence of PE** **Group1:** 0/23 **Group 2:** 10/31 **P value:** 0.003*	
			Symptomatic pulmonary embolism (confirmed by: Chest roentgenograms, ECGs, appropriate laboratory studies and repeated lung scans after injection of radioactive albumin macroaggregates on patients believed to have PE. Later in the study all patients (condition permitting) were scanned but asymptomatic events were not recorded.)	**Certain** **Group1:** 1/500 **Group 2:** 13/499 **P value:** 0.001 **Probable** **Group1:** 9/500 **Group 2:** 11/499 **P value:** 0.660* **Suspected** **Group1:** 4/500 **Group 2:** 11/499 **P value:** 0.074	
			Fatal Bleeding	**Group1:** 0/500 **Group 2:** 0/499 **P value:** NS	
			Major bleeding (description: Gross haematuria or 'other major bleed [1 case in treated group])	**Group1:** 10/500 **Group 2:** 3/499 **P value:** 0.090*	
			Upper GI bleeding	**Group1:** 3/500 **Group 2:** 3/499 **P value:** NS	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	2 severe complicating illness 2 developed MI following surgery 3 randomised >3 days after admission 3 other reasons **Age (mean):** No mean age given 21-40 49 41-50 275 51-60 364 61-70 152 71-75 103 >75 56 **M/F:** All male **Additional risk factors:** Gp1 Gp2 Previous infarction 1 104 104 2 or more 19 29 Angina pectoris 250 274 Hypertension 111 129 Congestive heart failure 36 48 Stroke 24 24 Peripheral vascular disease 52 38 Diabetes 54 77 Chronic pulmonary disease 68 65 Peptic ulcer 57 63 Liver disease 11 17 Renal disease 35 47 Thrombophlebitis of PE 13 9 **Group 1** **No. randomised:** 500 **No. of dropouts:** unclear **Group 2** **No. randomised:** 499 **No. of dropouts:** unclear	provided about additional prophylaxis.			Fisher Exact test.

UFH vs no prophylaxis and UFH adjuvant studies

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Ballard et al., 1973[30]	RCT	1+	**Total:** 110 Intervention: n = 55 Control: n = 55	**Type of surgery:** Elective major gynaecological surgery (& Duration of surgery)	**Type:** 5000 units of Calciparine (Laboratoire Choay, Pairs) or sodium heparin by deep subcutaneous injection	**Type:** no heparin	7 days post-operatively	**DVT** Confirmed by: ^{125}I-labelled fibrinogen	**Int:** 2/55 **Control:** 16/55 **p value:** <0.001	**Not reported:** PE PTS bleeding QoL **Funding:** not reported
				Intervention: Mean age: 53.1±9.9 yrs M/F: not reported	**Timing:** started 1 to 2 hours preoperatively and every 12 hours for 7 days..	**Timing:** n/a		**Distal DVT** Confirmed by: ^{125}I-labelled fibrinogen	**Int:** 2/55 **Control:** 16/55 **p value:** <0.001	
				Control: Mean age: 50.4±8.7 M/F: not reported	**Additional non-comparative prophylaxis:** routine postoperative exercises and physiotherapy, with mobilisation on the second or third day post-operatively 24/55 had epidural anaesthesia	**Additional non-comparative prophylaxis:** routine postoperative exercises and physiotherapy, with mobilisation on the second or third day post-operatively 21/55 had epidural anaesthesia				
				Pre-existing risk factors: Sever varicose veins: Int: 10/55 Cont: 14/55 not significant No. patients above interquartile weight for height: Int: 20/40 Cont: 27/42					

UFH vs no prophylaxis and UFH adjuvant studies

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Beisaw et al[39]	RCT	1+	**Total:** 128 **Intervention:** n = 65 **Control:** n = 63 148 randomised (11 intervention and 9 control excluded)	**Type of surgery:** Total hip replacement (& Duration of surgery)	**Type:** LDUH **Dose:** 5000 IU	**Type:** Placebo	**Both groups:** 7th-9th day post-op	**DVT** Confirmed by: I125 FUT daily until patient completed study. Venography on final day (earlier if FUT positive)	**Efficacy analysis:** **Int:** 16/65 **Control:** 34/65 **p value:** 0.0021 **Intention to treat:** (Venograms available for 136 patients) **Int:** 16/69 **Control:** 34/67 **p value:** 0.0013	**Also reported: Intraoperative blood loss,** **Not reported: N/A**
				Intervention: Mean age: 64 (range 43-81) yrs M/F:26/37	**Timing:** Begun 2hrs pre-op and repeated three times daily for at least 7 days (patients hospitalised for longer than 7 days were treated for up to two additional days).	**Timing:** Same schedule as intervention group		**PVT** Confirmed by: as above	**Int:** 3/63 **Control:** 12/65 **p value:** 0.0255	
				Control: Mean age: 66.2 M/F:26/39				**PE** Confirmed by: Clinical suspicion investigated by "scans of the lungs".	**Int:** 0/63 **Control:** 2/65 **p value:** 0.0003	
				Pre-existing risk factors: Obesity, previous fracture, varicose veins, previous DVT (no significant differences between groups).	**Additional non-comparative prophylaxis:** Not reported	**Additional non-comparative prophylaxis:** Not reported				

UFH vs no prophylaxis and UFH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Belch et al., 1981BELCH1981} **Country of study:** UK **Study design:** RCT **List who was masked to interventions:** No one **Evidence level:** 1+ **Duration of follow-up:** 14 days or until discharge (mean duration 8-9 days)	**Patient group:** Patients with cardiac failure and/or chest infection Gp1 Gp2 Heart Failure 21 17 Chest infection 18 19 Both 11 14 **Setting:** Department of medicine **Inclusion criteria:** patients admitted with heart failure and/or chest infection. • Heart failure defined as 2 or more of: raised jugular venous pressure, cardiomegaly, pulmonary edema or systemic edema. • Chest Infection defined as 2 or more of: fever, purulent sputum, or clinical and radiological signs of chest infection **Exclusion criteria:** Patients less than 40 or over 80 years old, patients with iodine sensitivity, those with a definite risk of bleeding, and those with a DVT or pulmonary embolus on admission or who had been confined to bed for more than 2 days prior to admission. **<u>All patients</u>** **N:** 100 **Age (mean):** Gp1: 66.6 Gp2: 65.0 **M/F:** 69: 31 **Additional risk factors:** Gp1 Gp2 Smokers/non smokers 32:18 39:21 Severity Gp1 Gp2 Moderate 40 39 Severe 10 11 Drugs Gp1 Gp2 Digoxin 7 9	**Group 1** Unfractionated Heparin (sodium) Start time: within 12 hrs of admission End time: Until mobile. Duration: information not provided Dose, and frequency: 5000U subcutaneously 8 hourly until mobile **Group 2** No prophylaxis **Additional non-comparative prophylaxis:** No details of any other prophylaxis provided.	**Symptomatic pulmonary embolism** (confirmed by: ventilation/perfusion lung scans) **DVT, asymptomatic or symptomatic** (screened for by: radiofibrinogen uptake test)	**Group1:** 0/50 **Group 2:** 2/50 **P value:** 0.495* **Group1:** 2/50 **Group 2:** 13/50 **P value:** 0.004*	**Funding:** Leo laboratories (pharmaceutical company) provided the heparin. **Limitations:** Paper did not present the number of participants randomised and details of any excluded patients. No information regarding randomisation method, allocation concealment is provided in the paper. The study is not blinded to treatment allocation. **Outcomes not reported:** All cause mortality, Fatal pulmonary embolism, all pulmonary embolism, Fatal and major bleeding, neurological bleeding, upper GI bleeding, post thrombotic syndrome, heparin induced thrombocytopaenia, pulmonary hypertension, quality of life, length of stay. **Additional outcomes reported:** Bruising at injection site, haemoglobin, blood urea and white cell count.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Diuretic 19 21 Antibiotic 7 10 Bronchodilator 15 10 Systemic edema 17 16 Obesity 11 11 Varicose veins 4 5 **Group 1** **No. randomised:** 50 **No. of dropouts:** unclear (none?) **Group 2** **No. randomised:** 50 **No. of dropouts:** unclear (none?)				**Notes:** * Calculated by the NCC team using Fisher Exact Test

UFH vs no prophylaxis and UFH adjuvant studies

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Christensen et al 1989[110]	RCT	1+	**Total:** 55 **Intervention:** n = 28 **Control:** n = 27 72 patients randomised	**Type of surgery:** Total hip replacement (& Duration of surgery) **All patients:** Median age: 70 (range 348-80) yrs M/F:21/34 No differences between the groups in age or sex	**Type:** LDUH (+DHE) **Dose:** 5000 IU (0.5 mg)	**Type:** Placebo	**Both groups:** clinical exam 3 months post-op	**DVT** Confirmed by: Tc plasmin test, confirmed by ascending venography on 2nd and 7th post-op day.	**Int:** 3/28 **Control:** 3/27 **p value:** 0.648	**Comments:** No further thromboembolic events were detected at 3 month follow up clinical exam
					Timing: Begun one hour pre-op and repeated twice daily for 7 days	**Timing:** Not reported		**PE** Confirmed by: All patients received V/Q on 2nd and 7th post-op day	**Int:** 1/28 **Control:** 1/27 **p value:** 1.000	**Not reported:** PVT, PTS, QoL, survival, LoS, funding
					Additional non-comparative prophylaxis: All patients wore thigh-length stockings until full ambulation	**Additional non-comparative prophylaxis:** All patients wore thigh-length stockings until full ambulation		**Bleeding related complications** Peri and post-operative blood loss: not defined	**Mean blood loss:** **Int:** 865ml **Control:** 902 ml **p value:** 0.79 Not significant	

UFH vs no prophylaxis and UFH adjuvant studies

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Clarke-Pearson et al., 1990[115]	RCT	1+	Total: 324 Int 1: n = 104 Cont: n = 103 (3rd arm n = 97 not included)	**Type of surgery:** major abdominal or pelvic surgical procedure for gynaecological malignancy (radical vulvectomy or pelvic exenteration). Patients stratified by risk factor.	**Type:** UFH (Calciparine) 5000 units in 1mL volume every 8 hours	**Type:** no treatment	7 postoperative days for intervention, followed clinically for 30 postoperative days	**DVT** Confirmed by: FUT.	**Int:** 9/104 **Control:** 19/103 **p value:** 0.04	**Comments:** 20 patients dropped out after randomisation mainly due to operation cancellation. None developed evidence of DVT or PE No additional prophylaxis used. **Other outcomes reported:** retroperitoneal suction output; no. with postoperative haematocrit <30%; wound separation; lymphocyst. **Not reported:** PTS, QoL, survival. length of hospital stay, funding.
								Bilateral DVT Confirmed by: FUT.	Int: 2/104 Control: 4/103 **p value:** 0.4451	
				Intervention: Median (range) age: 61.5 (43-85) yrs M/F: not reported	**Timing:** Started 2 hours preoperatively then every 8 hours for 7 days postoperatively.			**Symptomatic PE** Confirmed by: pulmonary arteriography	**Int:** 2/104 **Control:** 0/103 **p value:** 0.4976	
				Control: Median (range) age: 60 (40-84) yrs M/F: not reported	**Type (3rd arm):** UFH (Calciparine) 5000 units in 1mL volume			**Fatal PE**	Int: 0/104 **Control:** 0/103 **p value:** N/A	
				Pre-existing risk factors: Past history of DVT or PE Int: 5 Control: 3 3rd arm: 3 **Excluded:** past history of bleeding diathesis; thromboembolism within previous 3 months; warfarin or heparin treatment within previous 6 weeks	**Timing:** First dose immediately after randomisation then every 8 hours up to surgery. Because of differing lengths of preoperative stay patients in this group received varying numbers of doses: 14 received 2 doses 82 received 3-6 doses 2 received 8 or 9 doses **Additional non-comparative prophylaxis:** Not reported			**Postoperative thrombocytopenia**	**Int:** 6/104 **Control:** 12/103 **p value:** 0.1472	
								Median (range) estimated blood loss ml	**Int:** 500 (50-4520) ml **Control:** 500 (10-6000) **p value:** not significant	
								Intraoperative and postoperative transfusions	**Int:** 0 (0-6) U **Control:** 0 (0-24) U **p value:** not significant	

UFH vs no prophylaxis and UFH adjuvant studies

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Collins 1988 (74 studies included) [5-7,14,40,41,51,54,93,101,113,119,137,151,153,166,166,204,208,209,230,238,239,249,266,319,326,337,340-344,360,364,364-366,368,370-373,385,385,406,409,410,416,421,424,462,464,465,486,528,552-554,568,569,585,596,615,629,631,633,639,641,655,657-659,666,684,695,703,704,718] 63 of these studies were included in the guideline review [5-7,14,40,41,51,54,93,101,113,119,151,153,166,208,209,230,238,249,266,319,326,337,340-344,360,364-366,370-373,385,409,410,416,421,424,464,528,552,553,568,569,585,615,629,631,633,639,641,658,659,68	Systematic Review	1+	**Total:** 15598 **Intervention:** 8112 **Control:** 7486	**Type of surgery:** general, orthopaedic and urological.	**UFH** **Dose**: Subcutaneous and given perioperatively. **Additional non-comparative prophylaxis:** GCS: 8 studies Aspirin: 2 studies Dextran: 1 study IPCD: 1 study	**No prophylaxis** **Additional non-comparative prophylaxis:** GCS: 8 studies Aspirin: 2 studies Dextran: 1 study IPCD: 1 study	Given for 2-16 days or until ambulatory or discharged.	**DVT** confirmed by radiolabelled fibrinogen or scanning	**Int:** 436/3677 **Cont:** 922/3389 **p value:** 0.0000	**Not reported:** Funding, QoL, LoS or PTS. Event rates reported here are for all studies as published in the systematic review.
								PE	**Int:** 74/1840 **Cont:** 104/1837 **p value:** 0.0212	
								Major bleeds	**Int:** 168/4433 **Cont:** 110/4177 **p value:** 0.0027	
								Proximal DVT	**Int:** 54/1563 **Cont:** 114/1563 **p value:** 0.0000	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
4,695,703,704,718										

UFH vs no prophylaxis and UFH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Gallus et al., 1973[209] [Medical patients only] **Country of study:** Canada **Study design:** RCT **List who was masked to interventions:** No one **Evidence level:** 1+ **Duration of follow-up:** Mean follow up 10.6 days	**Patient group:** Paper includes patients admitted for elective surgery, or for emergency surgery after fracture of the femoral neck and medical patients suspected of having myocardial infarction **Setting:** Unclear **Inclusion criteria:** Patients with suspected myocardial infarction **Exclusion criteria:** Patients with a bleeding tendency, iodine allergy or a history of pulmonary embolism or venous thrombosis within the past year. **<u>All patients</u>** **N:** 78 **Age (mean):** Gp 1 Gp2 Mean (range) 65 (44-83) 63 (43-85) **M/F:** 59: 19 **Additional risk factors:** Gp1 Gp2 Myocardial infarction 14 13 Heart failure 11 15 **<u>Group 1</u>** **No. randomised:** 38 **No. of dropouts:** Unclear **<u>Group 2</u>** **No. randomised:** 40 **No. of dropouts:** Unclear	**Group 1** Heparin Start time: within 18 hours of admission End time: until mobile Duration: mean 10.2 days. Dose, and frequency: 5000U of heparin subcutaneously three times daily **Group 2** No treatment **Additional non-comparative prophylaxis:** No details on other prophylaxis.	**DVT, asymptomatic or symptomatic** (screened for by: radioactive fibrinogen scanning)	**Group1:** 1/38 **Group 2:** 9/40 **P value:** 0.014*	**Funding:** Supported in part by an Ontario Provincial Health Research grant. **Limitations:** The paper did not present information on the number of patients who were excluded from the study for any reason. The paper contains no Information about the method of randomisation or steps taken to conceal allocation. No patient or physicians were blinded to treatment. The paper does not present clear information about the number of patients dropping out in each arm, or intention to treat analysis. **Outcomes not reported:** All cause mortality, pulmonary embolism, bleeding, heparin induced thrombocytopaenia, post thrombotic syndrome, pulmonary hypertension, quality of life, length of stay. **Additional outcomes reported:** Activated partial thromboplastin time.,
			Thigh DVT (screened for by: radioactive fibrinogen scanning) Defined as popliteral or femoral vein	**Group1:** 1/38 **Group 2:** 3/40 **value:** 0.616*	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
					bruising on injection **Notes:** * Calculated by the NCC team using Fisher exact test.

UFH vs no prophylaxis and UFH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Gardlund, 1996[212] **Country of study:** Sweden **Study design:** RCT **List who was masked to interventions:** Zelen design so patients and healthcare professionals were unblended by pathologists performing autopsy were unaware of treatment groups **Evidence level:** 1+ **Duration of follow-up:** Up to 60 days	**Patient group:** Patients with infectious disease **Setting:** Departments of infectious disease at 6 hospitals **Inclusion criteria:** Consecutive patients aged 55 years or older admitted to department **Exclusion criteria:** Pre existing anticoagulation treatment, readmission with 60 days of randomisation, ability to be mobile, assessment of contraindications not possible (e.g. patient was comatose and no next of kin available), persistent haemorrhage or increased risk of bleeding complications (e.g. inherited bleeding disorders, platelet count below $70x10^9$ /L, or history or intraocular bleeding), heparin prophylaxis judged to be indicated by the responsible doctor, severe renal failure (requiring dialysis) or liver failure, HIV infection, terminal disease in which active treatment was withheld. **<u>All patients</u>** **N:** 14239 met inclusion criteria but only 11693 randomised **Age (mean):** 75.0 **M/F:** Not given **Additional risk factors:** **Admission diagnosis** **Gp1** **Gp2** Pneumonia 1617 1646 Skin and soft tissue infections 1063 1114 Fever/Sepsis 767 843 Urinary tract infection 560 586 Gastroenteritis 517 505 Upper respiratory tract infection 461 436 Bone/Joint infection 258 253	**Group 1** Unfractionated Sodium Heparin Start time: average delay of 9 hours from admission to starting heparin End time: Hospital discharge or 21 days of treatment, whichever was earliest. Duration: Mean duration 8.2 days (s.d. 7.3) Dose, and frequency: 5000IU subcutaneously every 12 hours. **Group 2** No prophylaxis **Additional non-comparative prophylaxis:** 75 patients in group 1 were treated with anticoagulants; 62 for confirmed or suspected PE or DVT 138 patients in control arm were treated with anticoagulants (no reasons given).	**All cause mortality**	**Group1:** 304/5776 **Group 2:** 333/5917 **P value:** 0.392*	**Funding:** Karolinska Institute, Dalarna Research Institute, TryggHansa Research Foundation and Lovens Lakemedel AB (aka. LEO pharmaceuticals) **Limitations:** High risk patients were excluded from this study. Zelen RCT design. Randomisation method and allocation concealment not mentioned within the paper. Difference between arms of 141 patients 2546 patients eligible but not randomised without reasons. Not all those dying had an autopsy **Outcomes not reported:** Symptomatic PE, DVT, Heparin induced thrombocytopaenia, Post thrombotic syndrome, quality of life, length of stay **Additional outcomes reported:** None **Notes:** * Calculated by NCC team using Fisher' exact
			Fatal pulmonary embolism (defined as: autopsy verified pulmonary embolism of a size likely to lead or contribute to death in a patient without rapidly fatal underlying disease or a vegetative state, and that has probably occurred after admission to the department of infectious diseases)	**Group1:** 15/5776 (194 out of 304 deaths had autopsy) **Group 2:** 16/5917 (189 out of 333 deaths had autopsy) **P value:** 0.853*	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Skin rash/ eruption 144 144 Meningitis 77 70 Liver disease 22 30 Other infectious disease 185 165 Other non-infectious 105 125 **Group 1** **No. randomised:** 5776 No refused consent: 695 No stopping heparin early: - withdrew consent: 245 - risk of bleeding: 88 - anticoagulant treatment: 75 - significant bleeding: 49 - decision to withhold treatment: 27 - other reasons: 31 **Group 2** **No. randomised:** 5917 **No. of dropouts:** 0 This group did not know they were in a trial				test

UFH vs no prophylaxis and UFH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Handley, 1972[251] **Country of study:** UK **Study design:** RCT **List who was masked to interventions:** No one **Evidence level:** 1+ **Duration of follow-up:** 2 weeks	**Patient group:** Myocardial Infarction **Setting:** Coronary Care Units **Inclusion criteria:** Patients admitted with a clinical diagnosis of myocardial infarction **Exclusion criteria:** Severely hypertensive, evidence of an active peptic ulcer, or who have had a previous cerebrovascular accident. **All patients** **N:** 70 **No of dropouts:** 20 (29%) **Age (mean):** No mean given <50 5 50-59 22 60-69 19 70-79 4 **M/F:** 37:13 **Additional risk factors:** Gp 1 Gp 2 Significant Varicose Veins 2 3 Mean Peel prognostic 8.1 10.5 Mean Norris prognostic 4.9 4.7 Obesity 9 7 Mean bed rest (days) 11.3 11.2 **Group 1** **No. randomised:** Not clear no analysed = 26 **No. of dropouts:** ? **Group 2** **No. randomised:** Not clear no analysed = 24 **No. of dropouts:** ?	**Group 1** Heparin Start time: unclear End time: 2 weeks Duration: 2 weeks Dose, and frequency: 5000U intravenously and 7500 units subcutaneously as soon as possible within the first 4 hours of admission Then 7,500 units subcutaneously 12 hourly for 7 days. In the few cases where there was slight prolongation outside the normal range, heparin was reduced to 5000U 12-hourly. **Group 2** No anticoagulants **Additional non-comparative prophylaxis:** All patients remained in bed for at least 8 days and were instructed to exercise their legs (no physiotherapy).	**All Cause Mortality**	Paper reports that 3/70 (4.3%) patients died before the study ended but not clear which group they were randomised to.	**Funding:** British Heart Foundation, Peel Medical Research Trust and Board of Governors of Westminster Hospital. **Limitations:** Trial was not blinded The reasons for the randomised patients who were not included in the analysis were not provided per treatment allocation. Intention to treat analysis was not used. **Outcomes not reported:** All cause mortality, , bleeding, heparin induced thrombocytopaenia, post thrombotic syndrome, quality of life, length of stay **Additional outcomes reported:** None **Notes:** * calculated by NCC team using Fishers exact test. Paper states tat no haemorrhagic episodes that could be attributed to therapy were recorded.
			Symptomatic pulmonary embolism (confirmed by: clinical and radiographic evidence)	**Group1:** 1/26 **Group 2:** 1/24 **P value:** NS*	
			DVT, asymptomatic or symptomatic (confirmed by: radioactive fibrinogen uptake test)	**Group1:** 6/26 **Group 2:** 7/24 **P value:** 0.0.751*	
			Thigh DVT (confirmed by: radioactive fibrinogen uptake test)	**Group1:** 1/26 **Group 2:** 1/24 **P value:** NS*	

UFH vs no prophylaxis and UFH adjuvant studies

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Killewich et al., 1997[345]	RCT	1+	**Total:** 100 Intervention: n = 50 Control: n = 50	**Type of surgery:** Patients undergoing aortic reconstruction for aneurismal or occlusive disease. Mean age 64 (44 to 83) years M/F:71/29	Combination of low dose heparin (5000 units) subcutaneously every 12 hrs and calf length IMC (intermittent mechanical compression) that were applied intra-operatively and continued postoperatively for 7 days or until the patient was fully ambulatory. **Additional non-comparative prophylaxis:** none reported	No prophylaxis **Additional non-comparative prophylaxis:** none reported	**Both groups:** 6 months?	**DVT** Confirmed by: venous duplex ultrasound	**Int:** 1/50 **Control:** 0/50 **p value:** not significant	**Comments:** At day 14 1 pt was scaned because of breathing problems and was detected with iliofemoral DVT **Not reported:** Post thrombotic leg, Bleeding related complications, Quality of Life, Survival

UFH vs no prophylaxis and UFH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Levi et al., 2007[397] **Country of study:** multicentre- US, Uk, Netherlands etc (20 countries) **Study design:** RCT, equivalence 1:1:2 randomisation of UFH, LMWH, placebo **List who was masked to interventions:** Patients, investigators and all study personnel **Evidence level:** 1+ **Duration of follow-up:** 28 days	**Patient group:** Patient with severe sepsis on drotrecogin alfa (Activated) (Drot AA) **Setting:** Multicentre, inpatient **Inclusion criteria:** 4. Aged ≥18 years old 5. Receiving inpatient treatment for severe sepsis 6. Indicated for DrotAA under an approved label in the country in which the patient enrolled, defined as one or both of the following: - Multiple organ dysfunction (MOD); EMEA label - Patients at higher risk of death (as defined by Acute Physiology Age and Chronic Health Evaluation [APACHE] II scores ≥ 25; US label) **Exclusion criteria:** 6. Contraindicated for treatment with prophylactic LMWH or UFH 7. Required a higher dose of heparin than specified in protocol or concurrent need for other anticoagulant medication 8. Acute or chronic renal failure with estimates creatinine clearance less than 30ml/min 9. Moribund or not expected to survive 28 days 10. Patient or family not committed to aggressive management of severe sepsis **<u>All patients</u>** **N:** 1935 (ITT population. 2002 enrolled, 2 had consent issues, 59 did not receive study drugs) **<u>Group 1 and Group 2</u>**	**Group 1** UFH 5000 U, subcutaneous, every 12 hours **Group 2** LMWH (enoxaparin) 40 mg, subcutaneous, one daily, (a second injection of placebo was administered after 12 hours to maintain blinding of 12 hourly injections. *Group 1 and 2 were combined in many section of the analysis as "heparin"* **Group 3** Placebo Administered twice daily <u>Start:</u> as soon as possible after initiating Drot AA, no more than 12 hours later <u>Stop</u>: Until completion of Drot AA infusion. <u>Duration:</u> 96 hours, during administration of Drot AA. If Drot AA infusion continued beyond Day 4 because of interruptions, study	**All cause mortality** (for 28 days, cause of death determined by investigator opinion). This was the primary objective of study. 8 patients had unknown 28-day survival status	**Heparin (Group 1 and 2):** 275/972 (28.3) **Group1:**145/495 (29.3%) **Group2:**130/477 (27.3%) **Group3:**305/955 (31.9%) **P value**: (reported) heparin vs placebo=0.08	**Funding:** Eli Lilly (designed and sponsored the study1) **Limitations:** The protocol only covered administration of Drot AA and placebo/heparin in Days 0-6. Any other aspects of care, use of heparin &/or mechanical methods, including the use of heparin after the completion of Drot AA Days 4-6 were at the discretion of the investigators. Subgroup analysis of the study had shown that: among the group of patients who were exposed to heparin at baseline, those randomised to placebo had higher mortality rate than those receiving heparin. **Outcomes not reported:** Fatal PE, Symptomatic PE, PE asymptomatic or symptomatic, symptomatic DVT DVT, asymptomatic or symptomatic Thigh DVT, Calf DVT, Upper GI bleeding, Minor bleeding, post thrombotic syndrome, pulmonary hypertension, Quality of life, Length of stay **Additional outcomes reported:** **Venous thrombotic events:** <u>Days 0-6:</u> **Heparin:** 45/976
			Fatal bleeding (overt bleeds considered the primary cause of death)	<u>Days 0-6</u> **Heparin:** 1/976 **Placebo:** 3/959 **P value**: 0.31 <u>Days 0-28</u> **Heparin:** 4/976 **Placebo:** 11/959 **P value**: 0.06	
			Major bleeding (described as <u>"serious bleeding events</u>" and included: fatal bleeding &/or non fatal serious bleeding defined as intracranial brain haemorrhage confirmed by brain imaging or autopsy, or bleeding at a critical location [e.g. retinal haemorrhage, major haemorrhage, or spinal haemorrhage] and/or an otherwise life threatening event bleed that did not meet other criteria)	<u>Days 0-6</u> **Heparin:** 22/976 **Placebo:** 24/959 **P value**: 0.72 <u>Days 0-28</u> **Heparin:** 38/976 **Placebo:** 50/959 **P value**: 0.16 Note: Bleeding events which were reported as non serious adverse events that occurred during infusion (Days 0-6) and led to or contributed to the need for transfusion of packed red blood cells were classified as "non serious bleeding events".	
			Neurological bleeding (central nervous system bleeding events)	<u>Days 0-6</u> **Heparin:** 3/976 **Placebo:** 3/959 **P value**: 0.98 <u>Days 0-28</u>	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No. randomised: 976 **Age (mean):** 59.6±16.1 **No. of dropouts:** **Additional risk factors:** Age ≥65 years: 411/976 Patient history: - Hypertension:378/976 - Recent surgery: 330/976 - COPD: 171/976 - Malignancy: 134/976 - Chronic liver disease: 55/976 - Congestive myopathy 49/976 - Deep vein thrombosis: 32/976 - Pulmonary thromboembolism: 12/976 - APACHE II score: 23.8±7.6 - APACHE≥25: 462/976 **Group 3** **No. randomised:** 959 **Age (mean):** 58.4±16.0 **No. of dropouts:** **Additional risk factors:** Age ≥65 years: 367/959 Patient history: - Hypertension: 356/959 - Recent surgery: 331/959 - COPD: 160/959 - Malignancy: 112 /959 - Chronic liver disease: 52/959 - Congestive myopathy: 46/959 - Deep vein thrombosis: 19/959 - Pulmonary thromboembolism: 13/959 - APACHE II score: 24.0±7.4 - APACHE≥25: 431/959	drug injections were continued every 12 hours until the infusion was completed. If the 12-hour time point for study drug administration occurred within 2 hours after completion of Drot AA infusion, the final study drug injection was administered then. **Other drugs:** Both groups received Drot AA at 24 microgram/kg/hour for 96 hours, according to local hospital guidelines **Additional non-comparative prophylaxis:** "all other patient care was at the discretion of the investigator, including the use of commercial heparin (commercial use of heparin use during Days 0-6 refers to use in the 1-2 d after Drot AA and study drug administration)". Commercial use of heparin was not statistically significant between treatment arms(data not shown)		**Heparin:** 10/976 **Placebo:** 7/959 **P value:** 0.49	**Placebo:** 49/959 **P value:** 0.60 Days 0-28: **Heparin:** 56/976 **Placebo:** 67/959 **P value:** 0.26 (defined as objectively confirmed non fatal or fatal pulmonary embolism (PE), asymptomatic lower extremity DVT, detected by bilateral compression ultrasonography performed at the end of study drug administration (Study Days 4-6), symptomatic lower extremity DVT confirmed by objective means (ultrasound or other accepted diagnostic modalities) an symptomatic central vein thrombosis, confirmed by objective means) **Ischaemic stroke:** Days 0-6 **Heparin:** 3/976 **Placebo:** 12/959 **P value:** 0.02 Days 0-28 **Heparin:** 5/976 **Placebo:** 17/959 **P value:** 0.01 **Any bleeding event:** Days 0-6 **Heparin:** 105/976 **Placebo:** 78/959 **P value:** 0.049 Days 0-28 **Heparin:** 121/976 **Placebo:** 105/959 **P value:** 0.32 **Notes:**
			Heparin induced thrombocytopaenia	Days 0-6 **Heparin:** 10/976 **Placebo:** 6/959 **P value:** 0.33 Days 0-28 **Heparin:** 12/976 **Placebo:** 11/959 **P value:** 0.87	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
		"The use of prophylactic heparin and mechanical methods between Study Days 7-28 were very similar in both groups"- details not reported			The study was designed to evaluate whether heparin interfered with the efficacy of Drot AA in adult patients with severe sepsis at high risk of death. Heparin may have direct therapeutic effects in severe sepsis and disseminated intravascular coagulation independent of their anti thrombotic properties. High doses of heparin lead to higher clearance of DrotAA through increasing the rate of inhibition of activated protein C by protein C inhibitors

UFH vs no prophylaxis and UFH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Macoviak et al., 1984[417] **Country of study:** US **Study design:** RCT **List who was masked to interventions:** Placebo used but there is no mention of whether patients or physicians were masked to interventions. Outcomes were recorded in a double blind manner by two radiologists **Evidence level:** 1+ **Duration of follow-up:** 2 weeks	**Patient group:** Adult male patients requiring indwelling catheters for total parenteral nutrition. Carcinoma: 25/37 (67.6%) **Setting:** Surgical service of a Veterans Administration medical centre **Inclusion criteria:** **Exclusion criteria:** Prior total parenteral nutrition, prior subclavian vein catheterisation, anticoagulation, coagulopathy, previous venous thrombosis, lung cancer and abnormal baseline venograms **<u>All patients</u>** **N:** 37 **Age (mean):** Gp1: 60.1 +/- 14.65 Gp2: 63.7 +/- 6.76 **M/F:** 37/0 **Additional risk factors:** Gp1 Gp2 No operation 2 2 TPN after op. 3 3 TPN before and after op. 12 15 Carcinoma 10 15 Benign Diagnosis 7 5 **<u>Group 1</u>** **No. randomised:** 17 **No. of dropouts:** 0 reported **<u>Group 2</u>** **No. randomised:** 20 **No. of dropouts:** 0 reported	**Group 1** Unfractionated Heparin Start time: start of TPN End time: unclear Duration: outcomes measured at 2 weeks after initiation of TPN Dose, and frequency: 1 unit of sodium heparin per ml of TPN **Group 2** Saline solution Start time: start of TPN End time: unclear Duration: outcomes measured at 2 weeks after initiation of TPN Dose and frequency: equivalent volume of normal saline solution. **Additional non-comparative prophylaxis:** Patients undergoing operations had 10% Dextran run through the catheter from morning of operation to first post operative morning. . Anticoagulation was an exclusion criteria.	**Subclavian venous thrombosis** (confirmed by: arm contrast venography)	**All venographic abnormalities** **Group1:** 3/20 (15%) **Group 2:**3/17 (17.6%) **P value:** NS* **Fibrin Sleeve formation** **Group1:** 2/20 (10%) **Group 2:** 1/17 (5.9% **P value:** NS* **Partial occlusion** **Group1:** 1/20 (5%) **Group 2:** 1/17 (5.9%) **P value:** NS* **Total Occlusion** **Group1:** 0/20 **Group 2:** 1/17 (5.9%) **P value:** NS*	**Funding:** No mention of funding **Limitations:** All patients were male and 89% received surgery. No mention of method of randomisation, allocation concealment or blinding (although placebo was used). **Outcomes not reported:** All cause mortality, Pulmonary embolism, DVT in lower limbs, bleeding, heparin induced thrombocytopaenia, post thrombotic syndrome, pulmonary hypertension, quality of life, length of stay **Additional outcomes reported:** None **Notes:** TPN – Total parenteral nutrition * calculated by NCC team using Fisher's exact test.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments

UFH vs no prophylaxis and UFH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
McCarthy et al., 1977MCCARTHY 1977} **Country of study:** UK **Study design:** RCT **List who was masked to interventions:** No one **Evidence level:** 1+ **Duration of follow-up:** 14 days for DVT 28 days for Death	**Patient group:** Stroke Patients **Setting:** Department of Geriatric Medicine **Inclusion criteria:** Diagnosis of stroke within previous 48 hours **Exclusion criteria:** • Blood in the cerebrospinal fluid (defined as 50 red cells per high-power field in tube 3 of a lumber puncture) • Sustained diastolic blood pressure higher than 120mmHg on admission or grades 3 or 4 hypertensive retinopathy; • History of active peptic ulceration; • History of subarachnoid haemorrhage; • Allergy to iodine; • Goitre or thyrotoxicosis; • Bleeding diathesis; • Recent Myocardial infarction; or **<u>All patients</u>** **N:** 32 **Age (mean):** Gp1: 78.9 (S.D 8.0) Gp2: 78.2 (SD 7.4) **M/F:** 11:21 **Additional risk factors:** Mean Severity: Gp1: 4.3 ± 1.8 Gp2: 3.4 ± 21.6 **<u>Group 1</u>** **No. randomised:** 16 **No. of dropouts:** 0 **<u>Group 2</u>** **No. randomised:** 16 **No. of dropouts:** 0	**Group 1** Unfractionated Heparin (calcium) Start time: Unclear Duration: 14 days Dose and frequency: 5000U subcutaneously every 8 hours **Group 2** No heparin **Additional non-comparative prophylaxis:** None listed	**All cause mortality** **DVT, asymptomatic or symptomatic** (confirmed by: Radiofibrinogen uptake test)	**Group1:** 3/16 **Group 2:** 5/16 **P value:** 0.685* **Group1:** 2/16 **Group 2:** 14/16 **P value:** 0.001*	**Funding:** No information provided **Limitations:** No information is provided about the method of randomisation or allocation concealment. Trial is not blinded and few baseline characteristics are provided. Pilot study for MCCARTHY1986 **Outcomes not reported:** Fatal PE, Symptomatic PE, Symptomatic DVT, Bleeding, Heparin induced thrombocytopaenia, Pulmonary hypertension, Post thrombotic syndrome, quality of life, length of stay. **Additional outcomes reported:** None **Notes:** * Calculated by NCC team using Fisher Exact Test.

UFH vs no prophylaxis and UFH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
McCarthy & Turner, 1986[434] **Country of study:** UK **Study design:** RCT **List who was masked to interventions:** No one **Evidence level:** 1+ **Duration of follow-up:** 14 days for DVT 12 weeks for death	**Patient group:** Stroke Patients **Setting:** Department of Geriatric Medicine **Inclusion criteria:** Diagnosis of stroke within previous 48 hours **Exclusion criteria:** • Sustained diastolic blood pressure higher than 120mmHg on admission or grades 3 or 4 hypertensive retinopathy; • History of active peptic ulceration; • History of subarachnoid haemorrhage; • Allergy to iodine; • Goitre or thyrotoxicosis; • Bleeding diathesis; • Recent Myocardial infarction; or • Diagnosed malignancy **<u>All patients</u>** **N:** 305 **Age (mean):** 76 (S.D 8.1) **M/F:** 132:173 **Additional risk factors:** Mean Severity: Gp1: 4.4 ± 2.38 Gp2: 4.8 ± 2.65 **<u>Group 1</u>** **No. randomised:** 144 **No. of dropouts:** Unclear **<u>Group 2</u>** **No. randomised:** 161 **No. of dropouts:** Unclear	**Group 1** Unfractionated Heparin (calcium) Start time: Unclear Duration: 14 days Dose and frequency: 5000U subcutaneously every 8 hours **Group 2** No heparin **Additional non-comparative prophylaxis:** None listed	**All cause mortality** **DVT, asymptomatic or symptomatic** (confirmed by: Radiofibrinogen uptake test)	**Group1:** 31/144 **Group 2:** 53/161 **P value:** 0.029* **Group1:** 32/144 **Group 2:** 117/161 **P value:** <0.001*	**Funding:** Chest Heart and Stroke association, Oxford locally organised research funds and Labaz & Evans biologicals **Limitations:** No information is provided about the method of randomisation or allocation concealment. Trial is not blinded and few baseline characteristics are provided. **Outcomes not reported:** Fatal PE, Symptomatic PE, Symptomatic DVT, Bleeding, Heparin induced thrombocytopaenia, Pulmonary hypertension, Post thrombotic syndrome, quality of life, length of stay. **Additional outcomes reported:** Pulmonary embolism at post mortem (not fatal

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
					PE) Gp1 Gp2 35/46 5/25 **Notes:** * Calculated by NCC team using Fisher Exact Test.

UFH vs no prophylaxis and UFH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Merli et al., 1988[442] **Country of study:** USA **Study design:** RCT **List who was masked to interventions:** investigators & patients blinded to heparin and placebo but not electrical stimulation **Evidence level:** 1+ **Duration of follow-up:** at least 28 days, study aim was for 42 days	**Patient group:** Acute spinal cord injury **Setting:** Hospital **Inclusion criteria:** • >15 years old • injured <2 weeks before initial evaluation • classified as having either motor complete or incomplete-preserved motor, non-functional (C_2 to T_{11}) lesions **Exclusion criteria:** • underlying bleeding disorder • myocardial infarction <6 months • long bone fractures • arterial trauma • postphlebitic syndrome • lower extremity cellulitis • hepatic or renal function twice normal • pregnant • receiving anticoagulant drugs **<u>All patients</u>** **N:** 53 * **No. of dropouts:** 5 **<u>Group I</u>** **No. randomised:** 19 **No. of dropouts:** 3 **Age (mean):** NR **M/F:** NR **Additional risk factors:** NR **Other factors:** **<u>Group II</u>** **No. randomised:** 17 **No. of dropouts:** 0 **Age (mean):** NR **M/F:** NR **Additional risk factors:** NR **Other factors:**	**<u>Group I</u>** Unfractionated Heparin Start: Unclear Duration: 28 days Dose and Frequency: 5000 IU every 8 hours **<u>Group II</u>** placebo * 3rd group in trial of UFH + electrical stimulation not reported in this table 88 patients evaluated for the study, 34 excluded because of venographically proven DVT before randomisation. **Additional non-comparative prophylaxis:** None reported	**DVT (asymptomatic & symptomatic)** (diagnosed by fibrinogen uptake test confirmed by venography. All patients who had normal fibrinogen uptake tests were also screened with bilateral venography to rule out DVT)	**Group 1:** 8/16 **Group 2:** 8/17 **P value:** not significant	**Funding:** Regional Spinal Cord Injury Centre of Delaware Valley Model SCI Systems grant from National Institute for Disability Research and Rehabilitation **Limitations** Treatment reduced from 42 to 28 days once found patients being discharged earlier. Unclear how many received 42 days treatment. **Outcomes not reported:** pulmonary embolism, DVT, major and minor bleeding, heparin induced thrombocytopenia, post-thrombotic syndrome, quality of life, length of stay **Additional outcomes reported:** **Notes:** Study terminated early as investigators in review board concerned about ethics of continuing a trial with 3 groups as 3rd group (UFH + electrical stimulation) significantly better than UFH or

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
					placebo.

UFH vs no prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Osman et al., 2007[504] **Country of study:** Egypt **Study design:** Prospective randomised open label study **List who was masked to interventions:** Open label? **Evidence level:** 1- **Duration of follow-up:** 2 weeks? Not clearly stated	**Patient group:** Non "high risk", isolated, live-donor renal transplantation. **Setting:** Dec 2003 to March 2005. Urology and Nephrology Centre, Mansoura University **Inclusion criteria:** Consecutive, isolated, live-donor renal transplantation operated by the same surgical team **Exclusion criteria:** Categorised as "risky " because - <16 years old - grafts with multiple arteries - a history of thromboembolic disease - artheromatous arteries - collagen vascular disease - intraoperative technical difficulties **All patients** **N:** 75 **M/F:** 52/23 **Group 1 (LMWH)** **No. randomised:** 25 **No. of dropouts:** M/F:14/11 Age (year): 28.3±8 Pre-transplant Hb level: 8.8±2 Ischaemia time (min): 44.7±11 Delayed diuresis: 1/25 Donor gender, M/F:11/14 Donor age (year): 35.9±11 Harvested kidney (right): 10/25 **Group 2 (UFH)** **No. randomised:** 25	**Group 1** LMWH Dose: 3500anti-Xa IU in 0.35 ml once daily Duration: 1week **Group 2** UFH Dose: 5000IU, twice daily Duration: 1 week **Group 3** Control Did not receive heparinisation **Additional non-comparative prophylaxis:** Not reported Note: All patients discharged 2 weeks post operatively if no post-operative complications were found	**All cause mortality** (confirmed by: no mortality reported) **Fatal pulmonary embolism** (confirmed by: screening method and frequency not specified) **Symptomatic pulmonary embolism** (confirmed by: screening method and frequency not specified) **Symptomatic DVT** (confirmed by: screening method and frequency not specified) **Major bleeding** (description: Reoperated. Found to be due to slipped ligature)	**Group1:** 0/25 **Group 2:** 0/25 **Group 3:** 0/25 **P value:** 1.0 **Group1:** 0/25 **Group 2:** 0/25 **Group 3:** 0/25 **P value:** 1.0 **Group1:** 0/25 **Group 2:** 0/25 **Group 3:** 0/25 **P value:** 1.0 **Group1:** 0/25 **Group 2:** 0/25 **Group 3:** 0/25 **P value:** 1.0 **Group1:** 1/25 **Group 2:** 0/25 **Group 3:** 0/25 **P value:** 0.37	**Funding:** None stated **Limitations:** - Open label study - No indication that patients or investigators were blinded – very likely open label study - Method of DVT screening not clearly specified, and frequency of screening not reported. - Duration of follow up not clearly stated **Outcomes not reported:** PE asymptomatic or symptomatic, DVT, asymptomatic or symptomatic, Thigh DVT, Calf DVT, Fatal bleeding, Neurological bleeding, Upper GI bleeding, Minor bleeding, Heparin induced thrombocytopaenia, Post thrombotic syndrome, Pulmonary hypertension, Quality of life, Length of stay **Additional outcomes reported:**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No. of dropouts: M/F:19/6 Age (year): 29.4±8 Pre-transplant Hb level: 9.7±1.6 Ischaemia time (min): 46.3±12 Delayed diuresis: 1/25 Donor gender, M/F: 15/25 Donor age (year): 35.3±10 Harvested kidney (right): 10/25 **<u>Group 3 (Control)</u>** **No. randomised:** 25 **No. of dropouts:** M/F:19/6 Age (year): 26±6 Pre-transplant Hb level: 8.6±1.7 Ischaemia time (min): 42.5±8 Delayed diuresis: 2/25 Donor gender, M/F:14/9 Donor age (year): 33±9 Harvested kidney (right): 11/25 Note: The groups were comparable, in all the above variables. However, there was a trend to significance for pretransplant haemoglobin levels, p=0.07				- Graft thrombosis - Number receiving transfusion - Mean transfused units - Haemoglobin drop in non transfused patients - Other transplant related parameters **Notes:**

UFH vs no prophylaxis and UFH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Pambianco et al., 1995[509] **Country of study:** USA **Study design:** RCT **List who was masked to interventions:** No one **Evidence level:** 1+ /- ? **Duration of follow-up:** 28 days	**Patient group:** Stroke patients (not necessarily newly defined) **Setting:** Rehabilitation centre **Inclusion criteria:** All cases with a diagnosis of non-haemorrhagic stroke identified by CT scan in the referring hospital and who have a paralysed or severely weakened lower limb. **Exclusion criteria:** • Patients on anticoagulation therapy • haemorrhagic stroke • more than 10 weeks after stroke • active cancer • 'other medical contraindications' including dementia, amputation, stroke not identifying specific area • Contraindications to heparin • diabetic ulcers. **<u>All patients</u>** **N:** 360 randomised – overall baseline data provided for only those completing study **Age (mean):** 72.2 ± 9.5 **M/F:** 41/59 **Additional risk factors:** BMI: 26.1 ± 5.7 Time from stroke to admission: 24.2 days **<u>Group 1:</u>** <u>No prophylaxis</u> **No. randomised:** 115 **No. of dropouts:** 9 (8%) **<u>Group 2</u>** <u>(Heparin)</u> **No. randomised:** 120 **No. of dropouts:** 30 (25%)	**Group 1** No prophylaxis **Group 2** Standard Sodium Heparin (no brand name) UFH Start time: 1st full day at centre End time: day 28 Duration: 28 days or discharge Dose and frequency: 5,000U every 8 hours, adjusted in 500U increments to maintain daily PTT between 30.0 – 39.9. Maximum dose 10,000U every 8 hours **Group 3** IPCD – Anti-thrombic pump (double lined stoking containing inflatable bladder) Start time: 1st full day at centre End time: day 28 Duration: 8 hours each night Length and compression profile: below knee. **Group 4** Mederomic Functional Electrical Stimulation Device (discontinued due to adverse events)	**All cause mortality** **DVT, asymptomatic or symptomatic** (screened for by: B-mode 2-dimensional imaging and pulsed doppler ultrasound at or above the popliteal vein twice a week until the completion of the study or discharge.)	**Group 1:** 0/115 **Group 2:** 0/120 **Group 3:** 0/117 **Group1:** 6/115 (completed study) **Group 2:** 5/120 (completed study) **Group 3:** 8/117 (completed study) **P value:** NR Grp 1 v Grp 2 = 0.76 Grp 1 v Grp 3 = 0.78 Grp 2 v Grp 3 = 0.41 *2-sided Fisher's exact test calculated by NCC-AC using ITT original numbers randomised*	**Funding:** US department of Education **Limitations:** - No details of randomisation provided - No blinding of analysts not mentioned - High patient drop out rates for heparin and IPCD group. **Outcomes not reported:** All cause mortality, PE (any type), Symptomatic DVT, Calf DVT, Thigh DVT, Bleeding (any type), HIT, PTS, Pulmonary Hyper tension, QoL, LoS **Additional outcomes reported:** Adverse events for heparin included: echymotic area over abdomen and areas distal to injection site. 10 point decrease in haematocrit level; nausea and vomiting with onset of heparin therapy, bleeding from the ear, haematochezia, haemepositive stools, blleding around tracheal stoma,

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 3 (IPCD) **No. randomised:** 117 **No. of dropouts:** 26 (22%) **Group 4** (Functional Electrical Simulation) **No. randomised:** 8 **No. of dropouts:** 6 (75%) Study arm discontinued	**Additional non-comparative prophylaxis:** All patients received bilateral below knee stockings (no compression).			thrombocytopaenia Adverse events for IPCD, bilateral skin changes **Notes:** High drop out rate in IPCD due to disruption of sleep. 21 patients were transferred to acute care for complications unrelated to study treatment

UFH vs no prophylaxis and UFH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Pitt et al., 1980[522] **Country of study:** Australia **Study design:** RCT **List who was masked to interventions:** No one **Evidence level:** 1+ **Duration of follow-up:** 2 weeks	**Patient group:** Patients with Myocardial Infarction **Setting:** Unclear **Inclusion criteria:** Patients with myocardial infarction of less than 48 hours duration **Exclusion criteria:** Contraindicated to anticoagulants, where the patient was already on anticoagulants or if cardiogenic shock was present. **All patients** **N:** 115 **No of dropouts:** 7 (6.1%) **Age (mean):** Gp 1(LD): 54.4 Gp 2(cont): 56.9 Gp 2 (full): 56.2 **M/F:** 90:18 **Additional risk factors:** Gp1 Gp2 Gp3 Mean admission time 7.1 7.8 9.5 Mean SGOT 232 193 225 Paper states that 'the groups were not significantly different when height, weight, body surface area or site of infarction as determined by ECG were compared. **Group 1** **No. randomised:** ? No analysed: 36 **No. of dropouts:** ? **Group 2** **No. randomised:** ? No analysed: 37 **No. of dropouts:** ? **Group 3** **No. randomised:** ? No analysed: 35 **No. of dropouts:** ?	**Group 1** Low dose heparin Start time: unclear End time: unclear Duration: 48 hrs Dose, and frequency: 500U in 5% dextrose by intravenous infusion every 12 hours for 48 hours. **Group 2** Control Start time: unclear End time: unclear Duration: 2-3 days Dose and frequency: 5% dextrose by intravenous infusion for 2-3 days **Group 3** Heparin and Warfarin Start time: unclear End time: 'until after cessation of heparin' Duration: unclear Dose and frequency: 5000 units of heparin intravenously as a loading dose and then 20,000 units by intravenous infusion every 12 hours for 48 hours, the dose being adjusted to maintain a whole blood clotting time between 30-90 minutes. These patients were also	**All cause mortality** (confirmed by:) **DVT, asymptomatic or symptomatic** (confirmed by: Radioactive fibrinogen uptake test)	Paper reports that 3 patients died before completion of the trial but they were excluded from the analysis. **Group1:** 5/36 **Group 2:** 11/37 **P value:** 0.157* **Group 1:** 5/36 **Group 3:** 4/35 **P value:** NS* **Group 2:** 11/37 **Group 3:** 4/35 **P value:** 0.082*	**Funding:** No information provided. **Limitations:** Study was unblinded. Paper did not use an intention to treat analysis and did not present the number of patients randomised. **Outcomes not reported:** Pulmonary embolism, bleeding, heparin induced thrombocytopaenia, post thrombotic syndrome, pulmonary hypertension, quality of life, length of stay. **Additional outcomes reported:** None **Notes:** * Calculated by the NCC team using Fishers exact test. Data is also analysed by categorising by cardiac failure status.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
		given warfarin on admission and continued after cessation of heparin in sufficient dosage to maintain the prothrombin index between 10% and 35%. **Additional non-comparative prophylaxis:** All patients undertook active leg and breathing exercises under the supervision of nursing staff			

UFH vs no prophylaxis and UFH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Prerovsky et al., 1988[539] **Country of study:** Czech Rep. **Study design:** RCT **List who was masked to interventions:** No masking. **Evidence level:** 1- **Duration of follow-up:** Not clear, until patient started to ambulate?	**Patient group:** Acute myocardial infarction (AMI) **Setting:** Coronary care unit (CCU) **Inclusion criteria:** Patients admitted to the CCU with the diagnosis of AMI according to WHO criteria **Exclusion criteria:** Patients in shock or coma. Diagnosis of AMI not confirmed. Hypersensitive to iodine Those dying within 3 days of admission without undergoing fibrinogen test. **All patients** **N:** n= 408 **No. of dropouts:** 0 Data provided by intervention groups **Group 1** (Low-dose heparin) **No. randomised:** n= 133 **Age:** 59.2 (8.6) **M/F:** 101/32 **AMI:** n=126 **Heart failure:** 61 **Arrhythmias:** 69 **Varices:** 34 **Thrombosis in patient's history:** 7 **Smokers:** 68 **Group 2** (Exercise) **No. randomised:** n=135 **Age:** : 57.7 (9.0) **M/F:** 109/26 **AMI:** n= 134 **Heart failure:** 53 **Arrhythmias:** 48 **Varices:** 34 **Thrombosis in patient's history:** 4 **Smokers:** 68	**Group 1 :** Heparin Start time: Within 24 hours of admission 5000u 12 hourly subcutaneous Duration: not stated, until the patient started to ambulate? **Group 2:** Exercise 1 -2 minutes dorsal and plantar flexion every hour, except for sleep Start time: within 24 hours of admission, and continued until patient ambulation. **Group 3 :**Control Standard protocol. Not subjected to any special techniques of prevention. **Additional non-comparative prophylaxis:** Not reported	**DVT, asymptomatic or symptomatic** ^{125}I-labelled fibrinogen test	**Group 1:**12/133 (9.0%) **Group 2:** 7/135 (5.2%) **P value:** *0.24* *[calculated by NCC-AC team from numbers randomised using Fishers exact test]* **Group 1:** 12/133 (9.0%) **Group 3:** 19/140 (13.6%) **P value:** *0.26* *[calculated by NCC-AC team from numbers randomised using Fishers exact test* **Group 2:** 7/135 (5.2%) **Group 3:** 19/140 (13.6%) **P value:** *0.02* *[calculated by NCC-AC team from numbers randomised using Fishers exact test]* **P value:** Group 2 vs. Group 3 $p<0.05$ (others are not significant)	**Funding:** Not reported. **Limitations:** No/not enough information provided: ▪ Randomisation generation and concealment ▪ Sample size calculation ▪ Blinding of assessors ▪ Length of follow-up. ▪ Method of symptomatic VT assessment not defined. Outcomes measured, mortality, withdrawals, drops outs not clearly reported. **Outcomes not reported:** Bleeding (Fatal, major, neurological, upper GI, major/minor); HIT, PTS, PH, QoL, LOS. **Additional outcomes reported:** Results reported, but not stated from which intervention arm: 1/408 fatal PE. Among the 38 VT patients, signs of VT in 8/38 and possible or probably VT in 18/38. (Signs of VT defined as oedema, tenderness, increased venous pressure or cyanosis)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 3 (Control) **No. randomised:** n=140 **Age:** 59.0 (8.3) **M/F:** 109/31 **AMI:** n= 136 **Heart failure:** 58 **Arrhythmias:** 51 **Varices:** 37 **Thrombosis in patient's history:** 9 **Smokers:** 72 Venous thrombosis (VT) in the patient's history was defined as oedema of the lower limb up to the knee or groin associated with limb tenderness Symptoms of left-heart failure were assessed by clinical signs (stage II of Killip-Kimball classification) Severe arrhythmia was defined as II-III degree block ventricular tachycardia or fibrillation, atrial fibrillation and ventricular ectopy requiring therapy.				Incidence of VT analysed by risk factors. P<0.01 for HF, NS for arrhythmia, p=0.001 for history of thromboembolism, p=0.01 for varices, p=0.001 for smoking. **Notes:** Authors refer to VT and DVT in this report.

UFH vs no prophylaxis and UFH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Warlow et al., 1973[672] **Country of study:** UK **Study design:** RCT **List who was masked to interventions:** Patients and Physicians **Evidence level:** 1+ **Duration of follow-up:** 10 days	**Patient group:** Myocardial Infarction **Setting:** Coronary Care Unit **Inclusion criteria:** Patients with a high probability of having suffered an MI aged 40 – 75. **Exclusion criteria:** Symptoms of infarction started more than 12 hours before heparin could be given, if they were moribund on admission, if there were signs of a DVT or if they had been confined to bed for more than 1 day in the previous 14 days, if they were already receiving anticoagulants, if they were allergic to iodine or might require thyroid function studies and if there was any history of abnormal bleeding in the preceding 6 months. **<u>All patients</u>** **N:** 146 No assessed: 127 (87%) **Age (mean):** Not recorded **M/F:** Not recorded **Additional risk factors:** Not recorded **<u>Group 1</u>** **No. randomised:** 73 **No. of dropouts:** 10 **<u>Group 2</u>** **No. randomised:** 73 **No. of dropouts:** 9	**Group 1** Sodium heparin Start time: unclear End time: unclear Duration: 10 days Dose and frequency: 5000U injected subcutaneously every 12 hours. **Group 2** 0.85 % saline solution Start time: Unclear End time: Unclear Duration: 10 days Dose and frequency: 0.2ml injected every 12 hours for 10 days **Additional non-comparative prophylaxis:** Apart from injections of heparin, patients were treated entirely at the discretion of their consulting physician.	**All cause mortality**	**Group1:** 6/63 **Group 2:** 5/64 **P value:** NS	**Funding:** Not stated. **Limitations:** No baseline characteristics given for the two groups, other than stating they were not significantly different. Intention to treat analysis not completed. **Outcomes not reported:** Pulmonary embolism, bleeding, heparin induced thrombocytopaenia, Post thrombotic syndrome, Quality of Life, Length of Stay, Pulmonary Hypertension. **Additional outcomes reported:** Ventricular tachycardia developed in 8/63 patients in heparin group and 4/64 patients in the control group. **Notes:** * Calculated by the NCC team using Fishers Exact Test Paper states that no haemorrhagic complications were found.
			Symptomatic DVT (confirmed by: Radiofibrinogen uptake test)	**Group1:** 1/63 **Group 2:** 4/64 **P value:** 0.365*	
			DVT, asymptomatic or symptomatic (confirmed by: Radiofibrinogen uptake test)	**Group1:** 2/63 **Group 2:** 11/64 **P value:** 0.016*	

UFH vs no prophylaxis and UFH adjuvant studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Zawilska et al., 1989[709] **Country of study:** Poland **Study design:** RCT **List who was masked to interventions:** No one **Evidence level:** 1+ **Duration of follow-up:** DVT follow up – 7 days 14-21 days	**Patient group:** Acute transmural myocardial infarction **Setting:** Coronary Care Unit **Inclusion criteria:** Severe retrosternal chest pain lasting longer than 20 min, typical ST segment displacement and T wave changes along with abnormal Q waves on the electrocardiogram and elevated levels of serum creatine kinase, its MB isoenzyme, as well as glutamic oxaloacetic transaminase **Exclusion criteria:** None stated **All patients** **N:** 103 **Age (mean):** Gp1: 58 Gp2: 59 **M/F:** 79:24 **Additional risk factors:** ECG localisation of AMI Gp1 Gp2 Anterior 17 18 Lateral 5 4 Inferior 17 25 Posterior 1 0 Extensive 10 6 Left ventricular function Compensated 28 31 Congested Heart Failure 7 12 Cardiogenic shock 15 10 **Group 1** **No. randomised:** 50 **No. of dropouts:** 0 **Group 2** **No. randomised:** 53 **No. of dropouts:** 0	**Group 1** Unfractionated Heparin (sodium) Start time: within first 24 hours Duration: 14-21 days Dose and frequency: 5000U subcutaneously within first 24 hours and thereafter twice a day for 14-21 days. **Group 2** No anticoagulation **Additional non-comparative prophylaxis:** No additional prophylaxis provided. Both groups received conventional therapeutic regimens (no details provided)	**All cause mortality**	**Group1:** 5/50 **Group 2:** 6/53 **P value:** NS	**Funding:** Not stated. **Limitations:** Paper does not present any exclusion criteria or the number of patients who dropped out of the study. No mention of randomisation method or allocation concealment within the paper. The study is not blinded **Outcomes not reported:** Fatal PE, symptomatic DVT, bleeding, pulmonary hypertension, post thrombotic syndrome, quality of life, length of stay, heparin induced thrombocytopaenia. **Additional outcomes reported:** Intramural thrombosis, arterial embolisation **Notes:** *Calculated by NCC using Fisher Exact Test
			Symptomatic pulmonary embolism (confirmed by: clinical and radiological examination)	**Group1:** 0/50 **Group 2:** 1/53 **P value:** NS	
			DVT, asymptomatic or symptomatic (screened for by: radiofibrinogen uptake test)	**Group1:** 2/50 **Group 2:** 10/53 **P value:** 0.029*	
			Thigh DVT(screened for by: radiofibrinogen uptake test and phlebography)	**Group1:** 0/50 **Group 2:** 1/53 **P value:** NS	

Evidence Table 28: VKA vs no prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Levine et al., 1994[398] **Country of study:** Canada **Study design:** Multicentre RCT **List who was masked to interventions:** Doctor and patient **Evidence level:** 1+ **Duration of follow-up:** Until 1 week after chemotherapy was stopped. Median duration of warfarin 181 days.	**Patient group:** Women with metastatic breast carcinoma receiving first- or second-line chemotherapy for 4 weeks or less **Setting:** Outpatients **Exclusion criteria:** • Eastern Cooperative Oncology Group (ECOG) performance status ≥3 • Underlying bleeding disorder or active peptic ulcer disease • Direct bilirubin > twice normal • INR ≥ 1.3 • Platelet count below $50x10^9/L$ • History of alcohol abuse • Overt brain metastases • Presence of underlying psychiatric or affective disorder • Requirement for long-term anticoagulant therapy • Expected survival <3 months • Concurrent receipt of hormonal therapy • Inability to attend follow up visits for geographical reasons **All patients** **N:** 315 **Group 1** **No. randomised:** 154 **No. of dropouts:** 27* **Mean ±SD age:** 57.1 ±10.2 **Additional risk factors:** family history of DVT 0, stroke 1, myocardial infarction 0, angina 1 **CVC in situ:** 4 **Group 2** **No. randomised:** 161	**Group 1** Adjusted low-dose warfarin: Warfarin 1mg for 6 weeks then adjusted for an anticoagulant effect equivalent to INR of 1.3 – 1.9. Warfarin dose after 6 weeks: • if INR: between 1.3 & 1.9, patient kept on 1mg warfarin • if INR <1.3, dose increased by 1mg every week until INR between 1.3-1.9 achieved **Group 2** Placebo and sham INR. INR results initially modelled on a cohort of patients receiving low-dose warfarin, later on generated from experiences of patients in warfarin arm of trial. **Additional non-comparative prophylaxis:** None reported	**Symptomatic DVT** (confirmed by venography **if** duplex sonography or impedance plethysmography was positive) **Symptomatic pulmonary embolism** (confirmed by ventilation perfusion lung scan) **Major bleeding** (associated with a fall in haemoglobin concentration of ≥20g/L; need for ≥2 units of blood transfusion; retroperitoneal or intracranial bleeding) **Minor bleeding** (overt but did not meet criteria for major bleeding) **Mortality** **Duration of warfarin or placebo treatment (mean ±SD) in days**	**Group1:** 0/152 **Group 2:** 6/159 **P value:** 0.08 **Group1:** 1/152 **Group 2:** 1/159 **P value:** 0.97 **Group1:** 1/152 **Group 2:** 2/159 **P value:** 0.59 **Group1:** 7/152 **Group 2:** 3/159 **P value:** 0.19 **Group1:** 87/152 **Group 2:** 99/159 **P value:** 0.37 **Group1:** 181 ±123 (n=152) **Group 2:** 166 ±139 (n=159) **P value:** 0.31	**Funding:** Supported by grant from National Cancer Institute of Canada **Outcomes not reported:** asymptomatic DVT or pulmonary embolism, post-thrombotic syndrome, pulmonary hypertension, quality of life. **Additional outcomes reported:** Average dose of study treatment; mean INR, mean time at risk of thrombosis (chemotherapy + 7 days). **Notes:** * dropouts: • 2/315 did not start chemotherapy so were not included in the analysis • 32/315 refused treatments • no symptomatic thrombosis in any of dropouts Randomisation stratified by whether or not a catheter was in situ

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No. of dropouts: 27* **Mean ±SD age:** 56.1 ±10.9 **Additional risk factors:** family history of DVT 2, stroke 1, myocardial infarction 1, angina 1 **CVC in situ:** 7				

VKA vs no prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Mismetti et al., 2004[451] 2 RCTs included [178,470] All of these studies were included in the guideline review.	Systematic review	1+	**Total:** 305	**Type of surgery:** Orthopaedic: 2 studies	**Type:** Oral anticoagulant (adjusted) Phenindione (1 study) Warfarin (1 study) **Timing:** Postoperative: 2 studies Administered until discharge (1 study)	No prophylaxis: 1 study Placebo: 1 study **Additional non-comparative prophylaxis:** none	3 months (1 study) 3 weeks (1 study)	**DVT** Confirmed by venography or FUT	**Int:** 9/44 **Cont:** 22/41 **p value:** 0.0018	**Not reported:** LoS, QoL, PTS **Funding:** Sanofi-Synthelabo grant
								Fatal PE Defined as specified in each report.	**Int:** 1/144 **Cont:** 2/141 **p value:** 0.6197	
								PE	**Int:** 4/144 **Cont:** 16/141 **p value:** 0.0050	
								Major bleeding	**Int:** 1/100 **Cont:** 2/100 **p value:** 1.0000	

VKA vs no prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Roderick et al., 2005[557] 9 RCTs included [74,189,248,414,463,521,530,533,633] All of these studies were included in the guideline review.	Systematic review	1+	**Total:** 884 Int: 524 Cont: 491	**Type of surgery:** orthopaedic: 6 studies gynaecological: 3 studies **Pre-existing risk factors:** not reported	Oral anticoagulant **Dose:** Adjusted dose: 6 studies Fixed dose: 2 studies Adjusted/fixed: 1 study **Timing:** Start time varied from admission or 1 week preoperatively to postoperatively. **Additional non-comparative prophylaxis:** none	No prophylaxis: 5 studies Placebo: 4 studies **Additional non-comparative prophylaxis:** none	End time varied from 1 week to 3 months	**DVT** Confirmed by venography or FUT	**Int:** 91/455 **Control:** 164/429 **p value:** 0.0000	**Not reported:** LoS, QoL, PTS
								PE (scan, x-ray or post-mortem for fatal)	**Int:** 0/163 **Cont:** 12/162 **p value:** 0.0002	
								Major bleeding: definition not given	**Int:** 45/449 **Cont:** 23/417 **p value:** 0.0160	
								Proximal DVT	**Int:** 12/254 **Cont:** 29/257 **p value:** 0.0085	

Evidence Table 29: Aspirin +/- antiplatelet therapy vs no prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Antiplatelet Trialists' Collaboration, 1994[21] 55 trials from 53 papers 1,12,22,69,98,99,109,111,135,153,172,188,211,232,255,258,261,263,297,298,300,310,376,406,407,436,437,464,498,511,519,528,533,550,551,587,590,609,612,648,665,666,669,682,700,703,710-716 28 of these studies were included in the guideline review 1,12,69,70,111,153,157,172,234,261,407,433,436,464,498,511,528,533,550,587,590,609,612,682,700,711,715,716 4 studies with heparin as background prophylaxis reported below in next table.	Systematic review	1+		**Type of surgery:** Surgical and high risk medical patients: General surgery patients: 24 trials Traumatic orthopaedic surgery patients: 11 trials Elective orthopaedic surgery patients: 16 trials	Antiplatelet therapy: Drugs included in review: Aspirin Aspirin & dipyridamole Ticlopidine Sulphinpyrazone Sulocidil Hydroxychloroquine Flurbiprofen unmarketed drugs	No intervention	Majority 1, 2 or 3 week studies	**DVT** Confirmed by: fibrinogen uptake test or venography	**Int:** 604/2551 **Control:** 711/2286 **p value:** <0.0001	Trials did not always define what was considered a major bleed Reported pulmonary emboli but did not state how if they were confirmed. **Not reported:** QoL, survival, LoS, PTS, funding
								Proximal DVT Confirmed by: fibrinogen uptake test or venography	**Int:** 65/641 **Control:** 92/556 **p value:** 0.0008	
								Major bleed	**Int:** 22/3264 **Control:** 11/2781 **p value:** 0.44	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
9 studies in high risk medical patients excluded from our analysis										

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Antiplatelet Trialists' Collaboration, 1994[21] **Country of study:** UK **Study design:** Systematic review with 58 trials in surgical patients and 11 trials in high risk medical patients **List who was masked to interventions:** Unclear from systematic review **Evidence level:** 1+ **Duration of follow-up:** Treatment varied between 1-78 weeks with 7/9 studies treating for 1-4wks	**Patient group:** High Risk Medical patients Population included within individual studies unclear **Setting:** Unclear **Study Inclusion criteria:** Unconfounded RCTs **Study Exclusion criteria:** Poor allocation concealment (e.g. odd or even dates, record numbers) if treatment comparisons were considered confounded. **<u>All patients</u>** **N:** 520 **<u>Group 1</u> -** Antiplatelets **No. randomised:** 275 **No. of dropouts:** Unknown **<u>Group 2</u>** - Control **No. randomised:** 283 **No. of dropouts:** Unknown	**Group 1** Various antiplatelets – see table below Duration: 1-78 weeks **Group 2** Control Duration: 1-78 weeks **Additional non-comparative prophylaxis:** Information not given	**All cause mortality**	**Group1:** 22/256 **Group 2:** 23/261 **P value:** NS	**Funding:** No information provided **Limitations:** Pulmonary embolism diagnosed using any method. Literature search did not include all medical databases. Lack of information about population or heterogeneity **Outcomes not reported:** LoS, QoL, PTS, Pulmonary hypertension, Fatal bleeding, minor bleeding, HIT **Additional outcomes reported:** No additional outcomes reported. **Notes:** Data presented for medical patients only. * P-value calculated by NCC team using 2-tailed Fisher's exact.
			Fatal pulmonary embolism (confirmed by: any method)	Group1: 2/256 Group 2: 4/261 P value: 0.686*	
			Pulmonary embolism, asymptomatic or symptomatic (confirmed by: any method)	**Group1:** 1/182 **Group 2:** 2/187 **P value:** NS	
			DVT, asymptomatic or symptomatic (confirmed by: see table below)	**Group1:** 39/256 **Group 2:** 56/264 **P value:** 0.089*	
			Thigh DVT(confirmed by: see table below)	**Group1:** 1/32 **Group 2:** 7/34 **P value:** 0.055*	
			Major bleeding (definition: severe enough to require transfusion)	**Group1:** 0/99 **Group 2:** 1/102 **P value:** NS	

Effectiveness - Single prophylaxis versus single prophylaxis

Evidence Table 30: Mechanical vs mechanical

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Anglen et al., 1998[20]	RCT	1+	**Total:** 117 **Intervention:** n = 68 **Control:** n = 49	**Type of surgery:** Trauma patients with fracture of pelvic ring, acetabulum or femur. **Intervention:** Average age: 38 (range: 17-82 yrs) M/F: 38/30 **Control:** average age: 41 (range: 18-88 yrs) M/F: 27/22	Intermittent plantar compression devices (foot pumps) NuTech PlexiPulse).	Sequential gradient knee-length pneumatic compression devices (Kendall Company) **Additional non-comparative prophylaxis:** Not reported	**Int:** Day 2, day 7 and day 14 after surgery if pt still in hospital **Cont:** Day 2, day 7 and day 14 after surgery if pt still in hospital	**DVT** Confirmed by: Color duplex US. On day 2, day 7 and day 14 after surgery if pt still in hospital	**Int:** 3/68 **Control:** 0/49 **p value:** not reported	
								PE Confirmed by: Unknown method 6 weeks after surgery	**Int:** 1/68 **Control:** 0/49 **p value:** not reported	

Mechanical vs mechanical

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Elliot et al., 1999[170] **Country of study:** USA **Study design:** RCT **List who was masked to interventions:** Clinician assessing outcome and analysts **Evidence level:** 1+ **Duration of follow-up:** 8 days	**Patient group:** Trauma patients (head injury) **Setting:** Shock trauma – Respiratory Intensive Care unit **Inclusion criteria:** • >13 years old • Recent head injuries within 24 hours (Glasgow coma score <9) and/or major trauma and expected to be bedridden for more than 72 hours **Exclusion criteria:** • Patients with external fixation devices or casts precluding interventions • Patients who were not expected to live more than 24 hours • Patients whose injuries occurred more than 24 hours before admission. **<u>All patients</u>** **N:** 149 **Age (mean):** Gp1 – 33.9; Gp2 – 30.2 **M/F:** 100:49 **Additional risk factors:** Femoral vein catheter – 27/149 **<u>Group 1</u>** **No. randomised:** 74 **No. of dropouts:** 12 **<u>Group 2</u>** **No. randomised:** 75 **No. of dropouts:** 13	**Group 1** Calf-Thigh sequential pneumatic compression device (Kendal) Start time: End time: Duration: 8 days Length: Calf to thigh Compression profile Each of the 4 calf and 2 thigh chambers sequentially inflate to 45mmHg for 5 seconds then all remain inflated for 5 seconds then deflate simultaneously **Group 2** Plantar venous intermittent pneumatic compression device (PlexipulseR) Start time: End time: Duration: Length: Foot Compression profile: single chamber inflates for 2 seconds and cycles every 20 seconds. Chamber pressure set to 160mmHg **Additional non-comparative prophylaxis:** None	**All cause mortality**	**Group1:** 6/74 **Group 2:** 5/75 **P value:** Not sig.	**Funding:** LDS Hospital Deseret Foundation, Salt Lake City **Limitations:** Baseline characteristics indicate that calf-thigh group were more seriously injured. **Outcomes not reported:** PE, HIT, PTS, Pulmonary Hypertension, QoL, LoS **Additional outcomes reported:** bilateral and unilateral DVT **Notes:** Stratification completed by presence of femoral vein catheter 2 patients in each group received the wrong intervention. Detail is reported on the location of the DVT
			DVT, asymptomatic or symptomatic (screened for by compression ultrasonography)	**Group1:** 4/62 **Group 2:** 13/62 **P value:** 0.009 *p = 0.037 (2-sided Fishers Exact test calculated by NCC-AC using ITT original numbers randomised)*	
			Proximal DVT (screened for by compression ultrasonography)	**Group1:** 1/62 **Group 2:** 3/62 **P value:** not significant	
			Major bleeding (description: NO DEFINITION)	**Group1:** 1/74 (ruptured aorta) **Group 2:** 0/75 **P value:** Not sig.	

Mechanical vs mechanical

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Hansberry et al., 1991[254]	RCT	1+	**Total:** n = 74 Intervention 1: n = 24 Intervention 2:n = 25 Control: n = 25	**Type of surgery:** Patients undergoing total urological operation **Interventions & control:** Age range: 45 - 75years **Pre-existing risk factors:** Malignancy, Anaesthesia >90mins, one person in Int 2 had a history of a previous DVT	**Intervention 1:** External sequential pneumatic compression stockings **Intervention 2:** Thromboembolic stockings	Heparin dihydroergotamine **Additional non-comparative prophylaxis:** Not reported	6 days postoperatively or discharge if sooner.	**DVT (overall)** Confirmed by: venography and In-labelled platelet scans	**Int1:** 3/24 **Int2:** 5/25 **Control:** 2/25 **p value:** not reported	The paper did not report any dropouts **Not reported:** PTS, Fatal PE, QoL, Survival
								PE Confirmed by: ventillation perfusion scans, platelet scintigraphy and lung scan - all patients here had DVT	**Int 1:** 1/24 **Int 2:** 1/25 **Control:** 1/25 **p value:** not reported	
								Wound related complications	**Int 1:** 1/24 **Int 2:** 2/25 **Control:** 1/25 **p value:** not reported	

Mechanical vs mechanical

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Howard et al., 2004[287]	RCT	1+	**Total:** 376 **Intervention1:** n = 127 **Intervention2:** n = 121 **Intervention3:** n = 128 Stratification of pts: High risk: 291 Moderate risk: 59 Low risk: 26	Breast & Oncology (73 pts) Ear nose throat (13 pts) Gastrointestinal (122 pts) Neurosurgery (34 pts) Orthopaedic (62 pts) Urology (58 pts) Vascular Venous Surgery (14 pts) **All population:** Mean age: 58 (16 to 88) yrs M/F:158/218	**1.** Kendall TED Thigh-length **2.** Medi thrombexin Thigh-length **Additional prophylaxis:** Subcutaneous injection of 20 mg LMWH the evening before the surgery. Enoxaparin injections given daily until discharge from hospital	**3.** Medi thrombexin knee-length **Additional prophylaxis:** Subcutaneous injection of 20 mg LMWH the evening before the surgery. Enoxaparin injections given daily until discharge from hospital	Second duplex imaging between days 5-7	**DVT** Confirmed by: Duplex imaging	**Int1:** 6/102 **Int2:** 2/93 **Int3:** 11/99 ***Pairwise comparison:*** **Int1 vs Int3:** OR 0.5 [0.18, 1.41], p = 0.19 **Int2 vs Int3:** OR 0.18 [0.04,0.82], p = 0.026 ***Preoperative LMWH:*** **Int1 vs Int3:** OR 0.5 [0.18,1.42], p = 0.132 **Int2 vs Int3:** OR 0.19 [0.04,0.88], p = 0.034 **Absolute:** OR 0.41 [0.16,1.06], p = 0.066	**Not reported:** Proximal DVT, Fatal PE, PTS, Bleeding related complications, QoL and LoS **Funding:** Not reported

Mechanical vs mechanical

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Nicolaides et al 1983 [487]	RCT	1+	**Total:** Intervention 1: n = 50 Intervention 2: n = 50 Control: n = 50	**Type of surgery:** Major abdominal (& Duration of surgery) **Intervention1:** Mean age: 57.3±13.4 yrs M/F: Not reported **Intervention2:** Mean age: 58.6±13.3 yrs M/F: Not reported **Control:** Mean age: 59.2±16.6 yrs M/F: Not reported **Pre-existing risk factors:** varicose veins, previous DVT, malignancy	**Intervention1** **Type:** thigh-length IPCD + stockings **Timing:** IPCD device worn during surgery and for 72 hours post-op or until ambulant, then stockings until discharge **Intervention 2** **Type:** UFH **Dose:** 5000 IU **Timing:** Begun 2 hrs pre-op and repeated twice daily until discharge	**Type:** Electrical calf stimulation **Dose:** 12 impulses/min **Timing:** Begun after induction of anaesthesia and worn for duration of operation **Additional non-comparative prophylaxis:** Not reported	**All groups: until discharge**	**DVT** Confirmed by: ^{125}I FUT on alternate days until discharge	**No of patients:** **Int1:** 3/50 **Int2:** 7/50 **Control:** 12/50 **p value:** Not reported **No of limbs:** **Int 1:** 4/100 **Int2:** 9/100 **Control:** 18/100 **p value:** **Int 1 vs int 2:** Not significant **Int 1 vs cont** < 0.0025 **Int 2 vs control** <0.05	**Comments:** Patients stratified according to risk (four levels) before randomisation to study groups. **Not reported:** PE, PTS, bleeding, QoL, survival, LoS **Funding:** Leventis foundation. Berk pharmaceuticals (UK) provided UFH. Kendall Coporation provided IPCD and stockings
								Proximal DVT Confirmed by:	**Int1:** 0/50 **Int2:** 1/50 **Control:** 2/50 **p value:** NR	

Mechanical vs mechanical

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Roderick et al., 2005[557] 2 RCTs included [532,694] All of these studies were included in the guideline review.	Systematic Review with 2 RCTs	1+	**Total:** 212 **Intervention** Above-knee stockings n = 104 **Control:** Below knee stockings n = 108	Adults having general surgery.	Above-knee stockings **Timing:** One study reports DVT assessment from postop to discharge and other study has not stated timing.	Below knee stockings. **Additional non-comparative prophylaxis:** Not reported	**DVT** assessed in one study at postop-discharge (alternate). The other study does not report follow-up.	**DVT** confirmed by: fibrinogen uptake	**Int:** 9/100 **Cont:** 9/102 **p value:** 1.0000 Not significant	**Not reported:** proximal DVT, PE, PTS, bleeding, QoL and LoS.

Mechanical vs mechanical

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Ryan et al., 2002[565]	RCT	++	**Total:** 100 **Intervention:** n = 50 **Control:** n = 50	Patients who were to undergo total hip arthroplasty. **Intervention:** n = 50 Mean age:70.1 Gender ratio (M:F):19:31 (38%:62%) **Control:** n = 50 Mean age:67.5 Gender ratio (M:F):19:31 (38%:62%)	Vena Flow pneumatic compression device applied to both lower extremities Duration: Started immediately after surgery and continued for duration of postoperative hospital stay	Elastic stockings	Until discharge (4-5 days on average)	**Proximal DVT** (confirmed by magnetic resonance venography)	**Int:** 4/50 (8%) **Control:** 11/50 (22%) **p value:** < 0.05	Detailed findings of the magnetic resonance venogram reported eg: size and location of clot etc. No clinically symptomatic DVT or PE developed in any patient. **Not reported:** DVT, PTS, QoL.
					Additional background prophylaxis Aspirin (325mg 2x/day) Epidural anaesthesia	**Additional background prophylaxis** Aspirin (325mg 2x/day) Epidural anaesthesia		**Symptomatic PE**	**Int:** 0/50 (8%) **Control:** 0/50 **p value:** N/A	

Mechanical vs mechanical

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Silbersack et al., 2004[602]	RCT	1+	**Total:** 131 **Intervention:** n = 68 **Control:** n = 63	**Type of surgery:** Patients > 18 years, awaiting primary unilateral THR or TKR **Intervention:** No of patients with THR: 33 No of pts with TKR: 35 MeanAge:63 (29 to 90) Gender ratio (M:F):28:40 **Control:** No of pts with THR: 28 No of pts with TKR: 35 MeanAge:65 (36 to 87) Gender ratio (M:F):19:44 **Risk factors:** **Intervention:** Previous VTE: 5/68 Varicose veins: 45/68 Previous cancer: 4/68 Oestrogen users: 4/68 **Control:** Previous VTE: 3/63 Varicose veins: 39/63 Previous cancer:	LMW Heparins plus calf intermittent pneumatic compression devices. Patients were given 40mg of anti-Xa enoxaparin-natrium daily beginning on the eve prior to surgery until postoperative day 30 (self administration). **Additional non-comparative prophylaxis:** Regional anaesthesia: 49/68 Aspirin users: 11/68 Non-steriodal anti-inflammatory drugs: 25/68	LMW Heparins plus GCS Patients were also given 40mg of anti-Xa enoxaparin-natrium daily beginning on the eve prior to surgery. **Additional non-comparative prophylaxis:** Regional anaesthesia: 46/63 Aspirin users: 8/63 Non-steriodal anti-inflammatory drugs: 26/63	First follow-up: between 6th and 12th post-operative day Second follow-up: between 6th and 12th post-operative weeks.	**DVT** (confirmed by colour duplex US)	First follow up: **Int:** 0/68 **Control:** 18/63 (28.6%) (P<0.0001) Second follow up: Only of 105 of 113 pts (93%) who received prolonged prophylaxis with LMWH and GCS One fresh thrombosis case detected.	Unrestricted grant from Aircast Europa GmbH, Neubeuren, Germany which made the VenaFlow system during the study period. - IPCD was often used incorrectly t the beginning of the study. - 27% of pts stopped using IPCD prematurely. - Night-time use of IPCD was refused. - In comparison with GCS, the IPCD requires more supervision.
								PE (confirmed by spiral CT of lungs)	No cases of symptomatic PE.	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
				2/63 Oestrogen users: 2/63						

Mechanical vs mechanical

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Soderdahl et al., 1997[611]	RCT	1+	**Total:** 90 **Intervention:** n = 47 **Control:** n = 43	**Type of surgery:** Urological, Duration of surgery not reported	**Type:** Thigh-length IPCD	**Type:** Calf-length IPCD	**Both groups:** mean FU 10 months (range 3-40 months). All clinically evaluated at 3 and 6 mo	**DVT** Confirmed by: Bilateral duplex US on post-op day 3/4 and 6/7	**Int:** 0/47 **Control:** 1/43 **p value:** 0.29	**Comments:** Post-surgery. Interviews with nursing personnel suggested that calf-length IPCDs were easier to apply and greater patient satisfaction. Cost analysis
				Intervention: Mean age: 64.8 (range 46-90) M/F:67/67	**Timing:** Begun pre-anaesthetic and continued until patient fully ambulatory or until discharge	**Timing:** Begun pre-anaesthetic and continued until patient fully ambulatory or until discharge		**PE** Confirmed by pulmonary angiography	**Int:** 1/47 **Cont:** 0/43 **p value:** 0.33	
				Control: Mean age: 58.6 (range 24-77) M/F:92/77				**Fatal PE** (not stated how confirmed)	**Int:** 0/47 **Cont:** 1/43 (at 17 months postoperatively **p value:** 0.4778	
				Pre-existing risk factors: previous VTE, obesity, malignancy, congestive heart failure, IBS, MI.	**Additional non-comparative prophylaxis:** None reported	**Additional non-comparative prophylaxis:** None reported				**Not reported:** PVT, PTS, Bleeding, QoL, LoS, Survival, funding.

Mechanical vs mechanical

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Stannard et al., 2001[621]	RCT	.	**Total:** 140 **Intervention:** n = 54 **Control:** n = 53	**Type of surgery:** Orthopaedic (hip fracture) Duration not stated Age and gender not reported **Pre-existing risk factors:** All patients had sustained a pelvic or acetabular fracture due to blunt trauma requiring surgery. Injury severity scores recorded	**Type:** bilateral thigh-calf low pressure compression device **Dose:** 45mm Hg **Timing:** (duration) mean 20.8 hrs/day (range 4 - 24hrs/day) (time started) as soon as possible following admission to trauma service (time finished) discharge	**Type:** bilateral combination calf-foot high pressure compression device **Dose:** 160 mm Hg **Timing:** (duration) mean 21.3 hrs/day (range 7 - 24hrs/day) (time started) as soon as possible following admission to trauma service (time finished) discharge **Additional non-comparative prophylaxis:** Not reported	**FU to discharge** **Control:** mean 6.0 days post-surgery **Int:** mean 6.5 days post-surgery	**DVT** Confirmed by: Duplex US, MRI	**Int:** 10/54 **Control:** 5/53 **p value:** 0.265 Not significant	33 patients dropped out. Paper doesn't state how many were lost from each group. Check comparison. May be best considered to be IPCD (leg) vs IPCD +footpump (if length of IPCD doesn't make a significant difference). Also reported whether DVTs were occlusive or non-occlusive and > or < 2 cm in size. Increased patient age and time elapsed from injury to surgery were associated with higher rates of thrombosis **Not reported:** PE, QoL, LoS, PTS, Bleeding
								Fatal PE Confirmed by:	**Int:** **Control:** **p value:** (Significant/Not significant)	
								Survival	134/140. Deaths not due to PE, don't know which groups these patients belonged too	

Mechanical vs mechanical

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Wood et al., 1997[701]	RCT	1+	**Total:** 160 134 completed the study. Not stated to which arms the dropouts were randomised. **Intervention:** n = 75 **Control:** n = 59	**Type of surgery:** Anterior lumbar interbody fusion, posterior spine fusion, posterior lumbar interbody fusion, thigh-high graduated compression stockings **Excluded:** History of VTE, preoperative assessment of at risk of DVT, congestive heart failure, previous anticoagulation treatment, contraindications to compression device use such as neuropathy, infection or chronic venous stasis. **Intervention:** Mean age: 39.4 (sd 17.2) yrs M/F: 39/36 **Control:** Mean age: 39.6 (sd 18.5) yrs M/F: 39/20 **Weight (mean):** Int: 80.3kg Control: 68.5kg **p value:** 0.001	Foot wraps (Plexi Pulse) to both feet Started at surgery and worn until ambulatory, then worn when in bed until discharge **Additional non-comparative prophylaxis:** Thigh-high compression stockings started before surgery and worn for hospital course.	Thigh high sequential Pneumatic Compression Wrap (Kendall) on both legs Started at surgery and worn until ambulatory, then worn when in bed until discharge **Additional non-comparative prophylaxis:** Thigh-high compression stockings started before surgery and worn for hospital course.	Scanning carried out between post-operative days 5 and 7	**DVT** Confirmed by: Duplex US **PE** Confirmed by: Duplex US **Visual analogue comfort scale** (mean ±SD)	**Int:** 1/75 **Control:** 0/59 **p value:** 1.0000 **Int:** 1/75 **Control:** 0/59 **p value:** 1.0000 **Int:** 5.84 ±2.8 **Cont:** 5.56 ±2.9 **p value:** 0.88	**Comments:** 36 patients (26%) complained of redness, itching, or actual discomfort with the use of the devices. No symptomatic DVTs of PEs **Not reported:** Survival, PTS, bleeding related complications, QoL and LoS

Evidence Table 31: Fondaparinux vs LMWH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Agnelli et al., 2005[10]	RCT	1+	**Total: Intervention:** n = 1433 **Control:** n =1425 **Int dropouts:** not treated: 32 not available for analysis: 406 **Comp dropouts:** not treated: 37 not available for analysis: 404	**Type of surgery:** High risk abdominal surgery Duration of surgery: **Int:** 2hr 30 (range 23min - 11 hr) **Cont:** 2hr 30 (range 16 min - 15 hr 27min) **Intervention:** Median age: 66 (31-92) yrs M/F:788/645 **Control:** Median age: 65 (17-93 yrs) M/F:92/77 **Pre-existing risk Factors:** Patients were >60 or >40 with the presence of an additional risk factor	**Type:** Fondaparinux **Dose:** 2.5 mg once daily **Timing:** Begun 6 hrs post-op and repeated daily for 5-9 days. Placebo injections given to match LMWH schedule. **Additional non-comparative prophylaxis:** Use of GCS permitted. Early mobilisation strongly recommended	**Type:** LMWH (Dalteparin) **Dose:** 2500 IU given 2 hours before preoperatively then 2500 IU given 12 hours later. 5000 units given once daily thereafter **Timing:** Begun 2hrs pre-op and repeated for 5-9 days. Placebo injections given to match fondaparinux schedule. **Additional non-comparative prophylaxis:** Use	Venography up until day 10 postoperatively.	**DVT** Confirmed by: Bilateral venography on 5-10th post-op day (but no more than 1 day after last injection).	**Int:** 4/1024 **Control:** 59/1018 **p value:** 0.1 Not significant	**Comments:** Multicentre trial in 131 hospitals in 22 countries. Lower age limits of patient groups do not correspond to inclusion criteria. Clinical PE in 5 Fondaparinux and 3 LMWH patients (of which 3 in each group were fatal). LMWH begun post-op in some patients (who received epidural anaesthesia) **Not reported:** PTS, QoL, LoS **Funding:** Sponsored by drug company (Sanofi-Synthlabo and NV
								Proximal DVT Confirmed by: As above	**Int:** 5/1076 **Control:** 5/1077 **p value:** 1 Not significant	
								Symptomatic pulmonary embolism confirmed by high probability lung scan, pulmonary angiography, helical computed tomography or autopsy	**Int:** 5/1465 **Control:** 3/1462 **p value:** not signiticant	
								Fatal pulmonary embolism confirmed by autopsy	**Int:** 3/1465 **Control:** 3/1462 **p value:** not signiticant	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
						of GCS permitted. Early mobilisation strongly recommended		**Bleeding related complications** Major bleeding: fatal, retroperitoneal, intracranial, intraspinal, or involved any other critical organ, bleeding leading to reoperation or intervention, or a bleeding index of 2.0 or more.	**Int:** 49/1433 **Control:** 34/1425 **p value:** 0.122 Not significant	organon). 2 company reps on steering committee. Data collection and statistical analysis performed by sponsor.
								All cause mortality:	**On 10th day** **Int:** 15/1433 **Control:** 34/1425 **p value:** 0.0060 **Day 32** **Int:** 32/1433 **Control:** 55/1425 **p value:** 0.0122	

Fondaparinux vs LMWH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Bauer et al., 2001[36]	RCT	1+	**Total:** 1049 **Intervention** n: 526 **Control** n: 523 **Dropouts (not treated):** Int: 9 Comp: 6 **Dropouts (not available for analysis):** Int: 156 Comp: 154	**Type of surgery:** Patients undergoing elective major knee surgery. Duration of surgery: 128 mins, SD: ±42 **Intervention:** Mean age: 67.5, SD: ±10.7; M/F:204/313 **Control:** Mean age: 67.5, SD: ±10.2; M/F:223/294 **Pre-existing risk Factors:** History of VTE: **Intervention:** 23% **Control:** 28%. Orthopaedic surgery within the previous 12 months: **Intervention:** :87% **Control:**: 27%	2.5 mg of Fondaparinux sodium postoperatively once daily and a placebo once daily subcutaneously till day 5 to 9. Day of surgery is day 1. **Additional non-comparative prophylaxis:** The use of graduated compression stockings and physiotherapy was recommended No. patients receiving/using: GCS = 298/361 Anticoagulant/antiplatelet therapy (not aspirin) = 4/361 NSAIDs or aspirin= 44/361	30 mg of Enoxaparin twice daily postoperatively until day 5 to 9. Day of surgery is day 1. **Additional non-comparative prophylaxis:** The use of graduated compression stockings and physiotherapy was recommended No. patients receiving/using: GCS = 294/363 Anticoagulant/antiplatelet therapy (not aspirin) = 11/363 NSAIDs or aspirin= 60/363	49 days	**DVT** Confirmed by: systematic bilateral ascending venography	**Int:** 45/361 **Control:** 98/361 **p value:** 0.001; RR: 54.1% (95% CI)	**Funding:** The authors have served as consultants to NV Organon and Sanofi-Synthelabo and the study supported by NVO & SS. ** defined as fatal bleeding; bleeding that was retroperitoneal, intracranial or intraspinal or that involved any other critical organ, bleeding that lead to reoperation; and overt bleeding with index of 2 or more.
								VTE	**Int:** 45/361 **Control:** 101/363 **p value:** <0.001 **Reduction in risk (95% CI)** 55.2 (36.2 to 70.2)	
								Symptomatic DVT	**Int:** 3/517 **Control:** 4/517 **p value:** 1.000	
								Proximal DVT Confirmed by: systematic bilateral ascending venography	**Int:** 9/368 **Control:** 20/372 **p value:** 0.06	
								Non-fatal PE Confirmed by: lung scan, pulmonary angiography or helical computed tomography or at autopsy	**Int:** 1/517 **Control:** 4/517 **p value:** 0.3738	
								Fatal PE Confirmed by:	**Int:** 0/517 **Control:** 0/517 **p value:** N/A	
								Major bleeding **	**Int:** 11/517 **Control:** 1/517 **p value:** 0.003	
								Bleeding leading to re-operation	**Int:** 2/517 **Control:** 1/517 **p value:** 1.000	
								Other bleeding –	**Int:** 14/517	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
								number (%)	**Control:** 19/517 **p value:** 0.4797	
								Postoperative transfusions – number (%)	**Int:** 222/517 **Control:** 197/517 **p value:** 0.1284	
								Death from any cause - number (%) Up to day 11	**Int:** 1/517 **Control:** 2/517 **p value:** 1.0000	
								Death from any cause - number (%) Up to day 49	**Int:** 2/517 **Control:** 3/517 **p value:** 1.0000	

Fondaparinux vs LMWH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Eriksson et al., 2001[175]	RCT	1+	Total: 1711 Intervention: 849 Control n: 862 **Dropouts (not treated):** Int: 18 Comp: 20 **Dropouts (not available for analysis):** Int: 205 Comp: 218	**Type of surgery:** Patients scheduled to undergo standard surgery for fracture of the upper third of femur, including femoral head and neck within 48 hours of admission. Duration of surgery: 104 mins, SD: ±44 **Intervention:** Mean age: 76.8, SD: ±12.3; M/F:187/644 **Control:** Mean age: 77.3, SD: ±12.6; M/F:224/698 **Pre-existing risk factors:** History of VTE: **Intervention:** 29 (3.5%) **Control:** 32 (3.8%). Orthopaedic surgery within the previous 12 months: **Intervention:** 33 (4.0%) **Control:**: 26 (3.1%)	2.5 mg of Fondaparinux sodium and a placebo. The first active dose was given 6±2 hrs postoperatively and the second 12 or more after the first. Treatment was scheduled to continue until day 5 to 9. Day of surgery is day 1. **Additional non-comparative prophylaxis:** The use of graduated compression stockings and physiotherapy was recommended No. patients receiving/using: GCS = 312/626 Anticoagulant/antiplatelet therapy (not aspirin = 23/626 NSAIDs or aspirin = 141/626	40 mg of Enoxaparin 1x/day and placebo. The first active dose was given 12±2 hrs preoperatively and the second 12 to 24 hours postoperatively. Treatment was scheduled to continue until day 5 to 9. Day of surgery is day 1. **Additional non-comparative prophylaxis:** The use of graduated compression stockings and physiotherapy was recommended No. patients receiving/using: GCS = 295/624 Anticoagulant/antiplatelet therapy (not aspirin) = 21/624 NSAIDs or aspirin = 126/624	49 days	**DVT** Confirmed by: systematic bilateral ascending venography	**Int:** 49/624 **Control:** 117/623 **p value:** <0.001; RR: 58.2% (95% CI)	**Funding:** The authors have served as consultants to NV Organon and Sanofi-Synthelabo and the study supported by NVO & SS. ** defined as fatal bleeding; bleeding that was retroperitoneal, intracranial or intraspinal or that involved any other critical organ, bleeding that lead to reoperation; and overt bleeding with index of 2 or more.
								VTE	**Int:** 52/626 **Control:** 119/624 **p value:** < 0.001 **Reduction in risk (95 % CI)** 56.4 (39.0 to 70.3)	
								Symptomatic DVT	**Int:** 1/831 **Control:** 1/840 **p value:** 1.000	
								Proximal DVT* Confirmed by: systematic bilateral ascending venography	**Int:** 6/650 **Control:** 28/646 **p value:** <0.001	
								Non fatal PE Confirmed by: lung scan, pulmonary angiography or helical computed tomography or at autopsy	**Int:** 1/831 **Control:** 1/840 **p value:** 1.000	
								Fatal PE Confirmed by:	**Int:** 2/831 **Control:** 2/840 **p value:** 1.000	
								Major bleeding **	**Int:** 18/831 **Control:** 119/842 **p value:** 0.52	
								Fatal bleeding	**Int:** 0/831 **Control:** 1/842 **p value:** 1.000	
								Bleeding leading	**Int:** 3/831	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
								to re-operation	**Control:** 2/842 **p value:** 0.6851	
								Minor bleeding – number (%)	**Int:** 34/831 **Control:** 18/842 **p value:** 0.0240	
								Postoperative transfusions – number (%)	**Int:** 421/831 **Control:** 422/842 **p value:** 0.8450	
								Death from any cause - number (%) Up to day 11	**Int:** 11/831 **Control:** 16/842 **p value:** 0.4386	
								Death from any cause - number (%) Up to day 49	**Int:** 38/831 **Control:** 42/842 **p value:** 0.7317	

Fondaparinux vs LMWH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Lassen et al., 2002[377]	RCT	1+	**Total:** 2309 **Intervention** n: 1155 **Control** n: 1154 **Dropouts (not treated):** Int: 15 Comp: 21 **Dropouts (not available for analysis):** Int: 232 Comp: 214	**Type of surgery:** Patients scheduled for primary elective total hip-replacement surgery or revision of at least one component of a previously implanted total hip prosthesis. Duration of surgery: 2.4 hours, SD: ±0.83 **Intervention:** Mean age: 67, range: 30-90; M/F:396/512 **Control:** Mean age: 67, range: 24-97; M/F:402/517 **Pre-existing risk factors:** History of VTE: **Intervention:** 35 (4%) **Control:** 40 (4%). Orthopaedic surgery within the previous 12 months: **Intervention:** 85 (9%) **Control:** 84 (9%)	2.5 mg of Fondaparinux sodium and a placebo. The first active dose was given 6±2 hrs postoperatively and the second 12 or more after the first. Treatment was scheduled to continue until day 5 to 9. Day of surgery is day 1. **Additional non-comparative prophylaxis:** The use of graduated compression stockings and physiotherapy was recommended No. patients receiving/using: GCS = 649/908 Anticoagulant/antiplatelet therapy (not aspirin = 29/908 NSAIDs or aspirin: 483/908	40 mg of Enoxaparin 1x/day and placebo. The first active dose was given 12±2 hrs preoperatively and the second 12 to 24 hours postoperatively. Treatment was scheduled to continue until day 5 to 9. Day of surgery is day 1. **Additional non-comparative prophylaxis:** The use of graduated compression stockings and physiotherapy was recommended No. patients receiving/using: GCS = 654/919 Anticoagulant/antiplatelet therapy (not aspirin) = 30/919 NSAIDs or aspirin: 493/919	49 days study period 11 days	**DVT** Confirmed by: systematic bilateral ascending venography (number of events/ total number)	**Int:** 36/908 **Control:** 83/918 **p value:** <0.0001; RRR:- 56.1% (95% CI)	**Funding:** study supported by NV Organon and Sanofi-Synthelabo. * ** defined as fatal bleeding; bleeding that was retroperitoneal, intracranial or intraspinal or that involved any other critical organ, bleeding that lead to reoperation; and overt bleeding with index of 2 or more.
								VTE	**Int:** 37/908 **Control:** 85/919 **p value:** < 0.0001 **RRR (95 % CI) -** 55.9 (-72.8 to -33.1)	
								Symptomatic DVT	**Int:** 3/1129 **Control:** 1/1123 **p value:** 0.6247	
								Proximal DVT * Confirmed by: systematic bilateral ascending venography	**Int:** 6/922 **Control:** 23/927 **p value:** 0.002	
								Non fatal PE Confirmed by: lung scan, pulmonary angiography or helical computed tomography or at autopsy	**Int:** 2/1129 **Control:** 2/1123 **p value:** 1.000	
								Fatal PE Confirmed by:	**Int:** 0/1129 **Control:** 0/1123 **p value:** N/A	
								Major bleeding **	**Int:** 47/1140 **Control:** 32/1133 **p value:** 0.57	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
								Fatal bleeding	**Int:** 0/1140 **Control:** 0/1133 **p value:** N/A	
								Bleeding leading to re-operation	**Int:** 5/1140 **Control:** 3/1133 **p value:** 0.7261	
								other bleeding – number (%)	**Int:** 44/1140 **Control:** 38/1133 **p value:** 0.5743	
								Postoperative transfusions – number (%)	**Int:** 714/1140 **Control:** 690/1133 **p value:**	
								Death from any cause - number (%) Up to day 11	**Int:** 0/1140 **Control:** 2/1133 **p value:** 0.4122	
								Death from any cause - number (%) Up to day 49	**Int:** 2/1140 **Control:** 4/1133 **p value:** 0.4122	

Fondaparinux vs LMWH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Turpie et al., 2002[651]	RCT	1+	**Total:** 2275 **Intervention** n: 1138 **Control** n: 1137 **Dropouts (not treated):** Int: 10 Comp: 8 **Dropouts (not available for analysis):** Int: 341 Comp: 332	**Type of surgery:** Patients scheduled for primary elective total hip-replacement surgery or revision of at least one component of a previously implanted total hip prosthesis. Duration of surgery: 2.42 hours, SD: ±0.98 **Intervention:** Mean age: 67, range: 26-92; M/F:386/401 **Control:** Mean age: 67, range: 19-91; M/F:375/422 **Pre-existing risk factors:** History of VTE: **Intervention:** 40 (5%) **Control:** 50 (6%). Orthopaedic surgery within the previous 12 months: **Intervention:** 99 (13%) **Control:** 84 (11%)	2.5 mg of Fondaparinux sodium and a placebo. The first active dose was given 4-8 hrs after surgery and the second 12 or more after the first. Treatment was scheduled to continue until day 5 to 9. Day of surgery is day 1. **Additional non-comparative prophylaxis:** The use of graduated compression stockings and physiotherapy was recommended No. patients receiving/using: GCS = 674/787 Anticoagulant/antiplatelet therapy (not aspirin) = 13/787 NSAIDs or aspirin = 107/787	30 mg of Enoxaparin twice daily. The first active dose was given 4-8 hrs after surgery and the second 12 or more after the first. Treatment was scheduled to continue until day 5 to 9. Day of surgery is day 1. **Additional non-comparative prophylaxis:** The use of graduated compression stockings and physiotherapy was recommended No. patients receiving/using: GCS = 676/797 Anticoagulant/antiplatelet therapy(not aspirin) = 11/797 NSAIDs or aspirin = 108/797	49 days study period 11 days	**DVT** Confirmed by: systematic bilateral ascending venography	**Int:** 44/784 **Control:** 65/796 **p value:** <0.047; RRR:- 31.3% (95% CI)	**Funding:** study supported by NV Organon and Sanofi-Synthelabo. ** defined as fatal bleeding; bleeding that was retroperitoneal, intracranial or intraspinal or that involved any other critical organ, bleeding that lead to reoperation; and overt bleeding with index of 2 or more.
								VTE	**Int:** 48/787 **Control:** 66/797 **p value:** 0.099 **RRR (95 % CI) -** 26.3 (-52.8 to -10.8)	
								Symptomatic DVT	**Int:** 5/1126 **Control:** 0/1128 **p value:** 0.0310	
								Proximal DVT* Confirmed by: systematic bilateral ascending venography	**Int:** 14/816 **Control:** 10/830 **p value:** 0.42	
								Non fatal PE Confirmed by: lung scan, pulmonary angiography or helical computed tomography or at autopsy	**Int:** 5/1126 **Control:** 0/1128 **p value:** 0.0310	
								Fatal PE Confirmed by:	**Int:** 0/1126 **Control:** 1/1128 **p value:** 1.0000	
								Major bleeding **	**Int:** 20/1128 **Control:** 11/1129 **p value:** 0.73	
								Fatal bleeding	**Int:** 0/1128 **Control:** 0/1129 **p value:** 1.0000	
								Bleeding leading	**Int:** 2/1128	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
								to re-operation	**Control:** 2/1129 **p value:** 1.0000	
								Other bleeding – number (%)	**Int:** 17/1128 **Control:** 24/1129 **p value:** 0.3447	
								Postoperative transfusions – number (%)	**Int:** 593/1128 **Control:** 555/1128 **p value:** 0.1192	
								Death from any cause - number (%) Up to day 11	**Int:** 3/1128 **Control:** 1/1129 **p value:** 0.3744	
								Death from any cause - number (%) Up to day 49	**Int:** 6/1128 **Control:** 3/1129 **p value:** 0.3427	

Evidence Table 32: LMWH vs UFH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Avikainen et al 1995[26]	RCT	1+	**Total:** 167 Intervention: n = 83 (DVT assessed in 79) Control: n = 84 (DVT assessed in 79)	**Type of surgery:** Hip replacement (& Duration of surgery)	**Type:** LMWH (Enoxaparin) **Dose:** 40mg/0.4 ml	**Type:** UFH **Dose:** 5000 IU	**Both groups:** Until discharge (10th post-op -).	**DVT** Confirmed by: US on 10-14th post-op day.	**US results for 158 patients** **Int:** 1/79 **Control:** 4/79 **p value:** >0.05	Also reported: **perioperative and postoperative blood loss, transfusion requirements** **Not reported:** PTS, QoL, survival, LoS, funding
				Intervention: Mean age: 65 (range 27-86) yrs M/F:30/53	**Timing:** Begun 12hrs pre-op and repeated daily for 10 days **Additional non-comparative prophylaxis:** Not reported	**Timing:** Begun 2hrs pre-op and repeated twice daily for 10 days		**PVT** Confirmed by: US on 10-14th post-op day.	**Int:** 1/79 **Control:** 4/79 **p value:** >0.05	
				Control: Mean age: 66 (range 34-86) M/F:25/59				**PE** Confirmed by: Not routinely assessed. Symptomatic confirmed by V/Q scan	**All patients:** **Int:** 0/84 **Control:** 1/83 **p value:** 0.4970	
				Pre-existing risk factors: varicose veins						

LMWH vs UFH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Beghi et al 1993[38]	RCT	1+	**Total:** 39 Intervention: n = 20 Control: n = 19	**Type of surgery:** Open heart surgery **Duration of surgery:** **Intervention:** 209±11.82 min **Control:** 224±13.37 min **Age & Gender:** **Intervention:** Mean age: 60.2±1.94 yrs M/F:15/5 **Control:** Mean age: 60.5±2.39 yrs M/F: 16/3	**Type:** LMWH (Fluxum) **Dose:** 3200 IU **Timing:** Begun 1st day post-op and repeated three times daily until 4th post-op day **Additional non-comparative prophylaxis:** Not reported	**Type:** LDUH **Dose:** 5000 IU **Timing:** Begun 1st day post-op and repeated daily until 4th post-op day	**Both groups:** 11 days	**DVT** Confirmed by: Doppler US (on 7th post-op day?)	**Int:** 0/20 **Control:** 0/19 **p value:** N/A	**Comments:** Patients with cardiac disease requiring post-operative oral anticoagulation were not included in the study. **Not reported:** Proximal DVT, PE, PTS, QoL, survival, LoS **Also reported:** units of transfused blood per patient; volume of bleeding; haemoglobin g/100cc; platelets n/mm^3

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Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Bergmann & Neuhart, 1996[45] **Country of study:** France **Study design:** RCT, double blind, multicentre, equivalence study. **List who was masked to interventions:** Physicians, nurses, patients and the independent expert reading the fibrinogen scans. **Evidence level:** 1+ **Duration of follow-up:** 10 days	**Patient group:** Elderly in patients bedridden due to an acute illness **Setting:** In-patients, multicentre **Inclusion criteria:** ▪ Age≥65 years ▪ Acute medical illness which led to a recent reduction of autonomous mobility (<4 days), unable to walk 10m unassisted. **Exclusion criteria:** ▪ Contraindication to anticoagulant treatment (uncontrolled hypertension, recent haemorrhagic stroke, any other haemorrhagic diseases) ▪ Any ongoing venous, arterial or cardiac disease requiring "curative" anticoagulant treatment ▪ History of allergy or thrombocytopenia induced by UFH or LMWH ▪ Haemostasis abnormality (in particular platelet count <100 x 10^9/l) ▪ Weight>80kg ▪ Use of heparin or anticoagulants, aspirin or NSAIDS, for more than 24 hours before inclusion ▪ Any contraindication to isotopic and/or venographic investigations ▪ Renal failure (creatinine >150microM) ▪ Local disorders of the lower limbs likely to interfere with the fibrinogen uptake test **<u>All patients</u>** **N:** 442 **Age (mean):** 83.2±0.34 **M/F:** 123/316 **Additional risk factors*** ▪ Cardiac failure: 125/423 ▪ Respiratory failure: 61/423 ▪ History of venous thromboembolism: 35/423 ▪ Cancer: 63/423	**Group 1** **UFH** Heparin calcium, 5000U (in 0.2 ml pre-filled syringe),every 12 hours Start time: Duration: 10 days **Group 2** **Enoxaparin** (Lovenox®) 20mg (in 0.2ml pre filled syringe), alternated with identical appearance placebo (mannitol), every 12 hours Duration: 10 days Mean duration of treatment for 439 patients was 9.5 ±0.1 days. **Additional non-comparative prophylaxis:** ▪ Use of heparin or anticoagulants, aspirin or NSAIDS, for more than 24 hours before inclusion was an exclusion criteria ▪ Mechanical prophylaxis not discussed	**All cause mortality**	**Group1:** 8/223 **Group 2:** 7/216 **P value:** 1.00 *calculated by NCC-AC team from numbers randomised using Fishers exact test]*	**Funding:** Rhone Poulence Rorer **Limitations:** ▪ This was an equivalence study, maximum difference of 7% in incidence of venous thrombosis between 2 groups. Powered at 80%, n required was 244 per group. Total number was less than calculated sample size because study stopped when I fibrinogen stopped being marketed in 1991. ▪ 37 patients in enoxaparin group and 34 patient sin UFH group had asymptomatic decrease in Hb≥20g/L, and was not counted as major bleeding. Hemodilution was cited as reason, but it was not reported whether these patients were the ones with hemoconcentration upon inclusion. **Outcomes not reported:** Fatal PE, PE asymptomatic or symptomatic, Fatal
			Symptomatic pulmonary embolism (confirmed by: perfusion lung scan)	**Group1:** 0/216 **Group 2:** 1/207 **P value:** 0.49 *calculated by NCC-AC team from numbers randomised using Fishers exact test*	
			DVT, asymptomatic or symptomatic (Fibrinogen scan, conducted within 24 hours of enrolment, and everyday, thereafter in both legs)	**Group1:** 10/216 **Group 2:** 9/207 **P value:** 1.00 *[calculated by NCC-AC team from numbers randomised using Fishers exact test]*	
			Thigh DVT(confirmed by: as in DVT)	**Group1:** 2/216 **Group 2:** 4/207 **P value:** 0.44 *[calculated by NCC-AC team from numbers randomised using Fishers exact test]*	
			Calf DVT (confirmed by: as in DVT)	**Group1:** 8/216 **Group 2:** 5/207 **P value:** 0.49 *[calculated by NCC-AC team from numbers randomised using Fishers exact test]*	
			Major bleeding (description: clinical, associated with either a fall of haemoglobin 20g/l, need for transfusion of ≥2 blood units, bleeding was retroperitoneal or intracranial)	**Group1:** 2/ 223 **Group 2:** 1/ 216 **P value:** 1.00 *[calculated by NCC-AC team from numbers randomised using Fishers exact test]*	
			Minor bleeding (description: haematuria in the LMWH group, 1 epistaxis, 1 haematemesis in the UFH group)	**Group1:** 2/223 **Group 2:** 1/216 **P value:** 1.00 *[calculated by NCC-AC team from numbers randomised using Fishers exact test]*	
			Heparin induced thrombocytopenia (patient had normal platelet count upon inclusion, asymptomatic	**Group1:** 1/223 **Group 2:** 0/216 **P value:** 1.0 *[calculated by NCC-AC team from numbers*	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	▪ Obesity: 58/423 ▪ Varicose veins: 103/423 ▪ Completely bedridden:223/423 (mean duration for confinement for bed ridden patients was 36.6 hours before enrolment) ▪ Infectious disease:139/423 ▪ Paralysis of the lower limbs: 40/423 *[*calculated by NCC-AC team from numbers in Tablle 2 of paper, in the results section. Both groups were described as "similar", although results not shown]* **<u>Group 1</u>** **No. randomised:** 225 **No. of dropouts:** 2 **Age (years ±sem):** 82.6±0.46 **M/F:** 60/163 **Weight (kg ± sem):** 57.0±0.78 **Reasons for hospitalisation (at baseline):** ▪ Heart failure:46/223 ▪ Bronchopulmonary infection: 58/223 ▪ Ischaemic stroke: 20/223 ▪ Cancer: 19/223 ▪ Malnutrition: 18/223 ▪ Dehydration: 41/223 ▪ Systemic infection: 7/223 ▪ Others: 121/223 **<u>Group 2</u>** **No. randomised:** 217 **No. of dropouts:** 1 **Age (years ±sem):** 83.8±0.51 **M/F:** 63/153 **Weight (kg ± sem):** 57.8±0.79 **Reasons for hospitalisation (at baseline):** ▪ Reasons for hospitalisation: ▪ Heart failure:40/216 ▪ Bronchopulmonary infection:49/216 ▪ Ischaemic stroke:18/216 ▪ Cancer: 11/216 ▪ Malnutrition: 15/216 ▪ Dehydration: 39/216 ▪ Systemic infection: 8/216 ▪ Others:125/216		thrombocytopenia on Day 9 which resolved spontaneously on 15 days after discontinuation of heparin)	*randomised using Fishers exact test]*	bleeding, Neurological bleeding, Upper GI bleeding , PTS, Pulmonary hypertension, QoL, LOS **Additional outcomes reported:** ▪ Symptomatic VTE- 7/20 of patients with VTE were symptomatic: 1 PE6 lower extremities. ▪ 18% presented with hemoconcentration upon inclusion. 37 patients in the enoxaparin group and 34 patients in the UFH group had asymptomatic decrease of ≥20g/L in Hb levels. The investigators considered that these were due to hemodilution. **Notes:**

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Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Cohn et al., 1999[124] **Country of study:** United states **Study design:** RCT **List who was masked to interventions:** Double blinded **Evidence level:** 1+ **Duration of follow-up:** Up to 30 days	**Patient group:** Trauma patients-moderate injuries (predominantly blunt trauma) **Setting:** Level 1 trauma centre (Yale, New Haven) **Inclusion criteria:** Trauma patients with at least one of the following risk factors: ▪ Age >45 ▪ Expectation of >2 days bed rest ▪ History of DVT or PE ▪ Coma (Glasgow coma score (GCS)<7) ▪ Spinal cord injury ▪ Pelvis fracture ▪ Lower extremity facture ▪ Repair of major lower extremity vein ▪ Complex wound of lower extremity ▪ Femoral catheter **Exclusion criteria:** Patient meet any of the following criteria ▪ Age<18 years ▪ Severe closed head injury (elevated intracranial pressure) ▪ Bleeding injuries not accessible to haemostatic control ▪ Active bleeding disorder ▪ Cardiovascular instability ▪ Nursing mothers ▪ Heparin, warfarin or heparinoid compounds within 7 days of the injury ▪ Allergy to heparin, bisulphites, or fish ▪ History of : ○ protein C deficiency ○ heparin associated thrombocytopenia ▪ Malignant blood pressure >250mmHg systolic, >130 mmHg diastolic ▪ Liver failure with encephalopathy ▪ Renal failure **All patients**	**Group 1** Unfractionated heparin (UFH) Dose: 5000IU subcutaneously Frequency: twice a day **Group 2** LMWH (which one?) Dose: 30mg subcutaneously Frequency: twice a day **Start:** within 24 hours of trauma **End time:** until patients were fully ambulatory or discharged, or 30 consecutive 24-hour period, which ever was longer, **Duration:** up to 30 days **Additional non-comparative prophylaxis:** None. Patients were not allowed any elastic stocking, calf compression boots or anti-platelet drugs while under evaluation Received vena cava filters: UFH: 3 LMWH:2	**DVT, asymptomatic or symptomatic** (confirmed by: Doppler ultrasound, weekly)	**Group1:** 2/32 (6.25%) **Group 2:** 0/34 **P value:** 0.23 *[#values calculated by NCC-AC staff, using Fisher's exact test]*	**Funding:** Not stated **Limitations:** ▪ High drop out rate-36.5%, power diminished. Not ITT analysis ▪ Which LMWH was used? **Outcomes not reported:** All cause mortality, Symptomatic PE, Symptomatic or asymptomatic PE, Symptomatic DVT, Thigh DVT, Calf DVT Fatal bleeding, Neurological Bleeding Upper GI bleeding, HIT, Post thrombotic syndrome, Pulmonary hypertension, QoL **Additional outcomes reported:** ▪ 5 patients of each arm had "bleeding complications". It was not clear whether these were major bleeding, as major bleeding had been defined. It was decided that the bleeding data not to be included after discussion among reviewers. ▪ Not stated from which treatment arm: (removed from evaluable group)Thrombocytopenia, n=2, excessive bleeding, n=1 **Notes:**
			Symptomatic pulmonary embolism (Confirmed by: patients with clinical signs of PE(hypoxia, tachypnea, chest pain, tachycardia) would be evaluated by ventilation and perfusion scan and/or angiogram	**Group1:** 0/53 **Group 2:** 0/51 **P value:** 1.0	
			Length of stay	**Group1:** 12±9 days **Group 2:** 12± 0 days **P value:** NS	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 104 **Age (mean):** not stated **M/F:** not stated **Additional risk factors:** ISS (injury severity score= 12) **Group 1:** UFH **No. randomised:** 53 **No. of dropouts:** 21 **Penetrative injury:** 0 **Orthopaedic injuries:**29 **ISS:** 13±14 **Penetrating injury:** 0 **Group 2:** LMWH **No. randomised:** 51 **No. of dropouts:** 17 **Penetrative injury:** 2 **Orthopaedic injuries:**32 **ISS:** 10±5 **Penetrating injury:** 2				Regular weekly ultrasound scan for DVT

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Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Colwell et al., 1995[130]	Multicentre RCT involving 25 centres.	1+	**Total:** 453 Intervention: n = 228 Control: n = 225	**Type of surgery:** Elective knee arthroplasty	**Type:** Enoxaparin 30mg every 12 hours	**Type:** Unfractionated heparin 5000 units every 8 hours	Treatment period up to 14 days, follow up approx 3 weeks after last dose	**DVT** Confirmed by: US or venography	**Int:** 54/145 **Control:** 74/143 **p value:** 0.02	**Comments:** Only 63.6% of patients evaluated. Multicentre study, not all centres used a valid diagnostic technique (same numbers in each group). An intention to treat analysis was followed. Results are available for patients diagnosed by valid test alone as well as all patients. Also reported: incidence of DVTs diagnosed from all means including symptomatic, broken down into distal and proximal.
				Intervention: Mean age: 67.5± 9.5 yrs M/F:107/121	**Timing:** started day of surgery (within 8hours of surgical closure) and continued for a minimum of 4 days and maximum of 14 days.	**Timing:** started day of surgery (within 8hours of surgical closure) and continued for a minimum of 4 days and maximum of 14 days.		**PE** Confirmed by: ventilation perfusion scan or pulmonary angiography	**Int:** 0/145 **Control:** 1/143 **p value:** 0.4965	
				Control: Mean age: 68.6± 8.8 yrs M/F:91/134				**Total haemorrhage episodes**	**Int:** 46/228 **Control:** 52/225 **p value:** 0.2470	
								Major haemorrhage episodes (major not defined)	**Int:** 3/228 **Control:** 3/225 **p value:** 1.000	
					Additional non-comparative prophylaxis: none reported	**Additional non-comparative prophylaxis:** none reported		**Minor haemorrhage episodes** (minor not defined)	**Int:** 43/228 **Control:** 49/225 **p value:** 0.4840	
								Length of Hospital Stay (Mean±SD, range)	**Int:** 7±2 days range: 1-14 days **Control:** 7.1±2 days range: 2-15 days **p value:** not significant	**Not reported:** PTS, QoL, length of hospital stay, survival.
										Funding: not reported

LMWH vs UFH

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Diener et al., 2006[165] (PROTECT trial) **Country of study:** EU **Study design:** RCT, double blinded, multicentre **List who was masked to interventions:** Investigators and patients. End point committee **Evidence level:** 1+ **Duration of follow-up:** 3 months	**Patient group:** Acute ischaemic stroke **Setting:** 37 centres in EU, most patients treated in stroke units **Inclusion criteria:** ▪ Age 18 to 85 years with clinical diagnosis of ischaemic stroke ▪ NIHSS score of 4 to 30, with mild to severe paresis of a leg. **Exclusion criteria:** ▪ Indication of thrombolysis ▪ No availability of CT scan ▪ Ct documented signs of intracerebral or subarachnoid bleeding ▪ Current bleeding or thrombosis ▪ History of bleeding or thrombosis within the past 12 months ▪ Recurrent gastrointestinal ulcerations ▪ Post thrombotic syndrome ▪ Acute or unstable cardiovascular disease ▪ Major infection ▪ Currently active, recurrent or metastatic cancer within the last 5 years ▪ Platelet count <75000/microL ▪ Severe diabetic retinopathy ▪ Estimated body weight <55jg ▪ Pregnant or breast feeding **All patients** **N:** 545 **Group 1** **No. randomised:** 273 **Per protocol:** 248 **M/F:** 164/109 **Age (mean ±SD):** 67.3 ±10.6 **Additional characteristics:** ▪ Body Mass Index: 27.1±3.9 ▪ NIHSS: 8.2±3.6 ▪ Leg paresis:2.0±0.9 ○ Grade 1:91	**Group 1** UFH 5000IU, 3 times daily, subcutaneously Start: 15.4±6.2 **Group 2** Certoparin 3000U anti Xa once daily, subcutaneously, plus 2 placebo injections Start: 15.4±6.2 All treatment started within 24 hours of stroke symptom onset Duration: 12-16 days **Additional non-comparative prophylaxis:** Ticlopidine, clopidogrel, or aspirin alone (≤325mg daily) or in combination with dipyramidole allowed Aspirin Group 1:78.4% Group 2:77.2% Aspirin + dipyramidole Group 1:11.7% Group 2:17.6% Clopidogrel Group 1: 17.6% Group 2: 16.9% Ticlopidine Group 1: 4.4% Group 2: 2.9%	**All cause mortality** (confirmed by: Autopsy whenever allowed. Stroke progression as cause of death: n=4 in certoparin, n=3 in UFH during treatment period. At 3 month follow up, n=3 in certoparin, n=1 in UFH)	Treatment period **Group1:** 7/273 **Group 2:** 7/ 272 **P value:** 1.0 Between treatment period and 3 month follow up: **Group1:** 8/273 **Group 2:** 14/ 272 **P value:** 0.2 Total: up to 3 month follow up: **Group1:** 15/273 **Group 2:** 21/ 272 **P value:** 0.31 *[p values calculated by team at NCCAC suing Fisher's exact test]*	**Funding:** Novartis **Limitations:** ▪ Percentages of patients with concurrent antiplatelet agents were not reported ▪ Seemed to have involved both stroke unit centres and non-stroke unit centres- outcomes not compared **Outcomes not reported:** Calf DVT, PTS, Pulmonary hypertension, QoL, LOS **Additional outcomes reported:** Causes of death **Notes:** ▪ Patients screened for DVT at baseline with duplex and compression ultrasonography.
			Fatal pulmonary embolism (confirmed by: Not autopsy performed. Suspected, because D-dimer positive but no signs of cardiac aetiology found)	**Group1:** 1/273 **Group 2:** 0/272 **P value:** 1.0 *[p values calculated by team at NCCAC suing Fisher's exact test]*	
			Symptomatic pulmonary embolism (confirmed by: no clinically suspected PE)	**Group1:** 1/273 **Group 2:** 0/272 **P value:** 1.0 *[p values calculated by team at NCCAC suing Fisher's exact test]*	
			Proximal DVT, asymptomatic or symptomatic (confirmed by: Duplex and compression ultrasonography. Routinely scanned at Days 3-4, 7-8, 12-16 and when clinical symptoms occurred)	**Group1:** 23/273 **Group 2:** 18/272 **P value:** 0.52 *[p values calculated by team at NCCAC suing Fisher's exact test]* Note: all were reported as proximal DVT	
			Fatal bleeding (description: 1 intracranial bleeding was confirmed by autopsy-during treatment period. At 3 month follow up, 1 severe bleeding in the UFH group was confirmed by autopsy. The	During treatment period **Group1:** 1/ 273 **Group 2:** 0/ 272 **P value:** Between treatment period and 3 month follow up:	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	○ Grade 2:110 ○ Grade 3:55 ○ Grade 4:17 ▪ Infarction in carotid territory:251 ▪ Previous stroke:37 ▪ Previous transient ischaemic attack: 7 ▪ Hypertension:207 ▪ Previous cardiac failure:8 ▪ Previous myocardiac infarction:15 ▪ Diabetes mellitus:71 ▪ Hyperlipidemia: 48 ▪ Previous severe respiratory disorder:13 ▪ Previous thrombosis:9 **Group 2** **No. randomised:** 272 **Age (mean ±SD):** 66.3 ±10.9 **Per protocol:** 242 **M/F:** 149/123 **Additional characteristics:** ▪ Body Mass Index: 27.4±4.6 ▪ NIHSS:8.7±4.0 ▪ Leg paresis: 2.1±0.9 ○ Grade 1:86 ○ Grade 2:108 ○ Grade 3:55 ○ Grade 4:23 ▪ Infarction in carotid territory:256 ▪ Previous stroke:42 ▪ Previous transient ischaemic attack:10 ▪ Hypertension:210 ▪ Previous cardiac failure:21 ▪ Previous myocardiac infarction:23 ▪ Diabetes mellitus:81 ▪ Hyperlipidemia: 51 ▪ Previous severe respiratory disorder:20 ▪ Previous thrombosis:6	No mention of mechanical prophylaxis methods	bleeding type of the LMWH group was not reported)	**Group1:** 1/ 273 **Group 2:** 1/272 **P value:** *[p values calculated by team at NCCAC suing Fisher's exact test]*	
			Major bleeding at 16 days (description: intracranial (only if parenchymal), retroperitoneal, gastrointestinal resulted in death, clinically overt and led to transfusion of ≥U of packed RBC/whole blood, or Hb fall of ≥2g/dL)	**Group1:** 5/273 **Group 2:** 3/272 **P value:** 0.73 *[p values calculated by team at NCCAC suing Fisher's exact test]*	
			Neurological bleeding CT scan performed at baseline, Days 7 to 8 routinely and anytime in the case of clinical suspicion of intracranial haemorrhage	**Group1:** 3/273 **Group 2:** 2/272 **P value:** 1.0 *[p values calculated by team at NCCAC suing Fisher's exact test]*	
			Upper GI bleeding	**Group1:** 2/273 **Group 2:** 0/272 **P value:** 0.5	
			Minor bleeding (description: bleedings which did not meet classification of major bleeding)	**Group1:** 5/273 **Group 2:** 7/ 272 **P value:** 0.58 *[p values calculated by team at NCCAC suing Fisher's exact test]*	
			Heparin induced thrombocytopaenia(suspected cases, not measurement of antibodies performed to confirm)	**Group1:** 2/273 **Group 2:** 1/ 272 **P value:** 1.0 *[p values calculated by team at NCCAC suing Fisher's exact test]*	

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Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Farkas et al 1993[181]	RCT	1+	**Total:** 233 Intervention : n = 122 Control: n = 111 269 patients randomised, 36 excluded	**Type of surgery:** Vascular surgery – aortic or aortoiliac and aneurysmectomy; aorto-femoral bypass for atherosclerotic disease; and femoropopliteal or femorodistal bypass.	**Type:** LMWH (Enoxaparin) **Dose:** 2100 IU pre-op, then 4200 IU	**Type:** Unfractionated heparin **Dose:** 5000 units pre-op, 7500 units post-op	1 month	**DVT** Confirmed by: Duplex US, confirmed by venography on 7th-10th day post-op. Earlier if clinical suspicion	**Int:** 10/122 **Control:** 4/111 **p value:** Not significant)	**Comments:** Numbers in each group for baseline data do not tally with text. Arterial patency also assessed by duplex US scanning. No significant differences observed between groups in terms of development of post-op arterial thrombosis. **Thrombocytopenia** (which resolved spontaneously within 3 days) reported in 2 LMWH patients. **Not reported:** PVT, PTS, QoL, LoS, **Funding**: Trial supported by grant from Labaratoires Pharmuka, France.
				Mean duration of surgery: Intervention: 4.2±1.4 h Control: 4.2±1.5h	**Timing:** Begun day pre-op and repeatedly daily until 7th day post-op	**Timing:** Begun day pre-op and repeated twice daily until 7th day post-op		**PE** Confirmed by: Clinical suspicion investigated by angiogram	**Int:** 0/122 **Control:** 0/111 **p value:** N/A	
				Intervention: Mean age: 65±11 yrs M/F:101/25	**Additional non-comparative prophylaxis:** Intraoperative use of UFH (94.4%) or protamine (7.9%) was authorised in both groups	**Additional non-comparative prophylaxis:** Intraoperative use of UFH (97.4%) or protamine (9.4%) was authorised in both groups		**Preoperative red blood cell units**	**Int:** 3.91±2.79 units **Control:** 3.61±1.91 **p value:** Not significant	
				Control: Mean age: 64±11 yrs M/F:99/18				**Post-operative suction drain volume**	**Int:** 423±438ml **Control:** 408±455ml **p value:** Not significant	
				Pre-existing risk factors: Past history of VTE, age, obesity, varicose veins, COPD (no significant diffs between groups apart from COPD – more in LMWH group, p=0.02).				**Survival**	**Int:** 120 /122 **Control:** 111/111 **p value:** not reported	

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Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Faunø et al 1994[183]	RCT	1+	**Total:** 185 Intervention: n = 92 Control: n = 93 224 patients randomised. 39 excluded (16 LMWH, 23 UH)	**Type of surgery:** Unilateral knee replacement **Duration of operation:** Intervention: 102±24 min Control: 104±20 **Intervention:** Mean age: 70±10 yrs M/F:38/55 **Control:** Mean age: 71±11 M/F:35/57 **Pre-existing risk factors:** Not reported	**Type:** LMWH (Enoxaparin) **Dose:** 40 mg **Timing:** Begun evening pre-op and repeated daily until 7-10th day post-op. **Additional non-comparative prophylaxis:** Short compression stocking on involved limb and long compression stocking on uninvolved limb.	**Type:** UH **Dose:** 5000 IU **Timing:** Begun evening pre-op and repeated 3 times daily until 7-9th day post-op. **Additional non-comparative prophylaxis:** Short compression stocking on involved limb and long compression stocking on uninvolved limb.	2 months	**DVT** Confirmed by: bilateral ascending venography on 7-9th day post-op	**Int:** 21/92 **Control:** 25/93 **p value:** 0.6 Not significant	**Also reported:** total blood loss, decrease in haemoglobin levels, transfusion requirements
								PVT Confirmed by: bilateral ascending venography on 7-9th day post-op	**Int:** 3/92 **Control:** 5/93 **p value:** Not reported	
								PE Confirmed by: Not routinely assessed. Clinical suspicion investigated with V/Q scan	**Int:** 0/92 **Control:** 0/93	
								Wound haematoma	**Int:** 8/92 **Control:** 12/93 **p value:** 0.5	

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Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Geerts et al., 1996[218] **Country of study:** Canada **Study design:** RCT, double blinded, patients stratified according to the presence or absence of lower extremity fractured **List who was masked to interventions:** Patients and investigators **Evidence level:** 1++ **Duration of follow-up:** Up to 14 days	**Patient group:** Major trauma patients, adult **Setting:** Level I trauma facility in Canada **Inclusion criteria:** Consecutive adult trauma patients admitted to the trauma centre, who did not have any of the exclusion criteria **Exclusion criteria:** Any of the following - Injury severity score (ISS) <9 - Likely to survive or remain in hospital for <7 days - Frank intracranial bleeding on computed tomographic scans (cerebral contusion, localized petechial haemorrhages, or diffuse axogonal damage were not excluded) - Bleeding that remained uncontrolled 36 hours after the injury - Systemic coagulopathy; prothrombin time (PTT) >3s above control value - Platelet count <50,000/mm^3 - Needed therapeutic anticoagulation - Cannot undergo venography (allergy to contrast material) - renal failure (defined as a serum creatinine level higher than 3.4 mg per deciliter [300 µmol per liter]) - pregnant - venous access could not be achieved because of amputation or a major foot injury **<u>All patients</u>** **N:** 344 **No of dropouts:** 13 **No of patients with sufficient venography:** 265 (77%)	**Group 1** heparin calcium, 5000u, 12hourly. **Group 2** Enoxaparin (Clexane), 30 mg For both groups: Given as 0.3-ml subcutaneous injections every 12 hours in a blinded fashion with preloaded syringes. Start: within 36 hours of the injury Duration: up to 14 days. **Additional non-comparative prophylaxis:** No mechanical or other pharmacologic methods of antithrombotic prophylaxis were allowed by the protocol The study drug was generally not withheld in the event of a surgical procedure, although in exceptional circumstances such as spinal fixation, a single preoperative dose was permitted to be withheld. Treatment with the study	**All cause mortality**	**Group1:** 0/173 **Group 2:** 2/171 **P value:** 0.25 *[calculated by NCC-AC team from numbers randomised using Fishers exact test]*	**Funding:** Ontario Ministry of Health, Rhone Poulenc Rorer provided study medications, Mallinckrodt Medical Inc provided contrast agent for venography **Limitations:** -Single site study -Method of randomisation concealment not well described **Outcomes not reported:** Upper GI bleeding QoL, Pulmonary hypertension **Additional outcomes reported:** <u>Blood transfusions:</u> Heparin: 99/173, 3.8±2.6 units Enoxaparin: 101/171, 4.2±3.1 units <u>Marder Scores:</u> Heparin (n=136): 2.3±5.0 Enoxaparin (n=129): 1.0±2.8 (P value: 0.012 by Wilcoxan rank sum test provided by report) **Notes:** Out of 1076 admissions into the unit, 698 (64.9%) were not eligible The neurological bleeding cases were included in major bleeding.
			Fatal pulmonary embolism (confirmed by: autopsy)	**Group1:** 0/173 **Group 2:** 0/171 **P value:** 1.00 *[calculated by NCC-AC team from numbers randomised using Fishers exact test]*	
			Symptomatic pulmonary embolism (Confirmed by: ventilation perfusion scan in patients with clinical presentation. Patients with nondiagnostic scans underwent pulmonary angiography, venous ultrasonography, contrast venography, or a combination of these, if necessary, within 24 hours after the scanning)	**Group1:** 0/136 **Group 2:** 1/129 **P value:** 0.49 *[calculated by NCC-AC team from numbers randomised using Fishers exact test]*	
			DVT, asymptomatic or symptomatic (confirmed by: venography of both legs with ioversol, a non-ionic contrast agent between Day 10 and 14, or just before discharged if it occurred earlier. DVT was defined as a constant intraluminal filling defect in a deep leg vein that was seen on ≥2. See above for symptomatic DVT))	**Group1:** 60/136 **Group 2:** 40/129 **P value:** 0.014 (reported) [**P=0.03,** *calculated by NCC-AC team from numbers randomised using Fishers exact test]*	
			Thigh DVT(confirmed by: Proximal-vein thrombosis was defined as thrombosis involving the popliteal or more proximal veins.)	**Group1:** 20/136 **Group 2:** 8/129 **P value:** 0.012 *[**P=0.03**, calculated by NCC-AC team from numbers randomised using Fishers exact test]*	
			Calf DVT (confirmed by: see DVT)	**Group1:** 40/136 **Group 2:** 32/129	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	M/F: 192/265* 99/136 group 1, 93/129 Group2 **Group 1** **No. randomised:** 173 **No. of dropouts:** 7 **Additional risk factors***: - Age (year): 37.0±16.5 - ISS: 22.7±9.0 - Predicted risk of DVT†: 54.7±26.3 - Surgery performed: 119/136, - Blood transfusion in the first 24 hours: 48/136, - Maximal mobility (mean of daily corrected score): 2.4±1.0 - Hospital stay (days): 23.5±13.8 - Site of major injury: ○ Head: 6/136 ○ Face, chest, abdomen: 53/136 Spine: 24/136 ○ Lower limb (orthopaedic injury): 75/136 **Group 2** **No. randomised:** 171 **No. of dropouts:** 6 **Additional risk factors***: - Age (year): 39.1±16.8 - ISS: 23.1±8.3 - Predicted risk of DVT†: 53.5±25.4 - Surgery performed: 107/129 - Blood transfusion in the first 24 hours: 55/129 - Maximal mobility (mean of daily corrected score): 22.4±1.0 - Hospital stay (days): 26.0± 15.4 - Site of major injury: ○ Head: 7/129 ○ Face, chest, abdomen: 47/129 ○ Spine: 16/129 ○ Lower limb (orthopaedic injury): 69/129 * Information based on patients with adequate	medication was then resumed at the first dosing time after the operation.		**P value:** 0.27 *[calculated by NCC-AC team from numbers randomised using Fishers exact test]*	
			Fatal bleeding (description: confirmed by autopsy)	**Group1:** 0/173 **Group 2:** 0/171 **P value:** 1.0	
			Major bleeding (description: Sites: chest tube, 1000ml of epistaxis, intraoperative, subdural haematoma, facial soft tissues, retroperitoneum)	**Group1:** 1/173 **Group 2:** 5/ 171 **P value:** 0.12 *[calculated by NCC-AC team from numbers randomised using Fishers exact test]*	
			Neurological bleeding (Subdural haematoma with hemiparesis 4 days after craniotomy for severe skull fracture)	**Group1:** 0/ 173 **Group 2:** 1/171 **P value:** 0.50 *[calculated by NCC-AC team from numbers randomised using Fishers exact test]*	
			Heparin induced thrombocytopenia (confirmed by heparin-dependent IgG antibodies)	**Group1:** 2/173 **Group 2:** 0/ 171 **P value:** 0.50 *[calculated by NCC-AC team from numbers randomised using Fishers exact test]*	
			Length of stay	**Group1:** 23.5±13.8 **Group 2:** 26.0± 15.4 **P value:**	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	venography (n=265) †Predicted risk of thrombosis was calculated using this formula: $\frac{e^x}{1+e^x}$				

LMWH vs UFH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Goldhaber et al., 2002[225]	RCT	1+	**Total:** 150 Intervention : n = 75 (DVT assessed in) Control: n = 75 (DVT assessed in)	**Type of surgery:** Patients undergoing craniotomy with suspected or metastatic brain tumour Excluded people with a history of overt bleeding, heparin allergy or VTE within the prior 6 months **Intervention:** Mean age: 48.33 (±15.07) yrs M/F:39/36 **Control:** Mean age: 48.87 (±12.52) yrs M/F:40/35 **Pre-existing risk factors:** not reported	**Type:** LMWH (Enoxaparin) **Dose:** 40mg/ in the morning, placebo in the evening **Timing:** Begun morning of 1st postoperative day and continued until discharge or VTE diagnosed. **Additional non-comparative prophylaxis:** graduated compression stockings (73/75 participants) intermittent pneumatic compression devices (72/75 participants)	**Type:** UFH **Dose:** 5000 IU twice per day **Timing:** Begun morning of 1st postoperative day and continued until discharge or VTE diagnosed. **Additional non-comparative prophylaxis:** graduated compression stockings (72/75 participants) intermittent pneumatic compression devices (71/75 participants)	**30 days**	**DVT** Confirmed by duplex ultrasonography	**Int:** 9/75 **Control:** 5/75 **p value:** 0.401	Patients scanned one day prior to, or on day of discharge **Funding** Research grant from Aventis **Not reported:** PTS, QoL
								Symptomatic DVT Confirmed by duplex ultrasonography	**Int:** 0/75 **Control:** 0/75 **p value:** not sig	
								Proximal DVT Confirmed by duplex ultrasonography	**Int:** 2/75 **Control:** 2/75 **p value:** 1	
								Unilateral calf DVT Confirmed by duplex ultrasonography	**Int:** 6/75 **Control:** 2/75 **p value:** 0.276	
								Bilateral calf DVT Confirmed by duplex ultrasonography	**Int:** 1/75 **Control:** 1/75 **p value:** 1	
								Major postoperative bleeding complications	**Int:** 2/75 **Control:** 1/75 **p value:** 0.57	
								Length of stay	**Int:** 6.07 ±3.56 days **Control:** 5.75 ±3.24 days **p value:** 0.566	
								Mortality	**Int:** 0/75 **Control:** 0/75 **p value:** not sig	

LMWH vs UFH

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Green et al., 1990[233] **Country of study:** USA **Study design:** RCT **List who was masked to interventions:** unclear **Evidence level:** 1+ **Duration of follow-up:** 8 weeks	**Patient group:** Trauma, complete motor paralysis after spinal cord injury **Setting:** A regional spinal cord injury care centre in US **Inclusion criteria:** ▪ Complete motor and spinal surgery sustained within the preceding 72 hours **Exclusion criteria:** ▪ Bleeding injuries not accessible to haemostatic control ▪ Severe trauma to the head or lower extremities as well as spinal column ▪ Coagulopathy or evidence of thrombosis at baseline examination ▪ Pregnancy ▪ Cardiovascular instability ▪ Refusal by patient or next of kin to give informed, written consent **<u>All patients</u>** **N:** 41 2 patients in each group failed to complete the planned 8 week trial, because they were transferred 4-29 days after initiation of therapy to other institutions. None of these patients experienced bleeding or thrombosis **<u>Group 1</u>** **No. randomised:** 21 **No. of dropouts:** 2 **Age (mean):** 31.4±15.5 **M/F:** 17/4 **Additional risk factors:** Spinal injury location: ▪ Cervical:13 ▪ Thoracic:6 ▪ Lumbar:2 Baseline activate thromboplastin time, aPTT (s): 28.0±2.5	**Group 1** Heparin 5000unit, 8 hourly, subcutaneous. **Group 2** logiparin (tinzaparin) 3500anti-Xa, subcutaneously, once daily <u>Start time:</u> at least 24 hours after injury. If patient require surgery, morning dose of either heparin or LMWH was withheld, and treatment resumed the following morning <u>End time</u> not explicitly stated. Patients on heparin received drugs for and average of 40±19 days (total of 843 days for 21 patients). Patients on LMWH received drugs for and average of 47±16 days (total of 945 days for 20 patients). **Additional non-comparative prophylaxis:** Other prophylactic measures such as calf-compression boots,	**All cause mortality** (confirmed by:) **Fatal pulmonary embolism** (confirmed by: autopsy) **Symptomatic DVT** (confirmed by: abnormal flow study) **DVT, asymptomatic or symptomatic** (confirmed by: 2 patients confirmed by venography, 3rd patients confirmed by symptom and abnormal flow study. Patients screened with impedence plethysomography, Doppler flow measurement and DUS twice weekly in the first 2 weeks, once weekly for the next two weeks, and biweekly for the next 4 weeks) **Thigh DVT** (confirmed by: see DVT. 1 patient; superficial femoral vein, 1 patient popliteal vein, patient had both femoral and popliteal vein) **Fatal bleeding** (description:) **Upper GI bleeding**	**Group1:** 2/21 **Group 2:** 0/20 **P value:** 0.49 *[calculated by NCC-AC team from numbers randomised using Fishers exact test]* **Group1:** 2/21 **Group 2:** 0/20 **P value:** 0.49 *[calculated by NCC-AC team from numbers randomised using Fishers exact test]* **Group1:** 1/21 **Group 2:** 0/20 **P value:** 1.0 *[calculated by NCC-AC team from numbers randomised using Fishers exact test]* **Group1:** 3/21 **Group 2:** 0/20 ***P value reported:** 0.02 (Kaplan Meier Log rank test.)* **P value:** 0.23 *[calculated by NCC-AC team from numbers randomised using Fishers exact test]* **Group1:** 3/21 **Group 2:** 0/20 **P value:** 0.23 *[calculated by NCC-AC team from numbers randomised using Fishers exact test]* **Group1:** 0/21 **Group 2:** 0/20 **P value:** 1.0 *[calculated by NCC-AC team from numbers randomised using Fishers exact test]* **Group1:** 1/ 21 **Group 2:** 0/ 0	**Funding:** National Institute of Disability and Rehabilitation Research, Department of Education. Novo Lab supplied logiparin. **Limitations:** ▪ Unmasked: different dosing regimen ▪ Duration of prophylaxis not stated a priori, criteria for discontinuation not stated. ▪ Haematoma, melaena and haematuria were considered bleeding events if they necessitated the discontinuation of prophylactic therapy and decisions made by ward physicians not participating in the study. Unclear if they were blinded to the study. ▪ 2 patients from each arm transferred out – not stated whether analysis based on randomised patient. **Outcomes not reported:** Symptomatic PE, PE asymptomatic or symptomatic, Calf DVT , Heparin induced thrombocytopaenia, PTS, Pulmonary hypertension, QoL **Additional outcomes reported:** ▪ aPTT for bleeding and thrombotic events ▪ Patients on LMWH had more venous studies

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 2 **No. randomised:** 20 **No. of dropouts:** 4 **Age (mean):** 28.3±11.8 **M/F:** 17/3 **Additional risk factors:** Spinal injury location: ▪ Cervical: 10 ▪ Thoracic: 9 ▪ Lumbar: 1 Baseline activate thromboplastin time, aPTT(s): 27.7±3.3 .	elastic stockings and aspirin were withheld.		**P value:** NS	completed, and more days on prophylaxis. **Notes:** ▪ Study did not report exclusion criteria based on age. Uncertain whether children/teenagers were included ▪ 2 patients in LMWH temporarily switched to heparin at Day 22 and Day 23 because LMWH was temporarily not available
			Minor bleeding (description: " 2 patients had bleeding severe enough to require discontinuation of heparin therapy; in both the aPTT was considerably prolonged" Patient 1: neck hematoma, aPTT: 44.5s Patient 2: gastrointestinal and genitourinary bleeding, aPTT: 38.0	**Group1:** 2/21 **Group 2:** 0/20 **P value:** 0.49 *[calculated by NCC-AC team from numbers randomised using Fishers exact test]*	
			Length of stay	**Group1:** 40±19 days **Group 2:** 47±16 days **P value:** not reported	

LMWH v UFH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Haas et al., 2005[244]	RCT	1+	**Total:** 23,078 Intervention : n = 11,542 60 did not undergo surgery but were included in the analysis as part of an intention to treat analysis Control: n = 11,536 44 did not undergo surgery but were included in the analysis as part of an intention to treat analysis	**Type of surgery:** Mixed: patients over 40 undergoing surgery not less than 30 minutes between 1991 and 1996 at 67 centres in Germany, Austria and the Czech Republic Procedure: General: 17,057 Gynaecology: 2351 Traumatology: 1580 Orthopaedics: 1425 Urology: 402 Other: 159 No surgery: 104 Exclusion criteria: severe hypertension imparied renal or hepatic function; any haemostatic or bleeding disorder; previous inclusion in a trial within the preceding 4 weeks; pregnancy; lactation or known contraindication to heparin. **Age & Gender: Intervention:** Median age: 58 yrs M/F: 5021/6521	**Type:** LMWH (Centoparin) **Dose:** 3000 anti Xa IU subcutaneously once per day plus placebo injections **Timing:** Begun not less than 2 hours prior to surgery and continued for a minimum of 5 days and maximum of 20 days. **Additional non-comparative prophylaxis:** Other drugs known to alter blood coagulation were restricted and only prescribed if unavoidable. Treatments such as GCS and other types of physiotherapy were used according to normal practice at those centres. Spinal anaesthesia: 1153/11542 Epidural anaesthesia: 65/11542	**Type:** LDUH **Dose:** 5000 IU subcutaneously 3 times per day **Timing:** Begun not less than 2 hours prior to surgery and continued for a minimum of 5 days and maximum of 20 days. **Additional non-comparative prophylaxis:** Other drugs known to alter blood coagulation were restricted and only prescribed if unavoidable. Treatments such as GCS and other types of physiotherapy were used according to normal practice at those centres. Spinal anaesthesia: 1086/11536 Epidural anaesthesia: 63/11536	14 days	**Fatal pulmonary embolism*** confirmed by autopsy.	**Int:** 17/11,542 **Control:** 18/11,536 **p value:** 1.0	**Comments:** * PE regarded as primary cause of death if autopsy revealed obstruction of the pulmonary trunk or fesh emboli in either two pulmonary arteries or two lobar arteries. **Not reported:** DVT, Proximal DVT, symptomatic PE, PTS, QoL, LoS **Also reported:** incidence of fatal PE and death by surgical procedure; blood loss in drainage tubes; no. of patients requiring and volume of blood transfusion,
								Mortality	**Int:** 166/11,542 **Control:** 146/11,536 **p value:** 0.28	
								No. of deaths having an autopsy	**Int:** 114/166 (68.7%) **Control:** 105/146 (71.9%)	
								Thrombocytopenia (not stated how confirmed)	**Int:** 21/11,542 **Control:** 16/11,536 **p value:** not sig	
								Bleeding complications	**Intervention group:** Postop wound bleeding: 34 Haemorrhagic stroke: 10 Gastric bleeding: 2 Intestinal bleeding: 4 Abnormal uterine bleeding: 1 **Comparison group:** Postop wound bleeding: 35 Haemorrhagic stroke: 7 Gastric bleeding: 7 Intestinal bleeding: 3 Abnormal uterine bleeding: 2	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
				Control: Median age: 58 yrs M/F: 4995/6541						

LMWH vs UFH

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Haas et al., 2006[242] (ECHOS trial) **Country of study:** Multicentre study: Europe **Study design:** RCT **List who was masked to interventions:** Double-blind study **Evidence level:** 1+ **Duration of follow-up:** 6-8 weeks after discharge (9-10 weeks in a proportion of cases).	**Patient group:** Patients undergoing elective total hip *(THR)-68.3%* or knee replacement *(TKR)-31.7%* **Setting:** Multinational study **Inclusion criteria:** Patients ≥40 years undergoing THR or TKR, whose projected hospital stay was al least 11 days. **Exclusion criteria:** ▪ Previous history of VTE ≤ 6 months ▪ a positive D-dimer bedside test (SimpliRed) or any signs of acute thrombosis ▪ body weight of < 45 kg or > 100 kg ▪ known contraindications to heparin ▪ allergy to contrast media ▪ congenital or acquired hemorrhagic diathesis ▪ thrombocytopenia (platelets < 100000 per cubic milimiter) ▪ macroscopic haematuria ▪ myocardial infarction ▪ cerebrovascular stroke ▪ intracranial or intraocular bleeding within past 6 months ▪ active peptic ulcer, other gastro-duodenal bleeding within past 6 months ▪ active advanced malignant disease ▪ impaired liver or renal function; nephritic syndrome ▪ uncontrolled hypertension ▪ Taking anticoagulants, platelet aggregation inhibitors (except for aspirin < 300 mg per day) up to 8 days before surgery ▪ Pregnant, breastfeeding, <6 months postpartum ▪ Childbearing potential, not taking contraceptive precautions	**Group1:** **LMWH** Reviparin 4200 IU once daily + one placebo injection **Group 2:** **UFH** 7500 IU subcutaneous bd <u>Start:</u> Evening before surgery, administered the following day 6-8 h after surgery and given at 6-8 a.m. and 6-8 p.m. on subsequent days. <u>Duration</u>: 11 to 14 days, until venography was performed. **Additional non-comparative prophylaxis:** ▪ All thromboprophylactic medication was withdrawn before treatment initiation. Aspirin <300mg/day allowed ▪ Postopreative NSAIDS allowed ▪ Mechanical methods e.g. GCS, physiotherapy, early mobilization, were routinely provided. ▪ Additional thrombophrophylaxis (e.g. sequential intermittent pneumatic compression) was	**All cause mortality:**	<u>Until Day 11-14</u> **Group 1;**2/813 **Group 2:** 2/815 **P value:** 1.00* (Two patients died of acute myocardial infarction (one in each group), one due to a fatal PE (UFH) and one due to sudden cardiac arrest (LMWH) Information from text (page 338)	**Funding:** Supported by Abbott GmbH & Co. KG, Ludwigshafen, Germany. **Limitations:** ▪ Reporting quality - discrepancy in numbers of deaths in table vs text **Outcomes not reported:** Symptomatic DVT Length of stay Quality of life Pulmonary hypertension Post thrombotic syndrome **Additional outcomes reported:** • % of patients using general vs regional anasthesia • Serious adverse events • Mean changes between baseline and discharge values for liver enzymes/ **Notes:** % of patients not evaluated for efficacy =19.2%
			Fatal pulmonary embolism (confirmed by: autopsy)	**Group 1;**0/813 **Group 2:** 1/815 **P value:** 1.00*	
			Symptomatic pulmonary embolism (confirmed by: Possible PE was assessed by ventilation- perfusion lung scan, pulmonary angiography, or by autopsy))	<u>Events until day 11-14</u> **Group1:**1/813 (0.1%) **Group 2:** 1/815 (0.1%) **P value:** 1.00* "Three patients were confirmed to have PE between days 15 and 68 including two patients who had previously experienced a DVT"- treatment arm not stated	
			DVT, asymptomatic or symptomatic. Screened by systematic bilateral ascending contrast venography between days 11-14 after surgery or earlier if clinical signs of DVT occurred. VTE during follow-up was determined by clinical symptoms and confirmatory venography.	**All patients** **Group1:**200/813 (24.6%) **Group 2:** 204/815 (25%) **P value:** 0.86* **THR patients** **Group1:**87/494 **Group2:** 81/495 **P value:** 0.61* **TKA patients** **Group 1:** 113/319 **Group 2:** 124/320 **P value:** 0.41*	
			Thigh DVT(screened for by: Proximal DVT was defined as an intraluminal defect proximal to the knee joint space on venograms)	**Group1:**25/813 (3.1%) **Group 2:** 42/815 (5.2%) **P value:** 0.045* **THR patients** **Group1:**19/494 **Group2:** 31/495	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	▪ Drugs or alcohol abuse ▪ Participated in investigational drug studies within 4 weeks prior to study entry. **<u>All patients</u>** **N:** 2018 **THR:** 1233 **TKR:** 782 **<u>Group 1 ; LMWH</u>** **No. randomised:** 1013 **No. of dropouts:** n=1 not included in safety outcomes n=200 not evaluated for efficacy outcomes **THR (n):** 620 (61.3 %) **TKR (n):** 392 (38.7%) **General anesthesia (%):**61.3% **Cement prosthesis (n):** 678 (67%) **Duration of surgery (min)- median (range):** 85 (30-320) **Age mean (+/- SD):** 66.1 +/- 9.3 **Weight (kg):** 76.6 +/- 12.1 **Height (cm):** 165.8 +/- 8.3 **Female (n):** 676 (66.8%) **BMI (kg/m²):**27.8 +/- 3.8 **<u>Group 2: UFH up</u>** **No. randomised:** 1005 **No. of dropouts:** n=2 not included in safety outcomes n= 190 not evaluated for efficacy outcomes **THR (n):** 613 (61.1%) **TKR (n):** 390 (38.9%) **Duration of surgery (min)- median (range):** 85 (28-260) **General anaesthesia (%):** 60.9% **Cement prosthesis (n):** 692 (69%) **Age mean (+/- SD):** 66.9 +/- 9.8 **Weight (kg):**77 +/- 12.4 **Height (cm):**166.3 +/- 8.45 **Female (n):**655 (65.3%) **BMI (kg/m²):** 27.8 +/- 3.9	excluded.		**P value:** 0.11* **TKA patients** **Group 1:** 6/319 **Group 2:** 114/320 **P value:** 0.33*	
			Calf DVT (screened for by: systematic bilateral ascending contrast venography between days 11-14 after surgery or earlier if clinical signs of DVT occurred)	**Distal DVT:** **Group1:**175/813 (21.5%) **Group 2:** 162/815 (19.9%) **P value:** 0.43* **THR patients** **Group1:** 68/494 **Group2:** 50/495 **P value:** 0.08* **TKA patients** **Group 1:** 107/319 **Group 2:** 112/320 **P value:** 0.08*	
			Fatal bleeding (description: Bleedings and death reported but no mention of fatal bleeding)	**Group1:** 0/1012 **Group 2:** 0/1003 **P value:** 1.0*	
			Major bleeding (description: any severe overt bleeding; associated with a Hb drop ≥2g/dL within 24 h of the 1st postoperative day, transfusion of > 1500 mL of whole blood (except autologus transfusion); sero-sanguinous secretion at the wound site after day 6; hemorrhage requiring re-intervention and any retroperitoneal or intracranial haemorrhage or warranting permanent treatment cessation)	**Major bleeding (during treatment period day 1-14)** **Group1:**9/1012 (0.9%) **Group 2:** 12/1003 (1.2%) **P value:** 0.52*	
			Minor bleeding (description: small wound hematoma, wound oozing or hematoma not at the operation area,	**Group1:**38/1012 (3.8%) **Group 2:** 29/1003 (2.9%) **P value:** 0.32*	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
			decreases of postoperative Hb concentration in the expected range and transfusion requirements within the normal range)		
			Heparin induced thrombocytopaenia	**Group1:**0/1012 (0%) **Group 2:** 0/1003 (0%) **P value:** 1.00*	

LMWH vs UFH

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Harenberg et al., 1990[256] **Country of study:** Germany **Study design:** RCT, double blinded **List who was masked to interventions:** Investigators, patients **Evidence level:** 1+ **Duration of follow-up:** 10 days	**Patient group:** Mixed, inpatients **Setting:** Inpatients, single centre(?) **Inclusion criteria:** ▪ Aged 40-80 years ▪ Confined bed rest for≥1 week due to general medical illness after admission **Exclusion criteria:** ▪ Underlying bleeding disorder ▪ Cerebral haemorrhage within last 6 months ▪ Hypertension BP systolic >200mmHg, diastolic 120mmHg ▪ Cirrhosis of liver-prothrombin time below 60% ▪ Renal insufficiency (creatinine >2.5mmHg) ▪ Increased bleeding risk of the Gastrointestinal or urogenital system ▪ Cute pancreatitis ▪ Disseminated intravascular coagulation ▪ Known intolerance to heparin ▪ Indications for therapeutic anticoagulation, fibrinolytic or antiplatelet therapy **<u>All patients</u>** **N:** 200 **No. of dropouts:** 34 (completed less than 7 days of treatment) **Main diagnosis** — **Gp1** — **Gp2** Malignancy — 17 — 23 Heart insufficiency — 11 — 12 Coronary Heart Disease — 11 — 12 Atrial Fibrillation — 3 — 4 Cerebral Ischaemia — 4 — 4 Infections — 5 — 3 Asthma Bronchiale — 2 — 2 Others — 16 — 17 **Risk Factors** — Gp1 — Gp2 Varicose veins — 56 — 58	**Group 1** UFH 5000IU subcutaneously, 3x daily **Group 2** LMWH 1.50 aPTT units subcutaneously , plus 2 placebo injections, 8 hourly Start time: not stated: Duration: 10days, range 7-12 days **Additional non-comparative prophylaxis:** No compression elastic compression stocking used. Injections discontinued if patients spend less than 20/24 hours in bed.	**All cause mortality** [Not certain whether these mortality figures referred to all patients recruited (n=200) or just the 166 patients who finished the protocol]	**Group1:** 1/83 **Group 2:** 3/89 **P value:** 0.62 [Calculated by NCCAC staff using Fishers exact test]	**Funding:** Not reported. Substances provided by Sandoz AG **Limitations:** ▪ Name of LMWH not stated- 3.8D 86 IU/mg and supplied by Sandoz ▪ Clarity of report-dated outcomes measures? **Outcomes not reported:** All cause mortality, DVT, asymptomatic or symptomatic , Fatal bleeding, Major bleeding, Upper GI bleeding, Minor bleeding, Heparin induced **Additional outcomes reported:** aPTT values **Notes:** Only patients who completed ≥ 7 days of treatment were included in the analysis
			DVT, asymptomatic or symptomatic (confirmed by: Doppler ultrasonography) 4 on each group was suspected based on impedance plethysmography In table 5 of report, 4 patients in heparin group and 2 patients in LMWH group was reported as "suspicion of thrombosis", 1 patient in LMWH group was reported as "thrombosis".	**Group1:** 1/83 **Group 2:** 1/ 89 **P value:** 1.0	
			Fatal bleeding (description: " 1 patient treated with heparin developed gastrointestinal bleeding on day 8 and dies of cardiac failure)	**Group1:** 1/83 **Group 2:** 0/89 **P value:** NS	
			Major bleeding (description: (description: " 1 patient treated with heparin developed gastrointestinal bleeding on day 8 and dies of cardiac failure))	**Group1:** 1/83 **Group 2:** 0/89 **P value:** NS	
			Upper GI bleeding (description: (description: " 1 patient treated with heparin developed gastrointestinal bleeding on day 8 and dies of cardiac failure)	**Group1:** 1/83 **Group 2:** 0/89 **P value:** NS:	
			Minor bleeding (description: hematomas at injection site)	**Group1:** 57% **Group 2:** 24% **P value:** Not certain whether percentages based on randomised group or efficacy group	

Study details	Patients			Interventions	Outcome measures	Effect size	Comments
	Cardiac Arrhythmias		42 31				
	Hypertension		36 28				
	Diabetes		32 19				
	Coronary heart disease		21 11				
	Stenosis A carotis	18	9				
	Renal insufficiency	17	8				
	Peripheral arterial disease		11 4				
	Smoking		10 17				
	Cerebral Sclerosis	6	4				
	Cardiomyopathy		3 7				
	Hyperthyrodism		3 4				
	Group 1 **No. randomised:** (not stated) 82 completed trial **No. of dropouts:** **Age (mean):** 65.8±9.9 **M/F:** 35/47 **Group 2** **No. randomised:** (not stated) 84 completed trial **No. of dropouts:** **Age (mean):** 66.2±8.8 **M/F:** 39/45						

LMWH vs UFH

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Harenberg et al., 1996[257] **Country of study:** Germany **Study design:** Multicentre double blind study **List who was masked to interventions:** Investigator and patients, critical event committee **Evidence level:** 1+ **Duration of follow-up:** 10 days	**Patient group:** Hospitalised, bed ridden patients with increased risk of thrombosis **Setting:** Inpatient, 10 centres in Germany **Inclusion criteria:** ▪ Aged 50-80 years ▪ Expected duration of bedrest >10 days ▪ ≥ 1 of the following risk factors present: ○ obesity ○ varicosis ○ chronic venous insufficiency ○ post thrombotic syndrome ○ intake of oral contraceptives or oestrogen ○ thrombocytosis >450,000/microL ○ hyperviscosity syndrome ○ previous myocardial infarction ○ thrombotic cerebral infarction ○ peripheral arterial ischaemic **Exclusion criteria:** ▪ known intolerance to heparin ▪ thrombocytopenia <80m000micro/L ▪ hereditary or acquired coagulation disorder ▪ acute DVT ▪ pre-treatment with heparin other than study medication ▪ regular intake of medication influencing blood coagulation ▪ unfavourable short term prognosis ▪ septicaemia with gram negative bacteria ▪ disseminated intravascular coagulation ▪ fixed hypertension ▪ history of any bleeding ▪ creatinine >3mg/dl ▪ prothrombin time <60% The post operative phase is not an exclusion criteria	**Group 1** UFH 5000IU , 3 times daily, subcutaneously, at 8 hour intervals **Group 2** Fraxiparine 36mg (3100IU of antiXa), plus 2 placebo injections, 3 times daily, at 8 hour intervals Start time: within 12 hours of admission to hospital End time: day 11 Duration: 10 days **Additional non-comparative prophylaxis:** (list or write not reported or not applicable)	**All cause mortality**	**Group1:** 9/780 **Group 2:** 23/810 **P value:** 0.02 In group1, causes of death were carcinoma (4), pneumonia (1), chronic obstructive pulmonary disease (1), cardiac insufficiency (1), atrial fibrillation (1) and renal insufficiency (1) respectively. In Group 2 causes of death were carcinoma (3), pneumonia (4), stroke (4), cardiac insufficiency (9), myocardial infarction (1) and *PE (1)* and diabetes (1) respectively.	**Funding:** Not stated **Limitations:** ▪ Reporting focused on safety outcomes (blood test results), DVT and PE reporting not clear ▪ Incidences of death and primary endpoints were not equally distributed between centres. In centres where no primary end points were observed, incidence of death the in LMWH group was 3.5x higher **Outcomes not reported:** PE asymptomatic or symptomatic DVT, asymptomatic or symptomatic, Thigh DVT, Calf DVT Fatal bleeding Neurological bleeding Upper GI bleeding Heparin induced thrombocytopaenia PTS, Pulmonary hypertension, QoL, LOS **Additional outcomes reported:** 4 cases of thrombocytopenia in UFH group, 0 in fraxiparine.
			Fatal pulmonary embolism (confirmed by: perfusion scintigraphy, additional angiography or ventilation scintiscan performed if results were low probability defects)	**Definite PE** **Group1:** 0/780 **Group 2:** 1/810 **P value:** **Probable PE** **Group1:** 3/780 **Group 2:** 3/810 **P value:** 16 patients' death was classified as "possible" PE, but it was not stated which group they belonged to.	
			Symptomatic pulmonary embolism (confirmed by: perfusion scintigraphy, additional angiography or ventilation scintiscan performed if results were low probability defects))	**Probable PE** **Group1:** 3/780 **Group 2:** 3/810 **P value:**	
			DVT, asymptomatic or symptomatic **Or** **Symptomatic DVT??** (screening at Day 1 and Day 11 and upon presentation of clinical signs)	**Group1:** 1/780 **Group 2:** 3/ 810 **P value:** Not described whether symptomatic or asymptomatic. Likely to be all symptomatic cases, as none of them occurred on the day of planned scans.	
			Major bleeding no description of criteria	**Group1:** 4/780 **Group 2:** 5/ 810	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	All patients **N:** 1968 randomised, 378 excluded from efficacy analysis Main Diagnosis Gp1 Gp2 Cardiac insufficiency 143 150 Cerebrovascular diseases 134 149 Coronary heart disease 131 139 Cancer 63 57 Diabetes 57 47 Gastro. Or neph. Disease 45 38 Chronic obstructive lung disease 46 41 Pneumonia or infections 16 26 Other diseases 144 166 **Group 1** **No. randomised:** 985 **No. of dropouts:** 205(140 dropped out, 65 not eligible) **Age (mean):** 70.4±7.9 **M/F:** 372/408 **Additional risk factors:** ▪ Smoker (no/ex/yes): 482/185/113 ▪ Adiposity: 250 ▪ Previous DVT:33 ▪ Previous PE: 13 ▪ *Varicosis: 137 ▪ Ulcus cruris: 35 ▪ Thrombocytosis: 33 ▪ Peripheral AD: 160 ▪ Previous MI: 113 ▪ Previous stroke: 121 ▪ Cardiac insufficiency: 343 ▪ Hyperviscosity: 118 ▪ Estrogen: 2 **Group 2** **No. randomised:** 983 **No. of dropouts:** 173 (119 dropped out, 54 not eligible) **Age (mean):** 70.5±8.3 **M/F:** 344/466 **Additional risk factors:** ▪ Smoker (no/ex/yes): 504/173/103			**P value:** 1.0 **Minor bleeding** no description of criteria **Group1:** 7/ 780 **Group 2:** 3/810 **P value:** 0.34	Various clinical chemistry results **Notes:** DVT and PE events were combined and reported as "primary end points". Study was designed as an equivalence study. Emphasis of report was on "safety"-clinical chemistry.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	▪ Adiposity: 254 ▪ Previous DVT: 50 ▪ Previous PE: 18 ▪ *Varicosis: 179 ▪ Ulcus cruris: 33 ▪ Thrombocytosis: 38 ▪ Peripheral AD: 167 ▪ Previous MI: 123 ▪ Previous stroke: 119 ▪ Cardiac insufficiency: 348 ▪ Hyperviscosity: 112 ▪ Estrogen: 4 *p=0.02				

LMWH vs UFH

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Hillbom et al., 2002[278] **Country of study:** Finland **Study design:** Multicentre, double blinded, randomised study **List who was masked to interventions:** Double blinded study **Evidence level:** 1+ **Duration of follow-up:** 3 months	**Patient group:** Acute ischaemic stroke **Setting:** 7 centres in Finland. Inpatient **Inclusion criteria:** ▪ Acute ischaemic stroke, defined as acute onset of paralysis lasting at least 24 hours and necessitating bed rest ▪ Confirmed by CT scan **Exclusion criteria:** ▪ Unconscious- Glasgow Coma Scale <9 ▪ Immobilised before onset of stroke ▪ Evidence of haemorrhagic stroke ▪ Stroke thought to be cardioembolic in origin ▪ History of DVT, PE myocardial infraction, recent neurosurgery (within the last 3 months) ▪ History of subarachnoid haemorrhage, gastrointestitinal bleeding or active peptic ulceration ▪ Hypersensitivity to heparin, LMWH or radio opaque contrast media ▪ Severe heart failure, uncontrolled hypertension, hepatic or renal impairment, malignant disease, endocarditis or haemorrhagic diathesis ▪ Current drug abuse ▪ Requiring anticoagulant or antiplatelet therapy ▪ Pregnant or lactating ▪ Abnormal blood clotting tests ▪ Treatment would not be started with 48 hours of stroke onset **All patients** **N:** 212 **Group 1** **No. randomised:** 106 **Efficacy population:** 72 **No. of dropouts:** 0 **M/F:** 59/47	**Group 1** Unfractionated heparin, 5000IU, subcutaneously, 8 hourly. **Group 2** Enoxaparin (Clexane), 40mg, subcutaneously, once daily. 2 placebo injections to maintain 8 hourly interval blinding. **In both arms** Start time: within 48 hours of stroke onset End time: 10±2 days later, or until discharge **Additional non-comparative prophylaxis:** Concomitant treatment with anticoagulant or antithrombotic therapy, NSAIDS, aspirin or other antiplatelet therapy, or any other treatment which could influence interpretation of study data was prohibited. No mention about mechanical prophylaxis methods	**All cause mortality** 16/17 patients died of stroke within treatment period, 22/32 during the follow up period	Within treatment period (10±2 days) **Group1:** 8/106 **Group 2:** 9/106 **P value:** 1.00 *[Calculated by NCC-AC team using Fisher's Exact test]* At 3 month follow up **Group1:** 28/106 **Group 2:** 21/106 **P value:** 0.33 *[Calculated by NCC-AC team using Fisher's Exact test]*	**Funding:** Aventis Pharma **Limitations:** ▪ Sample size of 400 was planned, but oly 212 recruited and 165 patients (81 in enoxaparin and 84 in UFH) group completed study ▪ NO mention about mechanical prophylaxis methods ▪ Significantly more obese patients in UFH group and higher percentages of diabetic patients **Outcomes not reported:** Upper GI bleeding **Additional outcomes reported:** Haemorrhagic transformation of the brain infarction **Notes:** # The number of DVT cases reported was 26/106 in the UFH group and 17/106 in the LMWH group respectively. However, 2 cases in the UFH group and 3 in the LMWH group were detected
			Fatal pulmonary embolism (confirmed by: autopsy) Of all the patients who died, 14 had autopsy. 4 in UFH and 2 in enoxaparin group had PE	**Group1:** 2/106 **Group 2:** 1/106 **P value:** 0.62 *[Calculated by NCC-AC team using Fisher's Exact test]*	
			Symptomatic pulmonary embolism (ventilation perfusion scan and pO2 when clinically indicated)	**Group1:** 4/106 **Group 2:** 2/106 **P value:** 0.68 *[Calculated by NCC-AC team using Fisher's Exact test]*	
			Symptomatic DVT (confirmed by: unilateral phlebography within 24h of clinical indication)	**Group1:** 3/ 72 **Group 2:** 1/ 76 **P value:** 0.36 *[Calculated by NCC-AC team using Fisher's Exact test]*	
			DVT, asymptomatic or symptomatic (confirmed by: as in symptomatic DVT, and bilateral ascending phlebography at day 10±2 or the last assessment, and autopsy)	**Group1:** 24/106 **Group 2:** 14/106 **P value:** 0.17 (# see notes) *[Calculated by NCC-AC team using Fisher's Exact test]*	
			Thigh (Proximal) DVT(confirmed by: as in DVT)	**Group1:** 4/72 **Group 2:** 2/76 **P value:** 0.43 *[Calculated by NCC-AC team using Fisher's Exact test]*	
			Calf (Distal)DVT (confirmed	**Group1:** 3/72	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Age: 69±10 Weight (kg): 77±16 **Risk factors for DVT:** Elderly (>70 years):48/106 Immobilised: 104/106 *Obesity: 28/106 *Alcoholism: 4/106 Varicose veins: 10/106 History of DVT: 3/106 **Risk factors for Stroke:** Hypertension: 48/106 Current smoking: 25/106 *Diabetes mellitus: 21/106 History of myocardial infarction: 5/106 History of stroke or TIA: 5/106 **Group 2** **No. randomised:** 106 **Efficacy population**: 76 **No. of dropouts:** 0 **M/F:** 68/38 **Age:** 68±12 **Weight (kg):**73±13 **Risk factors for DVT:** Elderly (>70 years):53/106 Immobilised: 101 /106 *Obesity: 10/106 *Alcoholism: 12/106 Varicose veins: 10/106 History of DVT:3/106 **Risk factors for Stroke:** Hypertension: 45/106 Current smoking: 28/106 *Diabetes mellitus: 12/106 History of myocardial infarction: 7/106 History of stroke or TIA: 8/106 * Obesity (p=0.002) , diabetes (p=0.13), alcoholism (p=0.066) [Values calculated by NCCAC staff using Fisher's exact test]		by: As in DVT)	**Group 2:** 1/76 **P value:** 0.36 *[Calculated by NCC-AC team using Fisher's Exact test]*	after the study period. This cases were excluded. Patients were analysed using both randomised number, and the efficacy subgroup
			Fatal bleeding (description: autopsy)	Of the patients who died, 14 had autopsy. 1 in enoxaparin group had cerebral haemorrhage	
			Major bleeding (description: intracranial haemorrhage)	**Group1:** 0/106 **Group 2:** 1/106 **P value:**	
			Neurological bleeding (intracerebral haemorrhage) confirmed by cerebral CT scan, within 24 hours of clinical indication and within 24 hours of the final administration	**Group1:** 0/106 **Group 2:** 1/106 **P value:** 1.0 *[Calculated by NCC-AC team using Fisher's Exact test]*	
			Neurological bleeding (Haemorrhagic transformation of the brain infarction) Confirmed by CT scan within 24 hours of final administration	**Group1:** 20/86 **Group 2:** 14/81 **P value:** 0.44 *[Calculated by NCC-AC team using Fisher's Exact test]*	
			Minor bleeding (description: included 3 in enoxaparin and 4 in UFH with hematomas>5cm in diameter at injection site)	**Group1:** 6/106 **Group 2:** 5/106 **P value:** 1.00 *[Calculated by NCC-AC team using Fisher's Exact test]*	

LMWH vs UFH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Horbach et al., 1996[285]	RCT	1+	Total: 305 Intervention n: 152 Control n: 153	**Type of surgery:** Patients undergoing elective hip replacement surgery. **Intervention:** Mean age: 64.2 ± 10.0 years M/F:72/80 **Control:** Mean age: 64.9 ± 9.8 years M/F:70/83 **Pre-existing risk factors:** Previous thrombosis: **Int:** n = 13 **Cont:** n = 16; Previous PE: **Int:** n = 3 **Cont:** n = 6; Varices: **Int:** n = 69 **Cont:** n = 79; Diabetes mellitus: **Int:** n = 10 **Cont:** n = 8; p=0.498; obesity: **Int:** n = 5 **Cont:** n = 26; obstructive pulmonary disease: **Int:** n = 3 **Cont:** n = 2; Cardiac insufficiency: **Int:** n = 0 **Cont:** n = 1; Malignancy: **Int:** n = 1 **Cont:** n = 1	**Type, dose and timing:** One dose daily of subcutaneous LMWH (3000 IU of Certoparin) plus 0.5mg DHE injections. Prophylaxis started 2 hours before surgery and continued for at least 14 post operative days or longer if patient was still institutionalised. **Additional non-comparative prophylaxis:** Not reported	**Type, dose and timing:** starting dose of 15000 IU/day was increased to a plateau value of 28,800 ± 7150 IU/ day to maintain the activated partial thromboplastin time in the prescribed range injected subcutaneously daily. Prophylaxis started 2 hours before surgery and continued for at least 14 post operative days or longer if patient was still institutionalised.	14 days	**VTE** total	**Int:**17/142 (12.0%) **Cont:** 14/147 (9.5%) p=0.50	Study on fixed dose combination of LMWH with Dihyroergotamine vs adjusted dose UFH (starting with 15,000 IU/day and increased to 28,800 IU/day ±7,150 IU/day) in prevention of DVT after total hip replacement. **Also reported:** intraoperative and postoperative blood loss, postoperative transfusions, revieion of vound, reoperation due to bleed ing complications, hematoma at injection site, patechlal,
								DVT confirmed by bilateral ascending venography.	**Int:**17/142 **Cont:** 13/147; p=0.76	
								Proximal DVT:	**Int:**0/142 **Cont:** 0/147	
								Distal DVT:	**Int:**15/142 **Cont:** 8/147; p=2.59	
								Proximal and Distal DVT:	**Int:**2/142 **Cont:** 5/147; p=1.21	
								PE Confirmed by pulmonal szintigraphy.	**Int:**0/142 **Cont:** 1/147; p=0.87	

LMWH vs UFH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Kakkar et al., 2000[327]	RCT	1+	Total: 298 Intervention n: 149 Control n: 149	**Type of surgery:** Patients scheduled for elective hip replacement surgery. **Duration of surgery:** **Int:** 110±55.1 **Control:** 100±58.7; p=0.207 **Age and gender:** **Intervention:** Mean age: 70.4 ± 10.9 years M/F:49/100 **Control:** Mean age: 70.5 ± 9.2 years M/F:45/104 **Pre-existing risk factors:** Previous DVT: **Int:** n = 4 **Control:** n = 12; Previous PE: **Int:** n = 1 **Control:** n = 3; Varicose veins: **Int:** n = 44 **Control:** n = 46; Varicose ulcer: **Int:** n = 3 **Control:** n = 6; obesity: **Int:** n = 23 **Control:** n = 27;	**Type, dose and timing:** One dose daily of subcutaneous LMWH (3500 IU of Bemiparin) plus a placebo injections of 0.9% saline. Prophylaxis started 2 hours before surgery and continued for at least 8 post operative days or longer if patient was still institutionalised. **Additional non-comparative prophylaxis:** Not reported	**Type, dose and timing:** 5000 units of Calcium heparin injected subcutaneously twice daily. Prophylaxis started 2 hours before surgery and continued for at least 8 post operative days or longer if patient was still institutionalised.	4 weeks	**VTE** total	**Int:** 9/125 (7.2%) **Cont:** 25/134 (18.7%) p=0.01	Financially supported by Laboratories Farmaceuticos Rovi S.A.; (Madrid, Spain) Who also provided supply of LMWH and std UFH sodium **Also reported:** Operative blood loss, postoperative drain loss
								DVT confirmed by bilateral elective venography.	**Int:** 9/101 (8.9%) **Cont:** 24/116 (20.7%) p=0.03	
								Proximal DVT:	**Int:** 3/101 (3.0%) **Cont:** 5/116 (4.3%) p=0.73	
								Distal DVT:	**Int:** 4/101 (4.0%) **Cont:** 13/116 (11.2%) p=0.08	
								Proximal and Distal DVT:	**Int:** 2/101 (2.0%) **Cont:** 6/116 (5.2%) p=0.23	
								PE Confirmed by ventilation perfusion scan.	**Int:** 1/125 (0.8%) **Cont:** 2/134 (1.5%) p=1.00	
								Patient transfused	**Int:** n = 74/149 **Control:** n = 66/149; p=0.42	
								Wound hematomas	**Int:** n = 8/149 **Control:** n = 7/149; p=1.00	

LMWH vs UFH

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Kleber et al., 2003[350] (The PRINCE study) **Country of study:** Germany **Study design:** Multicentre RCT, open label study **List who was masked to interventions:** Open label study. Central reviewers of efficacy end points (interpreting the screening tests and assessment of venous thromboembolic events) were masked. **Evidence level:** 1+ **Duration of follow-up:** 10±2 days	**Patient group:** Heart failure (n=333)and respiratory disease(n=332) patients **Setting:** inpatient **Inclusion criteria:** ▪ Aged ≥18 ▪ Hospitalised for severe respiratory disease (based on lung function test or blood gas analyses outside normal range and at ≥1 of these: severe functional loss ≥2 lung segments, severe secondary pulmonary hypertension, pneumonia, interstitial lung disease, lung cancer and/or metatstases with life expectancy > 2 months, or exacerbation of COPD)or heart failure (class III or IV according to New York Heart Association classification) ▪ Confined to bed >2/3 of the time **Exclusion criteria:** ▪ Advanced acquired immunodeficiency syndrome ▪ Contraindication to LMWH or UFH ▪ Hypersensitivity to contrast media ▪ Severe hepatic, pancreatic or renal disease, arterial hypertension ▪ Intracranial bleeding or haemorrhagic stroke in the preceding 6 months ▪ Ocular ocr CNS surgery in the preceding 4 weeks ▪ Coagulation disorders ▪ Drug/alcohol abuse ▪ Acute signs of DVT or PE ▪ Gastrointestinal ulcer ▪ Immobilised for > 24 hours before enrolment ▪ Patients on anticoagulants or platelet inhibitors, or NSAIDs. However, heart failure patients allowed 100mg aspirin **<u>All patients</u>**	**Group 1** UFH 5000IU 3 times daily, subcutaneously **Group 2** Enoxaparin 40mg once daily, subcutaneously Start time: Day 1(on enrolment day) Duration: 10±2 days **Additional non-comparative prophylaxis:** ▪ Patients on anticoagulants or platelet inhibitors, or NSAIDs. However, heart failure patients allowed 100mg aspirin ▪ Compression stockings applied up to 20% of patients in each treatment group	**All cause mortality** (confirmed by:)	**Group1:** 15/333 **Group 2:** 9/ 332 **P value:**	**Funding:** Aventis Pharma **Limitations:** ▪ Open label study ▪ More patients with malignancy in the enoxaparin group **Outcomes not reported:** Symptomatic DVT Calf DVT Fatal bleeding Neurological bleeding Upper GI bleeding Heparin induced thrombocytopaenia PTS, Pulmonary hypertension QoL, LOS **Additional outcomes reported:** **Notes:**
			Fatal pulmonary embolism (confirmed by: Autopsy. 1 heart failure patient in UFH group had both PE and DVT)	**Group1:** 1/212 **Group 2:** 0/239 **P value:**	
			Symptomatic pulmonary embolism (confirmed by: perfusion scintigram)	**Group1:** 0/212 **Group 2:** 1/239 **P value:**	
			DVT, asymptomatic or symptomatic (confirmed by: patients with positive D dimmer or fibrin monomer test underwent bilateral venography. Autopsy) 1 heart failure patient in UFH group had both PE and DVT	**By D-dimer test** **Group1:** 86/212 **Group 2:** 84/236 **P value:** By Venography/autopsy, including venogram conducted >24 hours after last dose **Group1:** 28/235 **Group 2:** 26/264 **P value:** By Venography/autopsy, in primary efficacy population **Group1:** 22/212 **Group 2:** 19/239 **P value:** **<u>In heart failure patients:</u>** By Venography/autopsy **Group1:** 15/93 **Group 2:** 11/113 **P value:** **<u>In respiratory failure patients</u>** By Venography/autopsy **Group1:** 7/119 **Group 2:** 8/126 **P value**	
			Thigh (Proximal)DVT(confirmed by:)	**Group1:** 4/ 212 **Group 2:** 9/ 239 **P value:**	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No randomised: 668 (3 withdrawn before receiving any study medication) **No. of dropouts:** 214/665 **Age (mean):** 70±14 **Risk Factors** **Gp1** **Gp2** Immobilisation 332 333 Congestive heart failure 186 186 Age >70yr 185 187 COPD 134 142 Venous Disease 137 129 Overweight 104 98 Diabetes Mellitus 101 104 Severe infection 61 56 Pervious myocardial infarction 41 41 Pre-existing malignancy 25 16 Dehydration 15 23 History of DVT 20 19 **Group 1** **No. randomised: 333** **M/F:183/150** No evaluated: 212 Severe respiratory disease:164 Heart failure:169 **Group 2** **No. randomised: 332** **M/F:160/172** No evaluated: 239 Severe respiratory disease:168 Heart failure:164		**Major bleeding** (description: 1 urogenital –enoxaparin and 1 haemorrhoidal-UFH. Defined as retroperitoneal or intracranial bleeding, overt bleeding with Hb)	**Group1:** 1/333 **Group 2:** 1/332 **P value:**	
			Minor bleeding (description:)	**Group1:** 11/333 **Group 2:** 4/332 **P value:**	

LMWH vs UFH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Koch 1997 (11 studies) [72,174,198,243,380,381,400,458,527,549,635] All of these studies were included in the guideline review.	Systematic Review	1+	Total: 3608 Int: 1800 Cont: 1808	**Type of surgery:** 11 orthopaedic studies	**LMWH** **Dose:** Ranged between 3100-5000 Anti X-a units **Timing**: Initiated preoperatively at diagnosis to postoperatively 12-24 hours. **Duration:** Ranged from greater than 6 to 14 days. **Additional non-comparative prophylaxis:** GCS (1 study) Leg bandages (1 study)	**UFH** **Dose:** 5000-7500 IU **Timing**: Initiated preoperatively at diagnosis to postoperatively 12-24 hours. **Duration:** Ranged from greater than 6 to 14 days **Additional non-comparative prophylaxis:** GCS (1 study) Leg bandages (1 study	NR	**DVT** confirmed by radiofibrinogen update test or phlebography.	**Int:** 250/1761 **Cont:** 284/1765 **p value:** 0.1212	**Funding**: grant from Deutsche Forschungsgemeinschaft. **Not reported:** QoL, LoS, PTS.
								Proximal DVT	**Int:** 84/1430 **Cont:** 120/1432 **p value:** 0.0017	
								PE (observed)	**Int:** 18/1570 **Cont:** 33/1570 **p value:** 0.0471	
								Major bleeding:	**Int:** 69/1604 **Cont:** 79/1619 **p value:** 0.4497	

LMWH vs UFH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Lastoria et al., 2006[383]	RCT	1+	**Total:** 75 **M/F:** 59/16 **Int:** 41 **Cont:** 34	**Type of surgery:** Vascular: Major lower extremity amputation (30 above-knee and 45 below-knee) **Inclusion criteria:** Patients over 18 years, undergoing elective or emergency lower-limb amputation for critical-limb ischemia. **Excluded** if had previous venous thrombo-embolism, and patients with contra-indication for anticoagulant prophylaxis.	**LMWH (enoxaparin)** **Dose:** 40mg/day **Timing:** 12 hours before surgery or in emergency cases in the first postoperative day. **Duration:** During hospitalisation **Additional non-comparative prophylaxis:** Not reported	**UFH** **Dose:** 5000 IU (subcutaneously) **Timing:** 12 hours before surgery or in emergency cases in the first postoperative day. **Duration:** During hospitalisation **Additional non-comparative prophylaxis:** Not reported	NR	**DVT** confirmed by duplex scanning (5-8 days after surgery)	**Int:** 4 (9.7%) **Cont:** 4 (11.7%) P=0.92	**Funding:** Paulista State University. **Not reported:** Proximal DVT's, PEs, duration of hospital stay, QoL or post-thrombotic syndrome. **Notes:** DVT: 1 bilateral thrombosis in each group. No significant difference between interventions in DVTs in level of amputation or sex of patient.

LMWH vs UFH

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Lechler et al., 1996[387] **Country of study:** Austria and Germany **Study design:** RCT, double blinded, multi centre **List who was masked to interventions:** Patients and investigators **Evidence level:** 1+ **Duration of follow-up:** 7 days	**Patient group:** Immobilised medical patients **Setting:** 26 medical centres **Inclusion criteria:** ▪ ≥18 years old ▪ expected immobilisation of >1/2 of the time for the whole study period of 7 days, *and* at least one of additional risk factors such as: ○ age >60 years ○ malignancy ○ obesity (>20%) ○ former thromboembolic event ○ cardiac insufficiency (NYHA III-IV) ○ paresis of lower limbs ○ hemiplegia/paraplegia ○ severe infection **Exclusion criteria:** ▪ Anticoagulation *and/or* treatment with aggregation inhibitors or NSAIDS for the preceding 7 days ▪ Regional anaesthesia ▪ Pregnancy or lactation ▪ Bleeding disorder ▪ Thrombocytopenia (<100,000/µL) ▪ Head trauma in the past 6 months ▪ Haemorrhagic stroke in the preceding 4 weeks ▪ Endocarditis ▪ Suspicion for internal bleeding ▪ Severe liver disease/renal insufficiency ▪ Thromboembolism on admission and participation in a clinical trial in the preceding 6 weeks **<u>All patients</u>** **N:** 959 **Age (mean):** 74±13 **Main Diagnoses (%):** **Gp1** **Gp2** Cardiovascular diseases 67.5 70.5 Endocrinologic diseases 27.9 30.1	**Group 1** UFH 5000IU 3 times daily, subcutaneously **Group 2** Enoxaparin 40mg, daily and 2 placebo injection(isotonic mannitol solution) (total of 3 injections daily) All injections were 0.2 ml Start time: within 24 hours of admission Duration: 7 days **Additional non-comparative prophylaxis:** Patients on anticoagulants, aggregation inhibitors and NSAIDs were excluded from study Mechanical prophylaxis unknown	**All cause mortality** (confirmed by:)	**Group1:** 11/482 **Group 2:** 7/477 **P value:** 0.47 [*calculated by NCCAC team using Fisher's exact test*]	**Funding:** **Limitations:** ▪ Not reported: ○ Method of randomisation/ concealment ○ Results across centres ○ Mortality causes ○ Mechanical prophylactic methods, or ambulation policies **Outcomes not reported:** Fatal PE, Symptomatic PE, Symptomatic DVT, Major bleeding, Minor bleeding, Heparin induced thrombocytopaenia PTS, Pulmonary hypertension, QoL, LOS **Additional outcomes reported:** 8 urogenital bleedings reported-not stated which group. Haematomas >5 cm in diameter: 52 events in UFH and 22 in enoxaparin **Notes:** All patients were screened for DVT at
			Symptomatic pulmonary embolism (confirmed by: perfusion scan, angiography and autopsy in cases of death if permitted)	**Group1:** 4/443 **Group 2:** 0/442 **P value:** 0.12 [*calculated by NCCAC team using Fisher's exact test*]	
			DVT, asymptomatic or symptomatic (confirmed by: duplex sonography at end of study period, or when clinically suspected. Positive cases were confirmed with phlebography)	**Group1:** 4/443 **Group 2:** 1/442 **P value:** 0.38 [*calculated by NCCAC team using Fisher's exact test*]	
			Major bleeding (description: decrease in Hb≥2g/dl, transfusion of >2 units of blood and/or retroperitoneal or intracranial bleeding)	**Group1:** 7/482 **Group 2:** 2/477 **P value:** 0.18 [*calculated by NCCAC team using Fisher's exact test*] 2 patients in heparin group were reported to have "severe bleeding". However, the definition was not provided.	
			Upper GI bleeding	9 gastrointestinal bleeding cases. Not stated which group it was from.	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Respiratory diseases 24.3 23.4 Gastrointestinal and urogenital diseases 22.6 21.8 Central nervous diseases 15.8 17.8 Cancer 14.7 12.9 Bone diseases 10.8 12.2 Skin diseases 3.5 3.1 Others 8.2 8.9 **Group 1** **No. randomised:** 482 **Stipulated efficacy evaluation conducted:** 443 **Per protocol population:**377 **M/F:** 178/304 **Age (mean):** 74±13 **Risk factors** (%) ▪ Immobilisation: 100 ▪ Age >60 years: 88.8 ▪ Heart failure: 35.9 ▪ Overweight: 32.8 ▪ Severe infection: 19.1 ▪ Malignant disease: 14.7 ▪ Paresis hemiplegia, paraplegia: 7.5 ▪ Previous VTE: 7.7 **Group 2** **No. randomised:** 477 **Stipulated efficacy evaluation conducted:** 442 **Per protocol population:**393 **M/F:** 183/294 **Age (mean):** 74±13 **Risk factors** (%) ▪ Immobilisation: 100 ▪ Age >60 years: 87.2 ▪ Heart failure: 34.2 ▪ Overweight: 28.7 ▪ Severe infection: 20.1 ▪ Malignant disease: 20.1 ▪ Paresis hemiplegia, paraplegia: 7.5 ▪ Previous VTE: 6.1				study entry using B-mode scan or duplex sonography.

LMWH vs UFH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Legnani et al., 1990[393]	RCT	1+	**Total:** 50 Intervention : n = 24 Control: n = 26	**Type of surgery:** Gynaecological laparotomy patients (& Duration of surgery)	**Type:** 4000iu LMWH (Alfa LMW1-OP 2123) subcutaneously once per day Patients with malignancy (11/24 patients) and/or undergoing Wertheim-Meigs laparotomy (2/24 patients) received 4000iu LMWH subcutaneously twice daily	**Type:** 5000iu calcium heparin (Italfarmaco) subcutaneously twice daily Patients with malignancy (12/26 patients) and/or undergoing Wertheim-Meigs laparotomy (2/26 patients) received 5000iu calcium heparin subcutaneously three times daily	8 days post-operatively	**DVT** Confirmed by: ^{125}I FUT	**Int:** 5/24 **Contol:** 5/26 **p value:** 1.0000	**Comments:** PE and survival not reported but it appears all patients completed the study as none lost to follow-up prior to discharge. **Not reported:** PE PTS bleeding QoL **Funding:** not reported
				Intervention: Mean age: 55.6±7.6 yrs M/F: not reported				**Fatal PE** (see comments):	**Int:** 0/24 **Control:** 0/26 **p value:** N/A	
				Control: Mean age: 55.7±10.5 M/F: not reported				**Survival** (see comments)	**Int:** 24/24 **Control:** 26/26 **p value:** N/A	
				Pre-existing risk factors: No previous history of DVT	**Timing:** started 2 hours preoperatively and continued until postoperative day 7	**Timing:** started 2 hours preoperatively and continued until postoperative day 7				
					Additional non-comparative prophylaxis: none reported	**Additional non-comparative prophylaxis:** none reported				

LMWH v UFH

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Levi et al., 2007[397] **Country of study:** multicentre- US, Uk, Netherlands etc (20 countries) **Study design:** RCT, equivalence 1:1:2 randomisation of UFH, LMWH, placebo **List who was masked to interventions:** Patients, investigators and all study personnel **Evidence level:** 1+ **Duration of follow-up:** 28 days	**Patient group:** Patient with severe sepsis on drotrecogin alfa (Activated) (Drot AA) **Setting:** Multicentre, inpatient **Inclusion criteria:** 7. Aged ≥18 years old 8. Receiving inpatient treatment for severe sepsis 9. Indicated for DrotAA under an approved label in the country in which the patient enrolled, defined as one or both of the following: - Multiple organ dysfunction (MOD); EMEA label - Patients at higher risk of death (as defined by Acute Physiology Age and Chronic Health Evaluation [APACHE] II scores ≥ 25; US label) **Exclusion criteria:** 11. Contraindicated for treatment with prophylactic LMWH or UFH 12. Required a higher dose of heparin than specified in protocol or concurrent need for other anticoagulant medication 13. Acute or chronic renal failure with estimates creatinine clearance less than 30ml/min 14. Moribund or not expected to survive 28 days 15. Patient or family not committed to aggressive management of severe sepsis **<u>All patients</u>** **N:** 1935 (ITT population. 2002 enrolled, 2 had consent issues, 59 did not receive study drugs) **<u>Group 1 and Group 2</u>** **No. randomised:** 976 **Age (mean):** 59.6±16.1 **No. of dropouts:**	**Group 1** UFH 5000 U, subcutaneous, every 12 hours **Group 2** LMWH (enoxaparin) 40 mg, subcutaneous, one daily, (a second injection of placebo was administered after 12 hours to maintain blinding of 12 hourly injections. *Group 1 and 2 were combined in many section of the analysis as "heparin"* **Group 3** Placebo Administered twice daily <u>Start:</u> as soon as possible after initiating Drot AA, no more than 12 hours later <u>Stop</u>: Until completion of Drot AA infusion. <u>Duration:</u> 96 hours, during administration of Drot AA. If Drot AA infusion continued beyond Day 4 because of interruptions, study drug injections were continued every 12 hours until the infusion	**All cause mortality** (for 28 days, cause of death determined by investigator opinion). This was the primary objective of study. 8 patients had unknown 28-day survival status	**Heparin (Group 1 and 2):** 275/972 (28.3) **Group1:**145/495 (29.3%) **Group2:**130/477 (27.3%) **Group3:**305/955 (31.9%) **P value**: (reported) heparin vs placebo=0.08	**Funding:** Eli Lilly (designed and sponsored the study1) **Limitations:** The protocol only covered administration of Drot AA and placebo/heparin in Days 0-6. Any other aspects of care, use of heparin &/or mechanical methods, including the use of heparin after the completion of Drot AA Days 4-6 were at the discretion of the investigators. Subgroup analysis of the study had shown that: among the group of patients who were exposed to heparin at baseline, those randomised to placebo had higher mortality rate than those receiving heparin. **Outcomes not reported:** Fatal PE, Symptomatic PE, PE asymptomatic or symptomatic, symptomatic DVT DVT, asymptomatic or symptomatic Thigh DVT, Calf DVT, Upper GI bleeding, Minor bleeding, post thrombotic syndrome, pulmonary hypertension, Quality of life, Length of stay **Additional outcomes reported:** **Venous thrombotic events:** <u>Days 0-6:</u> **Heparin:** 45/976 **Placebo:** 49/959 **P value:** 0.60
			Fatal bleeding (overt bleeds considered the primary cause of death)	<u>Days 0-6</u> **Heparin:** 1/976 **Placebo:** 3/959 **P value**: 0.31 <u>Days 0-28</u> **Heparin:** 4/976 **Placebo:** 11/959 **P value**: 0.06	
			Major bleeding (described as <u>"serious bleeding events"</u> and included: fatal bleeding &/or non fatal serious bleeding defined as intracranial brain haemorrhage confirmed by brain imaging or autopsy, or bleeding at a critical location [e.g. retinal haemorrhage, major haemorrhage, or spinal haemorrhage] and/or an otherwise life threatening event bleed that did not meet other criteria)	<u>Days 0-6</u> **Heparin:** 22/976 **Placebo:** 24/959 **P value**: 0.72 <u>Days 0-28</u> **Heparin:** 38/976 **Placebo:** 50/959 **P value**: 0.16 Note: Bleeding events which were reported as non serious adverse events that occurred during infusion (Days 0-6) and led to or contributed to the need for transfusion of packed red blood cells were classified as "non serious bleeding events".	
			Neurological bleeding (central nervous system bleeding events)	<u>Days 0-6</u> **Heparin:** 3/976 **Placebo:** 3/959 **P value**: 0.98 <u>Days 0-28</u> **Heparin:** 10/976 **Placebo:** 7/959	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Additional risk factors: Age ≥65 years: 411/976 <u>Patient history:</u> - Hypertension:378/976 - Recent surgery: 330/976 - COPD: 171/976 - Malignancy: 134/976 - Chronic liver disease: 55/976 - Congestive myopathy 49/976 - Deep vein thrombosis: 32/976 - Pulmonary thromboembolism: 12/976 - APACHE II score: 23.8±7.6 - APACHE≥25: 462/976 **<u>Group 3</u>** **No. randomised:** 959 **Age (mean):** 58.4±16.0 **No. of dropouts:** **Additional risk factors:** Age ≥65 years: 367/959 <u>Patient history:</u> - Hypertension: 356/959 - Recent surgery: 331/959 - COPD: 160/959 - Malignancy: 112 /959 - Chronic liver disease: 52/959 - Congestive myopathy: 46/959 - Deep vein thrombosis: 19/959 - Pulmonary thromboembolism: 13/959 - APACHE II score: 24.0±7.4 - APACHE≥25: 431/959	was completed. If the 12-hour time point for study drug administration occurred within 2 hours after completion of Drot AA infusion, the final study drug injection was administered then. **Other drugs:** Both groups received Drot AA at 24 microgram/kg/hour for 96 hours, according to local hospital guidelines **Additional non-comparative prophylaxis:** "all other patient care was at the discretion of the investigator, including the use of commercial heparin (commercial use of heparin use during Days 0-6 refers to use in the 1-2 d after Drot AA and study drug administration)". Commercial use of heparin was not statistically significant between treatment arms(data not shown) "The use of prophylactic heparin and mechanical methods between Study Days 7-28		**P value:** 0.49	<u>Days 0-28:</u> **Heparin:** 56/976 **Placebo:** 67/959 **P value:** 0.26 (defined as objectively confirmed non fatal or fatal pulmonary embolism (PE), asymptomatic lower extremity DVT, detected by bilateral compression ultrasonography performed at the end of study drug administration (Study Days 4-6), symptomatic lower extremity DVT confirmed by objective means (ultrasound or other accepted diagnostic modalities) an symptomatic central vein thrombosis, confirmed by objective means) **Ischaemic stroke:** <u>Days 0-6</u> **Heparin:** 3/976 **Placebo:** 12/959 **P value:** 0.02 <u>Days 0-28</u> **Heparin:** 5/976 **Placebo:** 17/959 **P value:** 0.01 **Any bleeding event:** <u>Days 0-6</u> **Heparin:** 105/976 **Placebo:** 78/959 **P value:** 0.049 <u>Days 0-28</u> **Heparin:** 121/976 **Placebo:** 105/959 **P value:** 0.32 **Notes:** The study was designed to evaluate whether heparin
			Heparin induced thrombocytopaenia	<u>Days 0-6</u> **Heparin:** 10/976 **Placebo:** 6/959 **P value:** 0.33 <u>Days 0-28</u> **Heparin:** 12/976 **Placebo:** 11/959 **P value:** 0.87	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
		were very similar in both groups"- details not reported			interfered with the efficacy of Drot AA in adult patients with severe sepsis at high risk of death. Heparin may have direct therapeutic effects in severe sepsis and disseminated intravascular coagulation independent of their anti thrombotic properties. High doses of heparin lead to higher clearance of DrotAA through increasing the rate of inhibition of activated protein C by protein C inhibitors

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Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Macdonald et al., 2003[415]	RCT	1+	**Total:** 100 Intervention : n = 51 Control: n = 49	**Type of surgery:** Patients undergoing craniotomy for brain neoplasm, including trans-sphenoidal surgery, intracranial aneurysm, vascular malformation, infection, spontaneous intracranial hematoma, closed head injury or cortical resection for epilepsy. **Age & Gender:** **Intervention:** Mean age: 51 ±15 yrs M/F:23/28 **Control:** Mean age: 49 ±15 yrs M/F: 23/26	**Type:** LMWH (Dalteparin) **Dose:** 2500 IU once per day **Timing:** Begun at time of surgery and continued for 1 week **Additional non-comparative prophylaxis:** Thigh length intermittent pneumatic compression devices worn from time of admission until discharge or the patient was ambulatory for more than 3 hours per day.	**Type:** LDUH **Dose:** 5000 IU twice per day **Timing:** Begun at time of surgery and continued for 1 week **Additional non-comparative prophylaxis:** Thigh length intermittent pneumatic compression devices worn from time of admission until discharge or the patient was ambulatory for more than 3 hours per day.	1 month	**DVT** Confirmed by: Doppler US (on 7th post-op day?)	**Int:** 2/51 **Control:** 0/49 **p value:** 0.30	**Comments:** Excluded patients with VTE, thrombocytopenia, abnormal prothrombin time, abnormal partial thromboplastin time, abnormal bleeding time, history of hypersensitivity to heparin or pork products, penetrating head injury or pregnancy. **Not reported:** Proximal DVT, PTS, QoL, LoS **Also reported:** anaesthesia time; blood loss; no. of patients requiring intraoperative transfusion, surgeon's impression of haemostasis, no. of patients requiring erythrocyte transfusion
								Symptomatic pulmonary embolism confirmed by ventilation perfusion scan or spiral CT.	**Int:** 0/51 **Control:** 0/49 **p value:** not sig	
								Intracranial haemorrhage confirmed by CT scan and MRI	**Int:** 2/51 **Control:** 1/49 **p value:** 0.59	
								Thrombocytopenia	**Int:** 2/51 **Control:** 0/49 **p value:** 0.30	
								Mortality	**Int:** 0/51 **Control:** 1/49 **p value:** 0.48	

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Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
McLeod et al., 2001[439]	RCT	1+	Total: 936 Intervention: 468 Control n: 468	**Type of surgery:** Patients undergoing colorectal surgery.	**Type, dose and timing:** One dose daily of subcutaneous LMWH (40 mg of Enoxaparin) plus 2 placebo injections of 0.9% saline every 8 hours for up to 10 days after surgery. Prophylaxis started 2 hours before surgery. **Additional non-comparative prophylaxis:** Not reported	**Type, dose and timing:** 5000 units of Calcium heparin injected subcutaneously every 8 hours for 10 days. Prophylaxis started 2 hours before surgery.	10 days	**VTE** rate was the same in both groups **DVT** confirmed by bilateral duplex compression US or venography. **PE** Confirmed by lung scan or pulmonary angiogram	44/468 (9.4%) (95% CI of the difference, 0 ±3.7%) **Proximal DVT:** **Int:** 2.8% **Control:** 2.6% **Int:** n = 1 **Control:** 0	Screening tests used are not consistent through out study.
				Intervention: Mean age: 52 ± 18 years M/F:376/298				**Bleeding complications:** Major bleeding Minor bleeding	**Int:** n = 18/653 **Control:** n = 10/643 **Int:** n = 52/653 **Control:** n = 32/643	
				Control: Mean age: 50 ± 17 years M/F:355/320						
				Pre-existing risk factors: History of prior thromboembolism: **Int:** n = 14 **Control:** n = 19 Malignancy: **Int:** n = 164 **Control:** n = 160 Inflammatory bowel disease: **Int:** n = 202 **Control:** n = 211 Rectal procedure: **Int:** n = 241 **Control:** n = 246						

LMWH vs UFH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Mismetti 2001[450] 48 studies [9,32,37,49,50,52,62,75,76,82,92,100,131,138,140,171,179,199,210,216,224,227,246,262,269-271,282,283,321,323-325,328,329,358,359,361,396,403,496,503,570,575-578,586,588,589,660,667,685] 45 of these studies were included in the guideline review [9,32,37,50,52,75,76,82,92,100,138,140,171,179,199,210,216,224,227,246,262,269-271,282,283,321,324,328,329,358,359,361,396,403,496,503,570,575,586,588,589,660,667,685]	Systematic review	1+	**Total:** 15349	**Type of surgery:** General (36 studies) Gynaecology (5 studies) T (thoracic? 1 study) Mixed (6 studies)	**Type:** LMWH **Timing:** Postoperative (1 study) Preoperative (47 studies) **Duration:** 3-10 days **Additional non-comparative prophylaxis:** Not reported	UFH **Additional non-comparative prophylaxis:** none	7 days – 3 months	**DVT** FUT, FUT + veno, Thermography, IPG, Doppler.	**Int:** 310/8100 **Cont:** 350/7319 **p value:** 0.0036	**Not reported:** LoS, QoL, PTS **Funding:** Sanofi-Synthelabo grant Event rates reported here are for all studies as published in the systematic review.
								PE	**Int:** 13/3895 **Cont:** 20/3857 **p value:** 0.2264	
								Major bleeding	**Int:** 219/7473 **Cont:** 245/6986 **p value:** 0.0528	
								Proximal DVT	**Int:** 6/1466 **Cont:** 20/1437 **p value:** 0.0053	

LMWH v UFH

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Osman et al., 2007[504] **Country of study:** Egypt **Study design:** Prospective randomised open label study **List who was masked to interventions:** Open label? **Evidence level:** 1- **Duration of follow-up:** 2 weeks? Not clearly stated	**Patient group:** Non "high risk", isolated, live-donor renal transplantation. **Setting:** Dec 2003 to March 2005. Urology and Nephrology Centre, Mansoura University **Inclusion criteria:** Consecutive, isolated, live-donor renal transplantation operated by the same surgical team **Exclusion criteria:** Categorised as "risky " because - <16 years old - grafts with multiple arteries - a history of thromboembolic disease - artheromatous arteries - collagen vascular disease - intraoperative technical difficulties **All patients** **N:** 75 **M/F:** 52/23 **Group 1 (LMWH)** **No. randomised:** 25 **No. of dropouts:** M/F:14/11 Age (year): 28.3±8 Pre-transplant Hb level: 8.8±2 Ischaemia time (min): 44.7±11 Delayed diuresis: 1/25 Donor gender, M/F:11/14 Donor age (year): 35.9±11 Harvested kidney (right): 10/25 **Group 2 (UFH)** **No. randomised:** 25	**Group 1** LMWH Dose: 3500anti-Xa IU in 0.35 ml once daily Duration: 1week **Group 2** UFH Dose: 5000IU, twice daily Duration: 1 week **Group 3** Control Did not receive heparinisation **Additional non-comparative prophylaxis:** Not reported Note: All patients discharged 2 weeks post operatively if no post-operative complications were found	**All cause mortality** (confirmed by: no mortality reported)	**Group1:** 0/25 **Group 2:** 0/25 **Group 3:** 0/25 **P value:** 1.0	**Funding:** None stated **Limitations:** - Open label study - No indication that patients or investigators were blinded – very likely open label study - Method of DVT screening not clearly specified, and frequency of screening not reported. - Duration of follow up not clearly stated **Outcomes not reported:** PE asymptomatic or symptomatic, DVT, asymptomatic or symptomatic, Thigh DVT, Calf DVT, Fatal bleeding, Neurological bleeding, Upper GI bleeding, Minor bleeding, Heparin induced thrombocytopaenia, Post thrombotic syndrome, Pulmonary hypertension, Quality of life, Length of stay **Additional outcomes reported:**
			Fatal pulmonary embolism (confirmed by: screening method and frequency not specified)	**Group1:** 0/25 **Group 2:** 0/25 **Group 3:** 0/25 **P value:** 1.0	
			Symptomatic pulmonary embolism (confirmed by: screening method and frequency not specified)	**Group1:** 0/25 **Group 2:** 0/25 **Group 3:** 0/25 **P value:** 1.0	
			Symptomatic DVT (confirmed by: screening method and frequency not specified)	**Group1:** 0/25 **Group 2:** 0/25 **Group 3:** 0/25 **P value:** 1.0	
			Major bleeding (description: Reoperated. Found to be due to slipped ligature)	**Group1:** 1/25 **Group 2:** 0/25 **Group 3:** 0/25 **P value:** 0.37	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No. of dropouts: M/F:19/6 Age (year): 29.4±8 Pre-transplant Hb level: 9.7±1.6 Ischaemia time (min): 46.3±12 Delayed diuresis: 1/25 Donor gender, M/F: 15/25 Donor age (year): 35.3±10 Harvested kidney (right): 10/25 **<u>Group 3 (Control)</u>** **No. randomised:** 25 **No. of dropouts:** M/F:19/6 Age (year): 26±6 Pre-transplant Hb level: 8.6±1.7 Ischaemia time (min): 42.5±8 Delayed diuresis: 2/25 Donor gender, M/F:14/9 Donor age (year): 33±9 Harvested kidney (right): 11/25 Note: The groups were comparable, in all the above variables. However, there was a trend to significance for pretransplant haemoglobin levels, p=0.07				- Graft thrombosis - Number receiving transfusion - Mean transfused units - Haemoglobin drop in non transfused patients - Other transplant related parameters **Notes:**

LMWH v UFH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Perhoniemi et al., 1996[515]	RCT	1+	**Total:** 165 Intervention: n = 80 Control: n = 81* Not reported to which group the other 4 patients were allocated nor what happened to them	**Type of surgery:** Patients over 40 requiring hip or knee (endoprosthesis or fracture) surgery. Excluded patients: if trauma happened >24 hours before admission. **Age & Gender:** **Intervention:** Mean age: 72 ±8.6 yrs M/F:22/58 **Control:** Mean age: 73.8 ±7.6 yrs M/F: 21/60	**Type:** LMWH (Enoxoparin) **Dose:** 40mg once per day **Timing:** Begun 12 hours before surgery and continued for 7 consecutive days **Additional non-comparative prophylaxis:** Spinal anaesthesia: 78/80	**Type:** Dihydroergotamin (0.5mg) + LDUH (5000 IU) 2 times per day **Timing:** Begun 2 hours before surgery and continued for 7 consecutive days **Additional non-comparative prophylaxis:** Spinal anaesthesia: 72/80	7 days	**DVT** Confirmed by: Doppler US **Symptomatic pulmonary embolism** confirmed by isotope scintigraphy.	**Int:** 1/80 **Control:** 0/80 **p value:** not sig **Int:** 0/80 **Control:** 2/80 **p value:** not sig	* reports 81 patients in UFH group but lists results for that group as 80. **Not reported:** Proximal DVT, PTS, QoL, LoS, major bleeds **Also reported:** duration of operation; volume of blood loss; volume of blood transfusion, haemaglobin values; no. of haematomas (did not distinguish between major and minor).

LMWH v UFH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Senaran et al., 2006[597]	RCT	1+	**Total:** 100 Intervention : n = 50 Control: n = 50	**Type of surgery:** Hip arthroplasty. Excluded patients: any history precluding anticoagulant therapy (i.e. blood dyscrasia, heparin induced thrombocytopenia, allergery to heparin). **Age & Gender:** **Intervention:** Mean age: 55.2 ±8.5 yrs M/F:12/38 **Control:** Mean age: 52.4 ±11.2 yrs M/F: 17/33	**Type:** LMWH (Enoxoparin) **Dose:** 40mg once per day **Timing:** Begun 12 hours before surgery and continued for 7 to 10 days **Additional non-comparative prophylaxis:** none reported	**Type:** UFH (5000 IU) 3 times per day **Timing:** Begun 8 hours before surgery and continued for 7 to 10 days **Additional non-comparative prophylaxis:** none reported	6 weeks	**DVT** Confirmed by: Doppler US	**Int:** 0/50 **Control:** 2/50 **p value:** not sig	~ defined as overt bleeding associated with at least one of the following: death or life-threatening event, bleeding confimed to be retroperineal, intracranial, or intraocular, postoperative transfusion of >2 units of packed red blood cells or whole blood, a decrease in haemoglobin level by more than 20g/l compared with relevant postoperative level. **Not reported:** Proximal DVT, PTS, QoL, LoS **Also reported:** serious discharge, hepatic dysfunction, renal complications, dysfunction and major haematoma
								Symptomatic DVT at 6 weeks Confirmed by: Doppler US	**Int:** 2/50 **Control:** 0/50 **p value:** not sig	
								Symptomatic pulmonary embolism confirmed by ventilation perfusion scan or pulmonary angiography.	**Int:** 0/50 **Control:** 0/50 **p value:** not sig	
								Major bleeding ~	**Int:** 1/50 **Control:** 4/50 **p value:**	

LMWH vs UFH

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Sherman et al., 2007[598] **Country of study:** International: US, Europe and Asia **Study design:** RCT, non blinded **List who was masked to interventions:** Nil-Open label **Evidence level:** 1+ **Duration of follow-up:** Total of 90 days, 14 days for main outcomes, 48 hours for bleeding events	**Patient group:** Acute Ischaemic Stroke **Setting:** 200 centres in 15 countries **Inclusion criteria:** ▪ ≥18 years ▪ Acute ischaemic stroke confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) ▪ Unable to walk unassisted because of motor impairment, indicated by National Institute of Health Stroke Scale (NIHSS) ≥2 for motor function of leg ▪ Onset ≤ 48 hours of randomisation **Exclusion criteria:** ▪ Evidence of VTE at screening or active bleeding ▪ Evidence of history of intracranial haemorrhage, heparin induced or enoxaparin induced thrombocytopenia or thrombosis or both ▪ Hypersensitivity to iodinated contrast media or iodine ▪ Spinal or epidural analgesia or lumbar puncture within the preceding 24 hours ▪ Thrombolytic treatment within the preceding 24hours ▪ Comatose at screening (NIHSS score ≥2 for level of consciousness) ▪ Known or suspected cerebral aneurysm or arteriovenous malformation ▪ Confirmed malignant disease that might have posed an increase risk of bleeding or compromise follow up or outcome assessment ▪ Impair haemostasis, e.g. baseline platelet count <100000 per microL, aPTT 1.5 times the laboratory upper limit of normal, INR>1.5 ▪ Major surgery or trauma within the preceding 3 months ▪ Expected need for full-dose treatment with therapeutic levels of an anticoagulant	**Group 1** Unfractionated heparin (UFH), Dose/route: 5000U , subcutaneously, every 12h Start: within 48 hours Duration: 10±4days **Group 2** Enoxaparin (Clexane) Dose/route: 40mg, subcutaneously, once daily Start: within 48 hours Duration: 10±4days **Additional non-comparative prophylaxis:** Mechanical prophylaxis not mentioned. Concomitant antiplatelet therapy was allowed. Number of patients receiving anti-platelet therapy: **In the randomised group:** At baseline: Enoxaparin: 825/884 (92%) UFH: 791/878 (90%) Received for >6	**All cause mortality** (up to Day 14 and 90 respectively)	Day 14 **Group1:** 45/872 **Group 2:** 48/877 **P value:** 0.58 Day 90 **Group1:** 103/872 **Group 2:** 100/877 **P value:**0.96 (P values were based on hazard ratio-log rank test)	**Funding:** Sanofi Aventis- funded and provided editorial support **Limitations:** ▪ Open label trial ▪ Safety (bleeding outcomes) not reported as stated in protocol-Minor extracranial haemorrhage (secondary safety outcome) not reported, "clinically important bleeding"- a post hoc definition was used ▪ No routine scanning of intracranial haemorrhage, a primary outcome. ▪ Use of mechanical prophylactic methods? **Outcomes not reported:** All cause mortality *at 48 hours*, PE asymptomatic or symptomatic, Major bleeding, Neurological bleeding, Upper GI bleeding, Minor bleeding Heparin induced thrombocytopaenia, post thrombotic symdrome, pulmonary hypertension QoL, LOS **Additional outcomes reported:** Subgroup analysis by patient characteristics (forest plots) Outcomes by NIHSS score (by Day 14?) **VTE**
			Fatal pulmonary embolism (up to 14 days, confirmed by autopsy)	**Group1:** 2/ 669 **Group 2:** 1/ 666 **P value:** 1.00 [Calculated by NCC-AC team using Fisher's Exact test]	
			Symptomatic pulmonary embolism (up to 14 days, confirmed by:)	**Group1:** 6/669 **Group 2:** 1/666 **P value:** 0.059	
			Symptomatic DVT (confirmed by: compression ultrasonography of the affected limb within 48 hours of symptom onset)	**Group1:** 4/669 **Group 2:** 1/666 **P value:** 0.18 Note this was on efficacy group (screened), rather than randomised group	
			DVT, asymptomatic or symptomatic (up to 14 day, confirmed by: Asymptomatic patients confirmed by bilateral contrast venography within 72 hours of last dose of study medication. Ultrasonography used for patients who were unable to do venography)	**Group1:** 118/669 **Group 2:** 67/666 **P value:**<0.0001 Note this was on efficacy group (screened), rather than randomised group	
			Proximal DVT(up to 14 days, confirmed by: see DVT)	**Group1:** 64/669 **Group 2:** 30/666 **P value:** 0.0003	
			Distal DVT (up to 14days confirmed by: see DVT)	**Group1:** 85/669 **Group 2:** 44/666 **P value:** 0.0002	

<table>
<tr><th>Study details</th><th>Patients</th><th>Interventions</th><th>Outcome measures</th><th>Effect size</th><th>Comments</th></tr>
<tr>
<td></td>
<td>

Treatment with LMWH or UFH at prophylactic dose for > 48h before inclusion
Allergy or known hypersensitivity to heparin or enoxaparin
Bacterial endocarditis
Prosthetic heart valve
Known or suspected anaemia (Hb<100g/L)
Uncontrolled arterial hypertension (systolic blood pressure (BP) >180mmHg or diastolic BP>100mmHg) at randomisation or clinical hypertensive urgency
Life expectancy <3 months due to comorbid disorders
Participation in another clinical study within the preceding 30 days
Any clinically relevant serious diseases, including severe liver disease or renal failure (creatinine clearance <30mL/min on ≥ 2 occasions)
Female patients, if breast feeding, pregnant, or could become pregnant during the study

<u>All patients</u>
N: 1762
Characteristics:
<table>
<tr><th></th><th>Group 1</th><th>Group 2</th></tr>
<tr><td>No randomised</td><td>878</td><td>884</td></tr>
<tr><td>No. dropouts
For safety population:
For efficacy population</td><td>
6

209</td><td>
7

218</td></tr>
<tr><td>Age (years)
<65
65-75
>75</td><td>66.1±12.9
372
265
241</td><td>65.9±12.9
371
312
201</td></tr>
<tr><td>M/F</td><td>473/405</td><td>521/363</td></tr>
<tr><td>BMI (kg/m³)
≥30</td><td>27.0±5.3
183</td><td>27.0±5.3
179</td></tr>
<tr><td>Race
White
Black
Asian
Hispanic
Others</td><td>
523
55
193
68
39</td><td>
523
68
182
73
38</td></tr>
</table>
</td>
<td><u>days after randomisation</u>
Enoxaparin: 82% 726/884
UFH group: 80% 698/878</td>
<td>
Fatal bleeding (description: within 48 hours of stopping treatment)

Major bleeding (intracranial and extracranial)

Major <u>(extracranial)</u> bleeding (description: Within 48 hours of stopping treatment, <u>overt</u> bleeding resulting in <u>either</u> death, drop of Hb level of ≥30g/L, need for transfusion≥2 units of blood, surgical intervention or decompression of closed space to s top or control event, bleeding in retroperitoneal or intraocular location)

Neurological (Intracranial) bleeding (within 48 hours of stopping treatment, symptomatic, confirmed by head CT or MRI scan, or autopsy)

Minor (extracranial) bleeding (within 48 hours of stopping treatment. Description: any clinically overt bleeding not meeting the criteria for major extracranial bleeding, and associated with at least one of the following: epistaxis lasting more than 5 minute or needing intervention, ecchymosis or haematoma >5 cm at its widest point, haematuria not associated with urinary catheter trauma, gastrointestinal haemorrhage
</td>
<td>
Group1: 4/872
Group 2: 5/877
P value: 1.0

Group1: 6/872
Group 2: 11/877
P value:0.33
[value calculated by NCC-AC team using Fisher's exact test]

Group1: 0/872
Group 2: 7/877
P value: 0.015

Group1: 6/872
Group 2: 4/877
P value: 0.55

Group1: 48/872
Group 2: 42/877
P value: 0.50
</td>
<td>
<u>NIHSS<14</u>
Grp 1: 14.0%(10.91-17.02)
Grp 2 : 8.3% (5.90-10.70)
P value: 0.004
<u>NIHSS ≥14</u>
Grp 1: 29.7%(22.94-36.49)
Grp 2 :16.3%(10.53-21.97)
P value: 0.004

<u>DVT</u>
<u>NIHSS<14</u>
Grp 1: 13.6%(10.54-16.58)
Grp 2 : 8.1%(5.73-10.48)
P value: 0.005
<u>NIHSS ≥14</u>
Grp 1: 29.1%(22.41-35.88)
Grp 2:16.3%(10.53-21.97)
P value: 0.005

<u>Clinically significant intracranial bleeding</u>
<u>NIHSS<14</u>
Grp 1: 0.3%(-0.12 to 0.77)
Grp 2: 0.3% (-0.12 to 0.74)
P value: 0.97
<u>NIHSS ≥14</u>
Grp 1: 1.6%(0.04 to 3.16)
Grp 2:16.3%(-0.33 to 2.05)
P value: 0.47

<u>Major extracranial</u>
<u>NIHSS<14</u>
Grp 1: 0%
Grp 2 : 0.5%(-0.06 to 0.99)
P value: 0.09
<u>NIHSS ≥14</u>
Grp 1: 0
</td>
</tr>
</table>

Study details	Patients			Interventions	Outcome measures	Effect size	Comments
	NIHSS score <14 ≥14	 626 252	 648 236		not related to intubation of nasogastric tube placement, wound haematoma or haemorrhagic wound complications not associated with features of over haemorrhage classified as major or subconjuctival haemorrhage needing end of study treatment)		**Grp 2:** 1.7%(0.05-3.40) **P value:** 0.04 **Notes:** Methodological paper published in year 2005
	Motor leg function (NIHSS score): 0 1 2 3 4	 0 10 381 293 387	 3 16 356 316 193				
	Venous stasis syndrome	11	3				
	Varicosis	16	19				
	Previous VTE	14	16				
	Previous thrombolytic therapy	58	50				
	Concomitant antiplatelet: Aspirin Aspirin with dipyramidole Clopidogrel Dipyramidole Ticlopidine other	791 738 45 174 47 28 56	815 767 36 189 40 28 52				

LMWH vs UFH

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Spinal Cord Injury Thromboprophylaxis Investigators, 2003[617] **Country of study:** Multi-centre study in 27 sites across US & Canada **Study design:** RCT **List who was masked to interventions:** Investigators blinded **Evidence level:** 1+ **Duration of follow-up:** Up to 6 weeks	**Patient group:** Spinal Cord Injury (SCI)-rehabilitative phase **Setting:** Rehabilitative SCI services-ICU, acute care ward and rehabilitation facility **Inclusion criteria:** • All patients who had completed the study on the effectiveness of hearpin + intermittent pneumatic compression (IPCD) vs LMWH in acute phase of SCI without objective evidence of DVT • Patients receiving UFH + IPCD received UFH in this study • Patients receiving LMWH 30mg bid received LMWH in this study **Inclusion criteria for the acute phase were:** • Age 15 or older • Sustained traumatic SCI from spinal cord level C2 to T12 within previous 72 hours • American Spinal Injury Association (ASIA) classification of A (complete motor or sensory deficit) or B (complete motor and incomplete sensory deficit) or C (incomplete motor deficit and sensory deficit with > half muscles having strength grade <3) **Exclusion criteria for the acute phase were:** • Objective evidence of bleeding around spinal cord • Intracranial bleeding • Uncontrolled bleeding at other sites or coagulopathy • GI bleeding within previous 2 weeks • Pregnancy • Conditions precluding use of bilateral IPCD, lower extremity ultrasound or contrast venography • Allergy to sulphating agents, heparin or contrast media	**Group 1: UFH** Low Dose Heparin 5000 U subcutaneous, 8 hourly **Start:** End of acute phase (Day 14) **End:** End of 8th week **Duration:** 6 weeks **Group 2: LMWH** LMWH Enoxaparin 40 mg once daily Start time: within 72 hours of injury **Start:** End of acute phase (Day 14) **End:** End of 8th week **Duration:** 6 weeks **Additional non-comparative prophylaxis:** Not Applicable	**All cause mortality** (confirmed by: NR)	**Group1:** 3/86 **Group 2:** 2/86 **P value:** 1.00# *[#values calculated by NCC-AC staff, using Fisher's exact test]*	**Funding:** Not stated, however, acute phase was funded by Rhone-Poulenc Rorer/Aventis Pharmaceuticals manufacturers of enoxaparin **Limitations:** This phase included only patients without objective evidence of DVT. However, number of subjects which were classified as without objective evidence of VTE was 172 (86 in each treatment arm), which was more than the number of assessable patients reported in the acute phase study (n=107). Discrepancy not explained. Only about 70% patients randomised were included in the efficacy analysis. Baseline characteristics were only reported for patients with evaluable outcomes. **Outcomes not reported:** Symptomatic PE Thigh DVT, Calf DVT Fatal bleeding, Neurological Bleeding Upper GI bleeding,
			Fatal pulmonary embolism (confirmed by: ventilation-perfusion lung scan, spiral CT or pulmonary angiography within 4 days of last dose)	**Group1:** 1/60 **Group 2:** 0/59 **P value:** 0.99# *[#values calculated by NCC-AC staff, using Fisher's exact test]*	
			Pulmonary embolism, asymptomatic or symptomatic (confirmed by: ventilation-perfusion lung scan, spiral CT or pulmonary angiography within 4 days of last dose)	**Group1:** 2/60 (3.3%) **Group 2:** 1/59 (1.7%) **P value:** 1.00# Reported value: 0.576 *[#values calculated by NCC-AC staff, using Fisher's exact test]*	
			DVT, asymptomatic or symptomatic (confirmed by: proximal and distal venography or proximal Doppler Ultrasound within 4 days of last dose)	**Group1:** 11/60 **Group 2:** 4/59 **P value:** 0.095# (Reported value=0.067) *[#values calculated by NCC-AC staff, using Fisher's exact test]*	
			Major bleeding -based on prior definition of transfusion of 2 units of packed red blood cells. Patient had hematuria, and even though there were no significant change in haemoglobin level, 2 bags of packed RBC were transfused	**Group1:** 1/86* **Group 2:** 0/86 **P value:** 1# *[#values calculated by NCC-AC staff, using Fisher's exact test]*	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	• Uncontrolled hypertension • Serum creatinase >2 mg/dL • Requirement for anticoagulation as treatment • Spinal cord surgery planned for 2 weeks after injury • Planned use of aspirin or NSAIDs **<u>All patients</u>** **N (randomised):** 172 Only information on assessable patients (n=119) was provided: **<u>Group 1 (UFH)</u>** **No. randomised:** 86 **No. of dropouts:** 26 **No assessable:**60 **Age (mean):** 34.0±16.5 **M/F:** 47/13 **Additional risk factors:** **BMI:** 24.5±3.8 **Surgery:** 8 **<u>Group 2 (LMWH)</u>** **No. randomised:** 86 **No. of dropouts:** 27 **No assessable:**59 **Age (mean):** 30.5±13.2 **M/F:** 53/6 **Additional risk factors:** **BMI:** 25.0 ± 5.5 **Surgery:** 7				HIT, Post thrombotic syndrome, Pulmonary hypertension Quality of life, Length of Stay

LMWH vs UFH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Ward & Pradhan, 1998[670]	RCT	+	Total: 552 Intervention n:271 Control n: 281	**Type of surgery:** Women undergoing major gynaecological surgery. **Intervention:** Mean age: 55 ± 17 years **Control:** Mean age: 55 ± 16 years **Pre-existing risk factors:** Previous VTE: presence indicated but no figures are given Malignant disease: **Int:** n = 222 **Control:** n = 239 Radical surgery: **Int:** n = 208 **Control:** n = 222 Non radical surgery: **Int:** n = 63 **Control:** n = 59	**Type, dose and timing:** One dose daily of subcutaneous 5000 LMWH Reviparin (Fragmin) injection at a site distant from the surgical site. Treatment was begun 12 hrs prior to surgery and continued for 5 days or until full activity was resumed whichever was longer. **Additional non-comparative prophylaxis:** The use of compression stockings and intermittent calf compression devices used by small number of women with previous history of DVT or PE.	**Type, dose and timing:** Twice daily subcutaneous dose of 5000 U Sodium Heparin. Injection at a site distant from the surgical site. Treatment was begun 12 hrs prior to surgery and continued for 5 days or until full activity was resumed whichever was longer. **Additional non-comparative prophylaxis:** The use of compression stockings and intermittent calf compression devices used by small number of women with previous history of DVT or PE.	6 Weeks	**DVT** confirmed by Doppler US or Venography **PE** Confirmed by V/Q lung scan. **Blood transfusion**	**Int:** n = 0; **Control:** n = 1 **Int:** n = 5; **Control:** n = 1 **Int:** n = 57; **Control:** n = 39	

Evidence Table 33: VKA vs UFH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Mismetti et al., 2004[451] 2 RCTs included [31,572] 1 of these studies was included in the guideline review [31]	Systematic review	1+	**Total:** 1366 (2 studies)	**Type of surgery:** Orthopaedic (2 studies)	**Type:** Warfarin (1 study) Acenocoumarol (1 study(**Timing:** postoperative both studies Preoperative (2 studies) 3 weeks (1 study) 6 weeks (1 study) **Additional non-comparative prophylaxis:** Not reported	**Type:** UFH 5000x2 for 3 weeks (1 study) LMWH (Reviparin 4200 IU x1) for 6 weeks	11-14 days 6 weeks	**DVT** (Clinical, confirmed by US or veno/FUT)	**Int:** 54/694 **Cont:** 52/662 **p value:** 1.0000	**Not reported:** LoS, QoL, PTS **Funding:** Sanofi-Synthelabo grant Event rates reported here are for all studies as published in the systematic review.
								Major Bleeding	**Int:** 35/645 **Cont:** 9/644 **p value:** 0.0001	
								Proximal DVT	**Int:** 4/636 **Cont:** 3/636 **p value:** 1.0000	

VKA vs UFH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Roderick et al., 2005[557] 4 RCTs included: [299,531,633,655] All of these studies were included in the guideline review.	Systematic review	1+	**Total:** 553 **Int:** 112 **Cont:** 110 **Note:** One study reported 331 subjects but not broken down between the two arms.	**Type of surgery:** Orthopaedic: 2 studies Gynaecological: 1 study Mixed surgery: 1 study Background agent: GCS in one study and Placebo dextran in one study.	**OAC-adjusted** **Dose:** Warfarin adjusted Warfarin 1 mg Nicoumalone adjusted Acenocoumarin adjusted **Timing:** 7 days pre-op to 1 day postoperatively. Dose ended between 7-14 days postoperatively. **Additional non-comparative prophylaxis:** Not reported	**UFH** **Dose:** H50000IU (three studies) and H4-5000 placebo OAC (one study). All taken subcutaneously. **Timing:** 2 hours preoperatively in all the studies. Continued until post-op (1 study), days 9-14 (one study), day 7 (in one study) and not reported in final study. **Additional non-comparative prophylaxis:** Not reported	From day 1 to day 14.	**DVT:** confirmed by fibrinogen uptake, venograph or doppler US	**Int:** 41/176 **Cont:** 29/184 **p value:** 0.0834	**Not reported:** LoS, QoL, PTS.
								PE by scan, angiogram, X-ray or post-mortem	**Int:** 9/80 **Cont:** 5/80 (reported from one study **p value:** 0.4022	
								Major Bleeds:	**Int:** 8/192 **Cont:** 15/190 **p value:** 0.1376	
								Proximal DVT	**Int:** 3/31 **Cont:** 0/37 (reported from one study) **p value:** 0.0897	

VKA vs UFH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Van Vroonhoven et al., 1974[656]	RCT	1+	**Total:** 100 Intervention: n = 50 Control: n = 50	**Type of surgery:** General (& Duration of surgery) **Intervention:** Mean age59 yrs M/F:NR **Control:** Mean age: 52 yrs M/F: NR **Pre-existing risk factors:** Obesity, Malignancy, Diabetes, Varicose veins (no significant differences between groups)	**Type:** acenocoumarol **Dose:** PTT 5-10% of normal **Timing:** Begun on evening of day of op, or 1st post-op day. Continued for 7 days **Additional non-comparative prophylaxis:** Routine post-op physiotherapy	**Type:** LDUH **Dose:** Not given **Timing:** Begun 2 hrs pre-op and repeatedly 12 hourly for 8 days **Additional non-comparative prophylaxis:** Routine post-op physiotherapy	**Both groups:** 7 days	**DVT** Confirmed by: Bilateral radioiodine (I, 125) fibrogin uptake test on days 0, 1, 3, 5, 7 post-op.	**Int:** 9/50 **Control:** 1/50 **p value:** <0.025 (Significant)	**Comments:** Thrombosis in OAC patients was associated with longer operation (p = 0.01) and greater peri-operative blood loss (p = 0.007). 1 OAC patient developed clinical symptoms of PE. **Not reported:** Proximal DVT, PE, PTS, QoL, survival, LoS, funding
								Bleeding related complications Peri-operative blood loss	**Int:** mean 436 ml (s.d. 584) **Control:** mean 317 ml (s.d. 303) **p value:** reported as not significant	

Evidence Table 34: VKA vs LMWH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Colwell et al., 1999[126]	RCT	1+	**Total**: 3011 Intervention : n = 1495 Control: n = 1516	**Type of surgery:** Elective total hip arthroplasty **Intervention:** Mean age: 64.1±13.21 (range: 19-99) M/F:659/836 **Control:** Mean age: 63.9±13.7 yrs (range: 18-100) M/F: 678/838 **Pre-existing risk factors:** Significantly more obese patients in enoxoparin arm **Int**: 378/1376 had BMI >30kg/m^2 (27.5%) (BMI reported for 92% of this group) **Control**: 459/1420 had >30kg/m^2 (32.3%) (BMI reported for 93.7% of this group) **p = 0.0055**	**Type**: Coumadin (adjusted dose warfarin) **Dose:** Started at 7.5mg, adjusted to maintain INR ratio between 2.0 to 3.0 **Timing:** Started between 48 hours preoperatively (at the discretion of the investigator) and 24 hours postoperatively. Administered until discharge. **Additional non-comparative prophylaxis**: Stockings permitted but not reported how many patients received these	**Type**: Enoxoparin (LMWH) **Dose**: 30mg **Timing:** Every 12 hours, started within 24 hours postoperatively once haemostasis (cessation of active bleeding as determined by the investigator) had been established Administered until discharge. **Additional non-comparative prophylaxis**: Stockings permitted but not reported how many patients received these	**Both groups:** 14 days treatment, 3 month follow up	**Symptomatic DVT** Confirmed by US or venography	**Int:** 44/1495 **Control:** 40/1506 **p value:** 0.6592	**Comments:** Results not stratified by BMI. No of VTEs by BMI: BMI >30 = 48/111 (43.2%) BMI ≤30 = 63/111 (56.8%) No of VTEs out of total no. of BMI group BMI >30 = 48/837 (5.73%) BMI ≤30 = 63/1959 (3.22%) **Also reported:** Minor bleeding **Not reported:** PTS, LoS, QoL, fatal PE **Funding**: No direct funding for this study. Indirect funding (i.e. authors' institution funding) Rhone Poulenc Rorer Pharmaceuticals
								Symptomatic DVT that occurred in hospital	**Int:** 15/1495 **Control:** 2/1506 **p value:** 0.0012	
								Symptomatic DVT that occurred after discharge	**Int:** 29/1495 **Control:** 38/1506 **p value:** 0.3232	
								PE Confirmed by ventilation perfusion scan or pulmonary angiography	**Int:** 9/1495 **Control:** 6/1506 **p value:** 0.4518	
								PE that occurred in hospital	**Int:** 2/1495 **Control:** 1/1506 **p value:** 0.6235	
								PE that occurred after discharge	**Int:** 7/1495 **Control:** 5/1506 **p value:** 0.5789	
								Both DVT & PE Confirmed by one of the above methods	**Int:** 3/1495 **Control:** 9/1506 **p value:** 0.1452	
								Both DVT & PE that occurred in hospital	**Int:** 0/1495 **Control:** 1/1506 **p value:** 1.0000	
								Both DVT & PE that occurred after discharge	**Int:** 3/1495 **Control:** 8/1506 **p value:** 0.2257	
								Major bleeds	**Int:** 4/1495 **Control:** 9/1506 **p value:** 0.2658	
								Adverse events	**Int:** 934/1495	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
								(most commonly reported were fever, anaemia, nausea)	**Control:** 987/1506 **p value:** 0.0870	
								Serious adverse events	**Int:** 134/1495 **Control:** 167/1506 **p value:** 0.0128	
								Survival (specify)	**Int:** 1485/1495 **Control:** 1497/1506 **p value:** 0.8226	

VKA vs LMWH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Roderick et al., 2005[557] 8 RCT studies included [186,195,200,250,274,292,293,389] All of these studies were included in the guideline review.	Systematic review	1+	**Total:** 7260 **Int:** 3197 **Cont:** 4063	**Type of surgery:** Orthopaedic: 9	**OAC-adjusted** Warfarin adjusted (5 studies), warfarin fixed (3 studies) and Acenocoumarin adjusted International Normalised Ratio 2-3 (1 study) **Timing:** Ranged from time admitted to 14 days postoperatively/discharge **Additional non-comparative prophylaxis:** Not reported	**LMWH** **Timing:** Ranged from time admitted to 14 days postoperatively/discharge **Additional non-comparative prophylaxis:** Not reported	Between day 1 to day 14.	**DVT:** confirmed by fibrinogen uptake, venograph or doppler US	**Int:** 772/2343 **Cont:** 638/3002 **p value:** 0.00001	**Not reported:** LoS, QoL, PTS.
								PE by scan, angiogram, X-ray or post-mortem	**Int:** 4/1790 **Cont:** 3/2098 **p value:** 0.56	
								Major Bleeds:	**Int:** 86/3052 **Cont:** 190/3919 **p value:** 0.0001	
								Proximal DVT	**Int:** 179/2343 **Cont:** 172/3002 **p value:** 0.005	

Evidence Table 35: VKA vs aspirin

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Harris et al., 1974[260]	RCT	1+	**Total**: 187 randomised (results for 168) **Intervention1**: n = 5 **Intervention2:** n = 62 **Control:** n = 51	**Type of surgery:** Total hip replacement. Duration of surgery not reported. **Intervention1:** Mean age: 58.4 yrs (s.d. not reported) M/F:20/33 **Intervention2:** Mean age: 55.5 yrs (s.d. not reported) M/F:35/26 **Control:** Mean age: 57.7. yrs M/F:21/29 **Pre-existing risk Factors:** Obesity (no significant differences between groups).	**Intervention 1:** **Type:** adjusted dose warfarin **Dose**: 5mg pre-op then adjusted PTT 1.5 x control (or for 18 secs) **Intervention 2:** **Type:** Low molecular weight dextran 10% w/v **Dose**: 500 ml **Duration – all interventions:** Continued until the patient was fully ambulatory and ready for discharge **Additional non-comparative prophylaxis**: All patients wore stockings during and post-surgery, leg elevation, foot and ankle exercises	**Type**: Aspirin **Dose:** 1200 mg started preoperatively **Duration:** Continued until the patient was fully ambulatory and ready for discharge **Additional non-comparative prophylaxis**: All patients wore stockings during and post-surgery, leg elevation, foot and ankle exercises	**All groups:** until discharge	**DVT** Confirmed by: Venography, radioiodine (I, 125) fibrogin uptake test	**Int1:** 10/55 **Int2:** 14/62 **Control:** 18/51 **p value:** No significant differences between groups.	**Comments:** Fourth group of patients received LDUH. This arm excluded due to a change in dose after 12 patients, and then discontinued after 20 patients. 2 patients in the dextran group received a clinical diagnosis of PE. Multiple thrombi were significantly more common in patients receiving aspirin than either warfarin or dextran. **Funding**:
								Proximal DVT Confirmed by: Venography, radioiodine (I, 125) fibrogin uptake test	**Int1:** 3/55 **Int2:** 8/62 **Control:** 10/51 **p value:** No significant differences between groups.	
								Length of Hospital Stay	**Mean (all groups):** 21 days. (No significantdiff between groups)	

VKA vs aspirin

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Lotke et al., 1996[408]	RCT	1+	**Total:** 388 (76 exclusions) **Intervention:** n = 146 **Control:** n = 166	**Type of surgery:** Total hip or knee arthroplasty (& Duration of surgery) **Intervention:** Mean age: 67.1 yrs (s.d. not reported) M/F:121/91 across both groups **Control:** Mean age: 66.4 yrs (s.d. not reported) M/F:121/91 across both groups **Pre-existing risk factors:**	**Type:** adjusted dose warfarin **Dose:** 10mg pre-op then PTT 1.2 – 1.5 x control **Timing:** 10mg eve before operation. Then adjusted dose from 2nd day post-op **Additional non-comparative prophylaxis:** Not reported	**Type:** Aspirin **Dose:** 325 mg twice daily **Timing:** Begun on day of admission **Additional non-comparative prophylaxis:** Not reported	**Both groups:** 9 – 10 days post-op. All patients observed for 6 months.	**DVT** Confirmed by: Venography (ipsalateral) on 7th-9th day post-op	**Int:** 78/146 **Control:** 100/166 **p value:** Not significant	**Comments:** No difference in size or location of clots between study groups. Patients with TKR had 2.6 x incidence of calf DVT than THR. Larger no of TKRs in aspirin group, but subgroup analyses showed no difference in DVT. **Not reported:** Fatal PE, PTS, QoL, Survival, LoS
								Proximal DVT Confirmed by: Venography (ipsalateral) on 7th-9th day post-op	**Int:** 18/146 **Control:** 16/166 **p value:** Not significant	
								Distal DVT Confirmed by: Venography (ipsalateral) on 7th-9th day post-op	**Small Int:** 42/146 **Control:** 45/166 **p value:** Not significant **Large Int:** 18/146 **Control:** 39/146 **p value:** Not significant	
								PE Confirmed by: V/Q scan on 8th – 10th day post-op	**High probability V/Q scan Int:** 12/146 **Control:** 16/166 **p value:** Not significant	
								Bleeding related complications Prolonged wound drainage (requiring immobilisation, attention in rehabilitation for wound problems, or surgical evacuation)	**Int:** 7/146 **Control:** 6/166 **p value:** Not significant	

VKA vs aspirin

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Mismetti et al., 2004[451] 1 RCT included [533]	Systematic review	1+	Total: 131 **Int:65** **Cont:66**	**Type of surgery:** Orthopaedic (hip replacement surgery)	**Type:** OAC-adjusted (Warfarin) **Timing:** Postoperative Discharge or 3 weeks **Additional non-comparative prophylaxis:** Not reported	**Type:** Aspirin 650x2	3 months	**DVT** (Venom)	**Int:** 13/65 **Cont:** 27/66 **p value:** 0.0133	**Not reported:** LoS, QoL, PTS **Funding:** Sanofi-Synthelabo grant
								Proximal DVT	**Int:** 6/65 **Cont:** 7/66 **p value:** 1.0000	
								PE	**Int:** 0/65 **Cont:** 1/66 **p value:** 0.0141	
								Major Bleeding	**Int:** 5/65 **Cont:** 1/66 **p value:** 0.1150	

Evidence Table 36: Aspirin +/- antiplatelet therapy vs LMWH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Dechavanne et al., 1975[153]	RCT	1+	**Total**: 60 Intervention: n = 20 Control: n = 20 (3rd arm of study for no intervention n = 20)	**Type of surgery:** Hip replacement for patients with osteoarthritis **Intervention:** Average age: 67 yrs M/F:9/11 **Control:** Average age: 62 yrs M/F:9/11 **Pre-existing risk factors:** Obesity: Int: 4/20 Control: 1/20 Previous DVT: Int: 1/20 Control: 1/20 Previous PE: Int: 1/20 Control: 1/20 Varicose veins: Int: 6/20, Control: 8/20	**Type:** aspirin **Dose:** 1.5g/day and dipyridamole 150mg/day **Timing:** Started day before surgery and continued until postoperative day 10 **Additional non-comparative prophylaxis:** none stated	**Type:** unfractionated heparin **Dose:** 5000 IU every 12 hours for first 48 hours post-operatively, then every 8 hours until postoperative day 8, progressively decreased until stopped on post-operative day 15 **Timing:** Started 2 hours preoperatively continued until postoperative day 15 **Additional non-comparative prophylaxis:** none stated	15 days post-operatively	**DVT** Confirmed by 125 I-labelled fibrinogen test.	**Int:** 10/20 **Control:** 1/20 **p value:** 0.01	**Not reported:** PE, PTS, no. of major bleeding episodes, QoL, length of hospital stay, survival **Also reported:** mean blood loss from drainage procedures **Funding** not reported

Aspirin +/- antiplatelet therapy vs UFH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Josefsson et al., 1987[318]	RCT	1+	**Total** 82 Intervention: n = 40 Control: n = 42	**Type of surgery:** Hip replacement patients >50 years of age **Mean age and gender not given** **Pre-existing risk factors:** none stated	**Type:** aspirin **Dose:** 1.5g twice daily **Timing:** started 24 hours preoperatively, continued twice daily for 9 days **Additional non-comparative prophylaxis:** ted stockings applied immediately after surgery and continued until discharge, physiotherapy and weight bearing started on postoperative day 1	**Type:** dyhydroergotamine-0.5mg with heparin 5000 IU **Timing:** started 2 hours preoperatively, continued twice daily for 9 days **Additional non-comparative prophylaxis:** ted stockings applied immediately after surgery and continued until discharge, physiotherapy and weight bearing started on postoperative day 1	9 days postoperatively	**DVT** Confirmed by: I-125 fibrinogen test	**Int:** 5/40 **Control:** 3/42 **p value:** 0.4772	**Not reported** PTS, QoL, survival, length of hospital stay **Also reported** mean preoperative and postoperative blood loss and compensation rates **Funding:** not reported
								PE Confirmed by: lung perfusion scintigraphy	**Int:** 4/40 **Control:** 3/42 **p value:** 0.7091	
								Episodes of major bleeding	**Int:** 0/40 **Control:** 0/42 **p value:** N/A	

Aspirin + antiplatelet therapy vs UFH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Loew et al., 1977[406]	RCT	1+	**Total** 187 randomised. 10 excluded. Intervention: n = 63 Control: n = 57 (3rd arm of 57 patients receiving aspirin and heparin not reported here)	**Type of surgery:** Elective thoracic or abdominal surgery patients >50 years of age. **Intervention:** Mean ±SD age: 62.8 ±11.8 yrs M/F:18/45 **Control:** Mean ±SD age: 58.4 ±10.8 yrs M/F:25/32 **Pre-existing risk factors:** Listed as a similar between groups (numbers not given): obesity, diabetes, varicose veins, previous history of thromboembolism, postthrombotic syndtrome and malignancy	**Type:** aspirin **Dose:** acetylsalicylic acid 500mg + placebo heparin **Timing:** started the evening prior to surgery, continued for 1 week **Additional non-comparative prophylaxis:** patients made to walk as early as possible	**Type:** unfractionated heparin **Dose:** 5000 units + placebo aspirin **Timing:** started the evening prior to surgery, continued for 1 week **Additional non-comparative prophylaxis:** patients made to walk as early as possible	1 week postoperatively	**DVT** Confirmed by: I-125 fibrinogen test	**Int:** 19/63 **Control:** 11/57 **p value:** 0.2076	**Comments:** not stated in the paper that everyone was screened for DVT or PE but a systematic review comparing the 3rd arm with the intervention and control implies that alll patients were screened **Not reported** PE, PTS, QoL, survival, length of hospital stay **Funding:** not reported
								Fatal PE Confirmed by: autopsy	**Int:** 0/63 **Control:** 2/57 **p value:** 0.2235	
								Major bleeding	**Int:** 0/63 **Control:** 0/57 **p value:** N/A	

Aspirin +/- antiplatelet therapy vs UFH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Plante et al., 1979[528]	RCT	1+	**Total** 146 Intervention: n = 38 Control: n = 42 (3rd arm of 62 patients receiving no intervention not reported here)	**Type of surgery:** Abdominal surgery patients **Intervention:** Average age: 45.1 yrs M/F:52.6%/47.4% Average duration of surgery: 146.4 mins (Aspirin group significantly younger than heparin group) **Control:** Average age: 58.8 yrs M/F:40.5%/59.5% Average duration of surgery: 159.04 mins **Pre-existing risk factors:** Obesity: Int 26.3% Control 31% Varicose veins: Int: 10.5% Control 19% Previous phlebitis: Int: 0% Control: 4.8%	**Type:** Aspirin & dipyridamole: **Dose:** 600mg lysine acetylsalicylate (equivalent to 300mg aspirin) + 30mg dipyridamole in an intravenous infusion from 2 hours before surgery then 3 times daily up to 2.3 postoperative days THEN 300mg aspirin + 50mg dipyridamole orally 3 times daily for a further 8 postoperative days. **Timing:** started 2 hours preoperatively and continued for at least 8 days **Additional non-comparative prophylaxis:** intensive physiotherapy from first day of operation	**Type:** Unfractionated heparin: **Dose:** 5000IU hog mucosae calcium heparinate twice daily **Timing:** started 2 hours preoperatively and continued for at least 8 days **Additional non-comparative prophylaxis:** intensive physiotherapy from first day of operation	8 postoperative days	**DVT** Confirmed by: I-125 fibrinogen test	**Int:** 3/38 **Control:** 3/42 **p value:** 1.000	**Comments:** **Not reported** PE, PTS, QoL, survival, length of hospital stay **Funding:** grant from I.NOT SIGNIFICANTE.R.M.

Aspirin +/- antiplatelet therapy vs UFH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Vinazzer et al., 1980[666]	RCT	1+	**Total** 1210 Intervention : 1 n = 404 Intervention 2: n = 404 Intervention 3: n = 402	**Type of surgery:** Elective abdominal, thoracic or vascular surgery patients >40 years old **Intervention:** Mean ±SD age: 62.0 ±11.5 yrs M/F:202/202 **Control:** Mean ±SD age: 61.4 ±10.9 yrs M/F:212/192 **Pre-existing risk factors:** Obesity: Int: 35/404 Contol: 39/404 Varicose veins: Int: 20/404 Control 12/404 Previous thromboembolism Int: 7/404 Control 4/404	**Intervention 1** **Type:** aspirin + placebo heparin: **Dose:** acetylsalicylic lysine salt 900mg (equivalent to 500mg aspirin) given intravenously up to postoperative day three THEN 500mg acetylsalicylic acid + placebo heparin **Timing:** started on evening before surgery and continued until patients were completely mobilised. Intervention applied for a minimum of 1 week. **Intervention 3** aspirin plus unfractionated heparin **Additional non-comparative prophylaxis:** early ambulation encouraged but no physiotherapy and no other antithrombotic prophylaxis	**Intervention 2** **Type:** unfractionated heparin + placebo aspirin: **Dose:** beef lung heparin 5000 units + placebo aspirin **Timing:** started on evening before surgery and continued until patients were completely mobilised. Intervention applied for a minimum of 1 week. **Additional non-comparative prophylaxis:** early ambulation encouraged but no physiotherapy and no other antithrombotic prophylaxis	1 week	**Proximal DVT** Confirmed by: ultrasonic doppler	**Int 1:** 14/365 **Int 2:** 9/378 Int 3: 1/350 **p value:** not significant	**Comments:** Diagnosis of DVT by ultrasonic doppler detectors in this study only permitted analysis of DVTs above the knee **Not reported** All DVTs, PEs confirmed by suitable diagnostic test, PTS, QoL. **Funding:** not reported
								Fatal PE Confirmed by autopsy	**Int1:** 1/365 **Int 2:** 1/378 Int 3: 0/402 **p value:** not significant	
								Major bleeds (Number of bleeds that lead to a discontinuation of prophylaxis)	**Int1:** 3/404 **Int 2:** 3/404 **p value:** not significant Int 3: 11/350 **p value:** <0.05	
								Mean ±SD length of Hospital Stay:	**Int 1:**14.0 ±7.4 days **Int 2:** 14.7 ±6.6 days Int 3: 14.4 ±7.2 days **p value:** not significant	
								Death prior to day 7 (i.e. within study period)	**Int 1:** 17/404 **Int 2: 7**/404 Int 3: 17/402 **p value:** <0.05 Int 2 compared to Int 1 & Int 3	
								Total no. dropouts from study	**Int 1:** 39/404 **Int 2:** 26/404 Int 3: 52/402 **p value:** <0.05 (each intervention compared to the others	

Aspirin +/- antiplatelet therapy vs UFH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Zanasi et al., 1988[708]	RCT	1+	**Total** 63 Intervention: n = 19 Control: n = 25 (3rd arm of 19 patients receiving defibrotide not reported here)	**Type of surgery:** Orthopaedic surgery (majority hip surgery) **Intervention:** Mean ±SEM age: 69.7 ±3.7 yrs M/F: 5/14 **Control:** Mean ±SEM age: 71.9 ±2.2 yrs M/F:4/21 **Pre-existing risk factors:** none stated	**Type:** aspirin: **Dose:** acetylsalicylic acid 100mg administered on alternate days **Timing:** started day before surgery and continued for 7 postoperative days. **Additional non-comparative prophylaxis:** none stated	**Type:** unfractionated heparin: **Dose:** beef lung heparin 5000 units + placebo aspirin **Timing:** started day before surgery and continued for 7 postoperative days **Additional non-comparative prophylaxis:** none stated	7 postoperative days	**DVT** Confirmed by: FUT	**Int:** 7/12 **Control:** 10/25 **p value:** 0.4821	**Comments:** Diagnosis of DVT by ultrasonic doppler detectors in this study only permitted analysis of DVTs above the knee **Not reported** PTS, QoL, bleeding complications, length of hospital stay **Funding:** not reported
								PE Not stated how confirmed	**Int:** 2/12 **Control:** 1/25 **p value:** 0.2407	
								Fatal PE Not stated how confirmed	**Int:** 1/12 **Control:** 1/25 **p value:** 0.5495	

Evidence Table 37: Mechanical vs Pharmacological prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Blanchard et al., 1999[66]	RCT	1+	**Total:** 130 **Intervention:** 63 **Control:** 67	**Type of surgery:** elective knee replacement. **Intervention** **M/F:** 11/52 **Mean age:** 72 **Control** **M/F:** 20/47 **Mean age:** 74	Intermittent pneumatic plantar compression (AVIS (Novomedix)) Started 12 hours preoperatively, discontinued for surgery, reapplied after surgery. Used at all times except during walking and physiotherapy **Additional prophylaxis:** none	LMWH (calcium nadroparin) injected subcutaneously 12 hours preoperatively the 12 hours postoperatively then once per day for 12 days. Doses adjusted to patient's body weight. **Additional prophylaxis:** none	2 to 3 months Diagnostic tests carried out 8 to 10 days after surgery. After screening for DVT, all patients received aceno-coumarol for 6 to 8 weeks.	**DVT** confirmed by phlebography or venous compression US	**Int:** 34/63 **Cont:** 16/.67 **p value:** <0.01	At 2 to 3 month follow up no patients had symptomatic DVT or PE and none died. **Also reported** Median intraoperative and postoperative blood loss, total blood transfused.
								Proximal DVT confirmed by phlebography or venous compression US	**Int:** 4/63 **Cont:** 2/.67 **p value:** 0.4	
								Distal DVT confirmed by phlebography or venous compression US	**Int:** 30/63 **Cont:** 14/.67 **p value:** <0.005	
								Symptomatic PE	**Int:** 0/63 **Cont:** 0/.67 **p value:** N/A	
								Major bleeds	**Int:** 0/63 **Cont:** 1/67 **p value:** not significant	

Mechanical vs Pharmacological prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Camporese et al., 2008[94] **Country of study:** Italy **Study design:** RCT **List who was masked to interventions:** Assessor **Evidence level:** 1+ **Duration of follow-up:** 3 months	**Patient group:** Knee arthroscopy patients **Setting:** Department of knee surgery **Inclusion criteria:** Consecutive outpatients scheduled for diagnostic arthroscopy or arthroscopy-assisted knee surgery for partial meniscectomy, cartilage shaving, cruciate ligament reconstruction, synovial resection, or combined surgical procedures. **Exclusion criteria:** Patients were excluded if the met any of the following criteria: younger than 18 yrears of age, pregnant, previous VTE, active cancer, known thrombophilia, receiving mandatory anticoagulation, hypersensitive to LMWH, recent major bleeding events, severe renal or hepatic failure, anticipated poor adherence, geographic inaccessibility, or tourniquet thigh time greater than 1 hour. **All patients** **N:** 1761 **Group 1** **No. randomised:** 660 **No. of dropouts:** 63 (9.6%) **Age (mean):** 42.3 (sd = 14.4) **M/F:** 1.66:1 **Additional risk factors:** Mean body mass index (kg/m²): 25.5% Smoker 23.3% Use of hormonal compounds: 8.9% Family history of VTE 0.9% **Type of surgical procedure [n (%)]** Anterior cruciate ligament reconstruction 229 (34.7%)	**Group 1** GCS on operated leg Start time: before weight bearing Duration: 7 days after operation Thigh lengths with pressure of 30-40 mmHg at the ankle **Group 2** LMWH (Nadroparin) Start time: 8 hours after operation Duration: 7 days after operation. 3800 anti-Xa IU daily subcutaneous injection. **Additional non-comparative prophylaxis:** None reported	**All cause mortality** (at 3 months)	**Group1:** 0/660 **Group 2:** 0/657 **P value:** N/A	**Funding:** No external funding was received. **Limitations:** The study was not blinded to healthcare professionals or patients, although the assessors were blinded. **Outcomes not reported:** Post thrombotic syndrome, pulmonary hypertension, quality of life, length of stay **Additional outcomes reported:** Clinically relevant non-major bleeding (hemarthrosis with joint drainage of 100-450mL that was not life threatening and did not required reintervention) Gp1 = 1/660, Gp2 = 4/657 **Notes:** * Calculated by NCC using fisher's exact test Three arms were originally planned. The 3rd arm (LMWH for 14 days) was stopped by the data monitoring committee after 444 patients had been recruited because of
			Fatal pulmonary embolism (confirmed by: autopsy)	**Group1:** 0/660 **Group 2:** 0/657 **P value:** N/A	
			Symptomatic pulmonary embolism (confirmed by: ventilation perfusion scanning)	**Group1:** 2/660 **Group 2:** 2/657 **P value:** 1.00	
			Symptomatic DVT (confirmed by: Doppler ultrasound)	**Group1:** 12/660 **Group 2:** 2/657 **P value:** 0.012*	
			DVT, asymptomatic or symptomatic (screened for by: Doppler ultrasound at 7 days)	**Group1:** 29/660 **Group 2:** 10/657 **P value:** 0.003*	
			Thigh DVT(screened for by: Doppler ultrasound)	**Group1:** 8/660 **Group 2:** 2/657 **P value:** 0.108*	
			Calf DVT (screened for by: Doppler ultrasound)	**Group1:** 21/660 **Group 2:** 8/657 **P value:** 0.023*	
			Fatal bleeding	**Group1:** 0/660 **Group 2:** 0/657 **P value:** N/A	
			Major bleeding (description: clinically overt haemorrhage associated with a haemoglobin decrease of at least 20 g/L or requiring transfusion of 2 or more units of packed red blood cells, a retroperitoneal or intracranial event, a bleeding event requiring re intervention, or a hemarthrosis with joint drainage of more than 450mL)	**Group1:** 1/660 **Group 2:** 2/657 **P value:** 0.624*	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Lateral and/or medial meniscectomy 251 (38.0%) Cartilage shaving 51 (7.7%) Anterior cruciate ligament reconstruction plus meniscectomy 50 (3.0%) Cartilage shaving plus meniscectomy 79 (11.9%) Other 30 (4.5%) **Group 2** **No. randomised:** 657 **No. of dropouts:** 54 (8.3%) **Age (mean):** 41.9 (sd = 15.1) **M/F:** 1.62: 1 **Additional risk factors:** Mean body mass index (kg/m²): 25.3% Smoker 29.5% Use of hormonal compounds: 9.2% Family history of VTE 0.6% **Type of surgical procedure [n (%)]** Anterior cruciate ligament reconstruction 223 (33.9%) Lateral and/or medial meniscectomy 254 (38.6%) Cartilage shaving 46 (7.0%) Anterior cruciate ligament reconstruction plus meniscectomy 43 (6.5%) Cartilage shaving plus meniscectomy 47 (7.1%) Other 45 (6.8%)		**Minor bleeding** (description: not defined)	**Group1:** 20/660 **Group 2:** 23/657 **P value:** 0.646*	concerns about the potential safety issues related to a longer LMWH regimen. The data from this group are reported in the paper but not reported here. A subgroup analysis found that meniscectomy involved knee surgery was independently associated with the development of VTE.
			Heparin Induced Thrombocytopenia	**Group1:** 0/660 **Group 2:** 0/657 **P value:** N/A	

Mechanical vs Pharmacological prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Chandhoke et al., 1992[104]	RCT	1+	**Total:** n = 100 Intervention: n = 47 Control: n = 53	**Type of surgery:** Patients undergoing urological surgery	Intermittent pneumatic calf compression (also referred to as calf pumps). IPCD was instituted intraoperatively and continued post-op for 5days or until patient became fully ambulant	Low Dose Warfarin begun on the night of the operation	1 to 2 weeks. The goal was to achieve prothrombin time of approx 1.5times the pre-op value by 3 or 4 days post-op	**DVT (overall)** Confirmed by: venography and US	**Int:** 4/47 **Control:** 0/53 **p value:** Not significant	**Not reported:** PTS, QoL, Survival
				Intervention: Mean age: 67.5±7.1 M/F:46/1				**PE** Confirmed by: venography and US	**Int:** 2/47 **Control:** 0/53 **p value:** Not significant	
				Intervention: Mean age: 66.1±6.4 M/F:53/0				**Bleeding related complications**	**Int: 0** **Control: 2** **p value:** Not significant	
				Pre-existing risk factors: malignancy Int: 98% control:100%. $% of patients who received IPCD had DVT				**Death**	**Int: 0** **Control: 0** **p value:** Not significant	
Clarke-Pearson et al., 1993[116]	RCT	1+	**Total:** 218 Int: 101 Cont: 107	gynaecologic oncology Intervention: Median age: 57 (22-89) years Control: Median age: 55 (27-84) years	Intermittent pneumatic calf compression **Timing:** initiated at induction of anaesthesia and continued to 5 days postoperatively or the patient was ambulatory. **Additional non-comparative prophylaxis:** none reported	Low dose heparin **Dose and timing:** 5000 units on admission and every 8 hours until surgery, 5000 units postoperatively every 8 hours for 7 days. **Additional non-comparative prophylaxis:** none reported	diagnostic tests until discharge, followed up clinically for 30 days postoperatively	**DVT** Confirmed by: Iodine 125 labelled fibrinogen	**Int:** 3/101 **Control:** 6/107 **p value:** Not significant	(total DVTs Int=4 and Cont=7 but one in each group clinically detected after discharge then confirmed by venograph

Mechanical vs Pharmacological prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Coe et al., 1978[119]	RCT	1+	**Total:** 84 in entire study, 59 for this comparison Intervention : n = 31 (2 subsequentl y dropped out) Comparison : n = 28	**Type of surgery:** Urological (open) Breakdown of surgery type given. Majority were simple prostatectomies. Duration of surgery not stated. **Intervention:** Mean age: 55±11 yrs M/F:not reported **Comparison:** Mean age: 63±16 M/F:Not reported **Pre-existing risk factors:** 36% malignant disease, 30% varicose veins (numbers distributed evenly between study groups)	**Type:** bilateral calf IPCD device **Dose:** 35 - 40 mm Hg **Timing:** from anaesthetic. Mean no of days treatment 3.2 ± 2.2 **Additional non-comparative prophylaxis:** Not reported	**Type:** LDUH **Dose:** 5,000 units subcutaneously **Timing:** begun 2hr prior to operation and continued every 12 hrs. Mean no of days treatment 8.3 ± 6.4 **Additional non-comparative prophylaxis:** none	**Both groups:** daily from day 1 post-op until discharge	**DVT** Confirmed by: I 125 fibrogen scanning of both legs, with positive venogram confirmation	**Int:** 6/28 **Comparison:** 5/24 **p value:** Not significant	HTA report the IPCD vs no prophylaxis. 2 patients excluded from IPCD group as they had received vitamin K antagonists. Patients in the heparin group were treated significantly longer than IPCD, primarily because of discontinuance of IPCD due to discomfort. 1 patient from each study group with a postive FUT test refused venogram. If these patients are analysed as having DVT the difference between IPCD and heparin is no longer significant **Not reported:** Proximal DVT, PTS, QoL, Bleeding, LoS
								PE Confirmed by: Not routinely assessed in all patients, but investigated where suspicion by chest X-ray, lung scan or pulmonary angiogram	**Int:** 1/28 **Control:** 1/24 **p value:** 1.000 Neither patient had been diagnosed with DVT	
								Bleeding related complications number of patients requiring transfusion	**Int:** 9/29 **Control:** 14/24 **p value:** 0.4424	

Mechanical vs Pharmacological prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Dickinson1998 [164]	RCT	1+	**Total:** 66 Int1: n= 21 Int 2: n=23 Control: n=22	**Type of surgery:** Neurosurgery for intracranial neoplasms **Intervention 1:** Mean age: 43 (28-61) yrs **Intervention 2:** Mean age: 50 (29-72) yrs **Control:** Mean age: 49 (20-72) **M/F numbers not reported** **Pre-existing Risk Factors:** Not reported **Ecluded patients:** history of DVT or PE, allergy to heparin or other anticoagulant agents, history of surgery or major trauma to the lower extremities, concurrent condition requiring anticoagulation therapy; cranial base neoplasms and pituitary adenomas	**Int 1:** LWMH (Enoxaparin) **Dose:** administered subcutaneously at a dose of 30mg in the anaesthesia holding room. He dose was continued at a dose of 30mg every 12 hours **Int 2:** Combination of Enoxaparin and SCD **Dose:** as before **Timing:**.started before induction of anaesthesia until discharge from Neurosurgery Service. **Additional non-comparative prophylaxis:** antiembolic stockings on lower extremities at time of admission to the hospital **Int 2:** Combination of LMWH and thigh high sequential compression device.	**Type:** Thigh high sequential compression device **Timing:** started before induction of anesthesia and continued postoperatively until patient was walking without assistance **Additional non-comparative prophylaxis:** antiembolic stockings on lower extremities at time of admission to the hospital	1 month	**DVT** Confirmed by: duplex imaging (on four occasions in the first 1 month after surgery)	**Int 1:** 1/21 **Control:** 3/22 **p value = 0.53** **Int 2:** 4/23 **Comp:** 3/22 **P**=0.90	**Comments:** Study terminated early when it was determined that the enoxaparin treated groups exhibited a greater incidence of postoperative neurological deficits secondary to intracranial haemorrhage. **Not reported:** Post thrombotic leg, length of stay. **Funding:** NR
								Symptomatic PE	**Int 1:** 0/21 **Int 2:** 0/23 **Comp:** 022	
								Bleeding related complications (intracerebral hemorrhage or epidural haematoma)	**Int 1:** 2/21 **Int 2:** 3/23 **Comp:** 0/22	
								Mortality	**Int 1:** 0/21 **Int 2:** 1/23 **Comp:** 122	

Mechanical vs Pharmacological prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Fasting et al., 1985[182]	RCT	1+	**Total:** 97 Intervention: n = 52 Control: n = 45 112 randomised 15 excluded (9 GCS, 6 UFH)	**Type of surgery:** General surgery under general anaesthesia and >1hr (& Duration of surgery) **Intervention:** Mean age: 60 yrs (range 39-7) M/F:29/23 **Control:** Mean age: 60 yrs (range 39-80) M/F:20/25 **Pre-existing risk factors:** Malignancy, obesity, previous DVT or varices	**Type:** Thigh-length graduated compression stockings **Timing:** Begun eve before surgery and worn for at least five days and stopped when patient mobile **Additional non-comparative prophylaxis:** Not reported	**Type:** Unfractionated heparin **Dose:** 5000IU **Timing:** Begun eve pre-surgery and repeated twice daily for at least 5 days until mobile. All patients received a dose 2-3hrs before surgery	Both treatments were continued for at least five days after operation and were only stopped when patients were mobile. Plasmin test performed five days after surgery.	**DVT** Confirmed by: ^{99m}Tc plasmin test on 5th post-op day	**Int:** 3/52 **Control:** 3/45 **p value:** Not significant	**Not reported:** PROXIMAL DVT, PTS, QoL, survival, LoS, funding
								Fatal PE Confirmed by: Autopsy	**Int:** 0/52 **Control:** 1/45 **p value:** Not significant	
								Bleeding related complications **Major post-perative haemorrhagic complications:** Not defined **Peroperative bleeding**: Not defined	**Major post-op haemorrhagic complications** **Int:** 0/52 **Control:** 0/45 **p value:** Not significant **Peroperative bleeding (ml)** **Int:** 505 (50 – 3250) **Control:** 554 (50 3500) **p value:** Not significant **Patients transfused:** **Int:** 26/52 **Control:** 29/45 **p value:** Not significant **Mean no of transfusions:** **Int:** 1.5 (range 0-9) **Control:** 2.3 (range 0-11) **p value:** Not significant	

Mechanical vs Pharmacological prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Ginzburg et al., 2003[222] **Country of study:** USA **Study design:** RCT **List who was masked to interventions:** No one **Evidence level:** 1+ **Duration of follow-up:** 30 days or until discharge from hospital.	**Patient group:** High risk trauma patients with injury severity score >9 259/422 ISS 9-19 148/422 ISS >19 **Setting:** Trauma centre **Inclusion criteria:** • At least one leg and one arm available for IPCD • No need systemic anticoagulation • No contraindications to LMWH **Exclusion criteria:** • <18's • ISS <9 • Patients who were unlikely to survive for at least 7 days • Renal failure • Pregnant patients • Patients unable to undergo Doppler US screening • Patients with BMI>25kg/m^2 • Patients with contraindication to anticoagulation, e.g. intracranial bleeding or uncontrolled haemorrhage. **<u>All patients</u>** **N:** 422 **Age (mean):** Group: 1- 40 Group 2 - 42 **M/F:** 337:115 **Additional risk factors:** MI: 12 CHF: 7 COPD:8 Obesity: 7	**Group 1** IPCD (Huntleigh Flowtron). Start time: within 24hrs of trauma End time: until walking independently or discharge from hospital **Duration:** Maximum disuse allowed– 8 hours consecutively Length: calf length (DVT10), compression: 40mmHg on a 60s cycle. First sleeve inflate 12 secs, deflate 48s then repeated in second sleeve. **Group 2** LMWH (enoxaparin) Start time: within 24 hrs of trauma End time: until walking independently or discharge from hospital **Duration:** Dose and frequency: 30mg subcutaneously every 12hrs. Withheld 12hrs before any surgical intervention (max 2 doses missed). **Additional non-comparative prophylaxis:** None	**All cause mortality** (confirmed by:)	**Group1:** 0/224 **Group 2:** 0/218 **P value:** NR	**Funding:** Partly funded by Huntleigh Flowtron. **Limitations:** Statistics analysis changed part way through due to low incidence of DVT identified. Intention to treat analysis not completed. **Outcomes not reported:** Asymptomatic PE, location of DVT, HIT, PTS, Pulmonary hypertension, QoL **Notes:** Where patients could not use leg for IPCD – it was placed on arm. 2 DVTs occurred in patients with IPCD on one leg and one arm. Subgroups by injury severity. Some patients underwent surgery during the study but there is no indication of how many and in which groups.
			Fatal pulmonary embolism (confirmed by:)	**Group1:** 0/224 **Group 2:** 0/218 **P value:** NR	
			Symptomatic pulmonary embolism (confirmed by: clinical suspicion verified by spiral computed tomography or ventilation-perfusion scintigraphy)	**Group1:** 1/224 **Group 2:** 1/218 **P value:** Not signf.	
			DVT, asymptomatic or symptomatic (screened for by: Doppler ultrasonography weekly and when DVT was suspected.)	**Group1:** 6/224 **Group 2:** 1/218 **P value:** 0.122 Break down is provided for severity USS 9- 19: Gp 1: 4 Gp2: 1 USS >19: Gp 1: 2 Gp2: 0	
			Fatal bleeding (description:)	**Group1:** 0/224 **Group 2:** 0/218 **P value:** NR	
			Major bleeding (description: haemorrhage leading to a fall in haemoglobin conc. of 2 g/dl, transfusion of 2 or more of packed red blood cells, intracranial or retroperitoneal bleeding or bleeding requiring surgical intervention)	**Group1:** 4/224 **Group 2:** 4/218 **P value:** NR	
			Minor bleeding (description: excessive bleeding from operative sites, gastrointestinal bleeding and/ or haematuria that did not meet the criteria for major bleeding)	**Group1:** 4/224 **Group 2:** 9/218 **P value:** 0.245	
			Length of stay	**Group1:** 20.9 (33.4) **Group 2:** 15.5 (15.0) **P value:** 0.040	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Cancer: 6 **<u>Group 1</u>** **No. randomised:** 224 **No. of dropouts:** 15 **<u>Group 2</u>** **No. randomised:** 218 **No. of dropouts:** 29				

Mechanical vs Pharmacological prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Haas et al., 1990[245]	RCT	1+	**Total:** 128 **Unilateral** Intervention : n = 36 Control: n = 36 **Bilateral** Intervention : n = 22 Control: n = 25	**Type of surgery:** Orthopaedic (unilateral or bilateral total knee arthroplasty) Duration of surgery not reported **Intervention:** **Unilateral** Mean age: 70.2 yrs (s.d. not reported) M/F:11/25 **Bilateral** Mean age: 71.1 yrs (s.d. not reported) M/F:7/15 **Control:** **Unilateral** Mean age: 67.7 yrs (s.d. not reported) M/F:10/26 **Bilateral** Mean age: 69.0 yrs (s.d. not reported) M/F:12/13 **Pre-existing risk factors:**	**Type:** IPCD thigh (Kendall) **Dose:** 35 - 55 mm Hg **Timing:** Applied to uninvolved leg pre-op and to involved leg immediately post-op. Worn continuously. Removed morning after post-op V/Q lung scan **Additional non-comparative prophylaxis:** All patients received standard physical-therapy protocol which included initiation of continuous passive motion in the recovery room and walking on the second post-op day	**Type:** aspirin **Dose:** 650mg 2x per day **Timing:** started day before surgery and continued until discharge **Additional non-comparative prophylaxis:** All patients received standard physical-therapy protocol which included initiation of continuous passive motion in the recovery room and walking on the second post-op day	**Control:** 5-7 days post-op **Int:** 5-7 days post-op	**DVT** Confirmed by: bilateral venography 4-6 days post-op **Proximal DVT** Confirmed by: bilateral venography 4-6 days post-op **PE** Confirmed by: V/Q lung scan 5-7 days post-op (No symptomatic PE reported in any patients) **Fatal PE**	**Unilateral:** **Int:** 8/36 **Control:** 17/36 **p value:** < 0.03 **Bilateral:** **Int:** 12/25 **Control:** 15/22 **p value:** <0.2 **Unilateral** **Int:** 0/36 **Control:** 0/36 **p value:** N/A **Bilateral** **Int:** 2/25 **Control:** 1/22 **p value:** Not significant **Unilateral** **Int:** 2/36 **Control:** 1/36 **p value:** Not significant **Bilateral:** **Int:** 1/25 **Control:** 0/22 **p value:** Not significant **Int:** 0 **Control:** 0	**Comments:** 9 patients dropped out (5 from intervention, 4 control). Reported which leg DVT developed in (un/involved in surgery) for unilateral patients. Classified thrombus as small, medium, large. In unilateral group no thrombi developed in uninvolved leg of IPCD patients ($p < 0.01$) and significantly less large thrombi ($p < 0.01$) **Not reported:** QoL, PTS, Bleeding, LoS. Survival **Funding:**

Mechanical vs Pharmacological prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Hansberry et al., 1991[254]	RCT	1+	**Total:** n = 74 Int 1: n = 24 Int 2: n = 25 Control: n = 25	**Type of surgery:** Patients undergoing total urological operation **Interventions & control:** Age range: 45 - 75years **Pre-existing risk factors:** Malignancy, Anaesthesia >90mins, one person in Int 2 had a history of a previous DVT	**Intervention 1:** External sequential pneumatic compression stockings **Duration:** started during induction of anaesthesia and continued for 48 hours **Intervention 2:** Thromboembolic stockings worn pre- and postoperatively until full ambulatory. **Additional non-comparative prophylaxis:** Not reported	**Type:** Heparin (5000 units) + dihydroergotamine mesylate (0.5mg) every 12 hours. **Duration:** started 2 hours preoperatively and continued for 48 hours	6 days postoperatively or discharge if sooner.	**DVT (overall)** Confirmed by: venography and In-labelled platelet scans	**Int1:** 3/24 **Int2:** 5/25 **Control:** 2/25	**The paper did not report any dropouts**
								PE Confirmed by: ventillation perfusion scans, platelet scintigraphy and lung scan **-** all patients here had DVT	**Int 1:** 1/24 **Int 2:** 1/25 **Control:** 1/25	**Not reported:** PTS, Fatal PE, QoL, Survival
								Wound related complications	**Int 1:** 2/24 **Int 2:**2/25 **Control:** 1/25	

Mechanical vs Pharmacological prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Kaempffe et al., 1991[322]	RCT	1+	**Total:** 149 Int: 48 Cont: 52 49 patients excluded after randomisation: Protocol broken: 24 Surgery cancelled: 14 Refused to participate: 8 Death: 3	**Type of surgery:** Elective total hip or knee replacement **Intervention** average age (range): 60 (40-80) years; M/F 47/1 **Control** average age (range): 45 (18-77) years; M/F 51/1 **Pre-existing risk factors:** Average number 2.4 (0 to 6) Previous DVT/PE, varicose veins, heart disease, obesity, hypertension, malignancy, smoking history, previous cerebrovascular accident or diabetes).	Intermittent pneumatic compression (Kendall) (calf and thigh segments) **Timing:** Started at surgery, not stated when stopped. **Additional non-comparative prophylaxis:** none reported	Coumadin: 10mg the evening before surgery, 5mg the evening of surgery, then dose adjusted to maintain the prothrombin time level at 15 seconds with a control of 11 to 12 seconds. **Timing:** Started evening before surgery, not stated when stopped **Additional non-comparative prophylaxis:** none reported	Not stated	**DVT** Confirmed by venography*	**Int:** 12/48 **Control:** 13/52 **p value:** 1.0000	*Venography performed on operated leg only. Other leg scanned if operated leg had a positive scan. Performed on average at postoperative day 10 2 deaths (1 in each group) suspected as a result of PE. Not confirmed by autopsy. **Not reported:** PE, LoS, QoL, PTS **Funding:** not reported
								Proximal DVT Confirmed by venography*	**Int:** 8/48 **Control:** 6/52 **p value:** 0.5681	
								Mortality	**Int:** 1/48 **Control:** 2/52 **p value:** 1.0000	
								Average (range) number of units of packed red blood cells transfused per patient during the perioperative period	**Int:** 1.4 (0 to 6) **Control:** 2.0 (0 to 6) **p value:** not reported	

Mechanical vs Pharmacological prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Killewich et al., 2002[346]	RCT	1+	Total :45 Int1: 13 Int2: 15 Cont: 16	Patients undergoing major abdominal surgery (35 bowel & 10 aortic reconstructions). Mean age:67 Gender ratio (M/F):44:1 (98%:2%)	**Intervention 1:** IPCD (thigh-length) + Heparin (5000 units) subcutaneously twice a day **Intervention 2:** IPCD (thigh-length) during surgery and for the first 48 hrs after. **Additional non-comparative prophylaxis:** Not reported	Heparin (5000 units) subcutaneously twice a day	5 days or until day of discharge	**Proximal DVT** Confirmed by venous duplex US scan	**Int 1:** 0/13 **Int 2:** 0/15 **Control:** 0/16	It appears that the treatment was different to pts with aortic reconstructions. DVT prophylaxis was initiated in the operating room after induction of anaesthesia and continued until post op day 5 or discharge **Not reported:** PE, PTS, Bleeding related complications, QoL, Survival

Mechanical vs Pharmacological prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Knudson et al., 1996[354] **Country of study:** USA **Study design:** RCT **List who was masked to interventions:** None **Evidence level:** 1+ **Duration of follow-up:** Not reported.	**Patient group:** Trauma **Setting:** San Fransisco General Hospital Trauma Center. **Inclusion criteria:** Patients admitted to trauma centre meeting one or more of the following conditions: • Injury Severity Score >10 Abbreviated Injury Scale score ≥3 in any category (n=316) • Head injury with Glasgow Coma Scale ≤8 (n=42) • unstable spine fracture without neurologic deficit (n=16) • stable spine fracture with deficit (n=25) • major pelvic fracture (n=13) • fracture of the lower extremity above the ankle (n=101) • age >50 (n=78) **Exclusion criteria:** • presence of DVT • major neurologic injury (head or spinal) • presence of solid organ injury managed nonoperatively • coagulation abnormalities or active bleeding beyond 36 hours • neck hematomas secondary to initial trauma • platelet counts <50,000 at 24 hours after injury **All patients** **N:** 202 **Age (mean):** 38.6 years **M/F:** NR **Additional risk factors:** NR **Group 1**	All interventions started within 24 hours of admission. Not stated for how long the study continued. Possibly until discharge or transfer to another unit. **Group 1** LMWH (enoxaparin, Rhone Poulnec), 30mg subcutaneously every 12 hours **Group 2** bilateral sequential gradient compression devices (SCD) (length not stated) and antiembolic stockings TED (Kendall Healthcare Products) 61/82 OR arteriovenous impulse device (AVI) requiring only a foot pad if unable to wear SCD 21/82 **Additional non-comparative prophylaxis:** none	**All cause mortality**	**Group1:** 0/120 **Group 2:** 0/82 **P value:** NA	**Funding:** Supported by grant from Rhone Poulnec **Outcomes not reported:** All cause mortality, symptomatic, calf, thigh and/or proximal DVT, heparin induced thrombocytopenia, post-thrombotic syndrome, bleeding outcomes, pulmonary hypertension, quality of life & length of stay **Additional outcomes reported:** Bleeding from drain site, reoperation for bleeding, drop in hematocrit, bruise at injection site, non-compliance rate, units of blood transfusion Specific details of patients with DVT occuring during study period. **Notes:** * p values calculated by NCC-AC using Fisher Exact test. The paper also includes a 3rd arm of patients (not reported here) of patients excluded from this randomised part and all assigned to mechanical compression
			Fatal pulmonary embolism (confirmed by: autopsy)	**Group1:** 0/120 **Group 2:** 0/82 **P value:** NA	
			Symptomatic pulmonary embolism (confirmed by: ventilation perfusion scan)	**Group1:** 0/120 **Group 2:** 0/82 **P value:** NA	
			DVT, asymptomatic or symptomatic (confirmed by: duplex ultrasonography)	**Group1:** 1/120 **Group 2:** 2/82 **P value:** NR *p = 0.57* *	
			Length of stay (mean no. of hospital days)	**Group1:** 12.7 days (n=120) **Group 2:** 11 days (n=82) **P value:** not significant	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No. randomised: 120 **No. of dropouts:** 0 **Group 2** **No. randomised:** 82 **No. of dropouts:** 0				

Mechanical vs Pharmacological prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Kosir et al., 1998[363]	RCT	1+	Total :***136*** Int: n = 68 Cont: n = 68	Patients for general surgeries lasting at least 1 hr and general or spinal anaesthesia. **Intervention:** MeanAge:62.4 **Control:** MeanAge:62.5	Sequential pneumatic compression devices applied before induction of anaesthesia and for 48 hrs post-op.	Unfractionated heparin (5000 units) subcutaneously every 12 hrs starting 1 hr before surgery until 48 hrs postop.	30 days	**DVT** Confirmed by Duplex venous studies of the lower extremities	**Int:** 1/68 **Cont:** 1/68 **p value:** not significant	Mortality not clearly explained
								PE Confirmed by Duplex venous studies of the lower extremities	**Int:** 1/68 **Cont:** 1/68 **p value:** not significant	
								Fatal PE: Confirmed by not stated	**Int:** 0/68 **Cont:** 1/68 **p value:** not significant	
								Survival:	10 deaths within 30 days, one due to PE. Not stated from which groups.	

Mechanical vs Pharmacological prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Maxwell et al., 2001[429]	RCT	1+	**Total:** 228 **Intervention:** n = 106 **Control:** n = 105	**Type of surgery:** "Major" procedure for gynaecological malignancy **Intervention:** Median age: 62 (35-85) yrs Gender not reported Mean duration of surgery: not reported **Control:** Median age: 60 (41-87) years Gender not reported Mean duration of surgery: not reported	**Type:** External pneumatic compression sleeves **Timing:** Started with induction of anaesthesia and continued for first 5 days postoperatively. Device stopped when patient was walking and restarted when back in bed. **Additional non-comparative prophylaxis:** Not reported	**Type:** Low molecular weight heparin (Dalteparin) **Dose:** 2500 units subcutaneously 1-2 hours before surgery and 2500 units 12 hours after first dose. Then from postoperative day 1 5000 units per day up to post operative day 5. If the patient was confined to bed after day 5, continued prophylaxis until day of discharge or ambulatory.	**Control:** 5 days **Int:** 5 days (patients also telephoned 30 days postoperatively and questioned for signs and symptoms of delayed VTE)	**DVT** Confirmed by: real-time US compression technique with duplex and colour Doppler imaging.	**Int:** 1/106 **Control:** 2/105 **p value:** 0.6214	**Comments:** Screened everyone for DVTs, only reported proximal. Outcomes measured at postoperative days 3 to 5, only followed up by telephone call 30 days after surgery. Trial designed to detect differences in complications. Discrepancy with randomisation: claimed to have carried out an intention to treat analysis but 17 patients that were randomised were not included in results. These patients dropped out for various reasons, not stated to which group they were randomised. Funding: not reported **Not reported:** All DVTs, PE, postthrombotic leg, QoL, survival, length of hospital stay **Also reported:**
								Proximal DVT Confirmed by: Doppler flow US at postoperative day 3	**Int:** 1/106 **Control:** 2/105 **p value:** 0.6214	
								PE	**Int:** 0/106 **Control:** 0/105 **p value:** N/A	
								Bleeding related complications	**Median external blood loss:** Int: 350mL Control: 350mL **p value:** 0.81	
								Thrombocytopenia	**Int:** 4/106 **Control:** 2/105 **p value:** 0.68	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
										number of transfusions, wound separation, ecchymosis, hematoma - none significant

Mechanical vs Pharmacological prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
McKenna et al., 1980[436]	RCT	1+	**Total:** 46 IPCD: 10 Placebo: 12 Low dose aspirin: 9 High dose aspirin: 12 2 low dose and 1 high dose aspirin participants were excluded from the analysis because valuation incomplete or aspirin administered incorrectly	**Type of surgery:** Elective total knee replacement **Intervention:** Gender M/F: 3/7 **Controls:** Low dose aspirin: Gender M/F: 0/9 High dose aspirin: Gender M/F: 1/11 Placebo: 3/9 **Pre-existing risk factors:** none reported	**Type:** IPCD thigh and calf cuffs **Timing:** started at beginning of surgery for unoperated leg and at the end of surgery for operated leg. Both continued until discharge **Additional non-comparative prophylaxis:** none reported	**Type:** Aspirin low dose: 325mg 3x per day Aspirin high dose: 1300mg 3x per day **Timing:** started immediately after admission and continued until discharge **Additional non-comparative prophylaxis:** none reported	Studied until discharge. Median hospital stay after operation was 16 days	**DVT** Confirmed by phlebography or fibrinogen test	**IPCD:** 1/10 **Low dose aspirin:** 7/9 **p value:** <0.005 **High dose aspirin:** 1/12 Not significant	**Comments:**
								Proximal DVT Confirmed by phlebography or fibrinogen test	**IPCD:** 0/10 **Low dose aspirin:** 3/9 **High dose aspirin:** 0/12 **p value:** not reported	**Not reported:** QoL, post-thrombotic syndrome, LoS
								PE Confirmed by V/Q lung scan	**IPCD:** 1/10 **Low dose aspirin:** 2/9 **High dose aspirin:** 1/12 p values not reported	
								Major Bleeds	**IPCD:** 0/10 **Low dose aspirin:** 0/9 **High dose aspirin:** 1/12 p values not reported	**Funding**
								Mortality	**IPCD:** 0/10 **Low dose aspirin:** 0/9 **High dose aspirin:** 0/12 p values not reported	

Mechanical vs Pharmacological prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Norgren et al., 1998[493]	RCT	1+	**Total:** n = 40 **Intervention:** n = 21 **Control:** n = 19 11 patients dropped out so results based on 29 patients: Int:15 & cont:14	**Type of surgery:** Patients scheduled for elective knee replacement. Overall M/F: 13/27 Mean age (range): 72 (49-87) years **Intervention M/F: 4/11** **Control M/F: 7/7**	Type: foot pump (ActOne) mechanical compression plus graduated compression stockings Started evening before surgery, removed during surgery, reapplied immediately after and continued until full mobilisation. A torniquet was used during surgery. **Additional non-comparative prophylaxis:** Not reported	**Type:** LMWH 40mg once per day Not stated when first dose was administered. used until full mobilisation **Additional non-comparative prophylaxis:** Not reported	**Control:** 3mths **Int:** 3mths	**DVT (overall)** **Confirmed** by: venography performed on day 7-10. **Fatal PE** Confirmed by autopsy:	**Int:** 4/15 **Control:** 0/14 **p value:** <0.05 **Int:** 1/15 **Control:** 0/14 **p value:** Not significant	**Comments:** 11 patients dropped out from the study, 5 in the LMWH group and 6 in the foot pump group **There were no signs of proximal thrombosis** **Not reported:** PTS, Bleeding related complications, QoL, Survival

Mechanical vs Pharmacological prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Paiement et al., 1987[507]	RCT	1+	**Total:** 165 (138 completed study) **Interventio n:** n = 66 (17 left study) **Control:** n = 72 (8 left study)	**Type of surgery:** Total hip replacement Duration of surgery not reported **Intervention:** Mean age: Not reported M/F:70/68 in the study. **Control:** Mean age: Not reported M/F:70/68 in the study.	**Type:** Bilateral thigh-length IPCD device **Dose:** 45-55 mmHg **Timing:** Started eve before operation. Worn continuously **Additional non-comparative prophylaxis:** Not reported	**Type:** Warfarin (low-dose) **Dose:** 10 mg pre-op, 5 mg post-op, thereafter adjusted to maintain PTT at 15 secs for control at 11 - 12 secs **Timing:** Started eve before operation, discontinued 2 days post phlebography if negative result **Additional non-comparative prophylaxis:** Not reported	10 days	**DVT** Confirmed by: Venography 10th day post-op. Performed on operated limb first. If negative, contralateral limb also assessed	**Int:** 11/66 **Control:** 12/72 **p value:** Not significant	**Comments:** Patients stratified by sex and previous history of VTE prior to randomisation. 4 of 17 patients who withdrew from IPCD group did so due to intolerance of IPCD device. None of DVTs occurred in patients with previous history of VTE **Not reported:** PTS, LoS, QoL, Survival, Funding info
								Proximal DVT Confirmed by: Venography	**Int:** 9/66 **Control:** 4/72 **p value:** < 0.057	
								PE Not routinely screened for. Symptomatic PE investigated by V/Q and angiogram if high probability	**Int:** 0 **ontrol:** 0 **p value:** not reported	
								Bleeding related complications Major bleeding (overt and associated with decrease in haemoglobin level of ≥ 2g/dl; required transfusion of 2 or more units; retroperitoneal or occurred in major prosthetic joint; intracranial); Intraoperative and post-operative blood loss (weight of sponges; suction drainage blood	**Major bleeding:** **Int:** 0/66 **Control:** 0/72 **p value:** N/A **Overall blood loss for primary procedures: Int:** 1821 ± 721 ml **Control:** 1861 ± 648 ml Not significant **Revision cases** **Int:** 3122 ± 1700 ml **Control:** 3218 ± 2076 ml Not significant	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
								loss; estimates of blood on wound drapes)		

Mechanical vs Pharmacological prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Rasmussen et al., 1988[546]	RCT	1+	**Total:** 249 in study, 159 in this comparison Intervention : n = 74 Control: n = 85	**Type of surgery:** Major abdominal (included urological and gynaecological patients) **Duration of surgery:** mean int: 2.75 hrs control: 2.5 hrs **Intervention:** Mean age: 63 yrs (range 41-87) M/F:33/41 **Control:** Mean age: 62 yrs (range 40-90) M/F:40/45	**Type:** Bilateral knee-high GCS **Timing:** from evening prior to operation until complete mobilisation, or for not less than five days post-op **Additional non-comparative prophylaxis:** none reported	**Type:** LDUH **Dose:** 5000 IU **Timing:** every 12 hours from evening prior to operation until complete mobilisation, or for not less than five days post-op **Additional non-comparative prophylaxis:** none reported	**Both groups:** until discharge	**DVT** Confirmed by: 99m Tc-labelled plasmin test on 4/5 post-op day	**Int:** 22/74 **Control:** 25/85 **p value:** Not significant	**Comments:** HTA report GCS + LDUH vs LDUH comparison. 1 patient excluded after randomisation. Paper does not report from which group. No DVTs systematic. **Not reported:** Proximal DVT, PTS, Bleeding, QoL, LoS **Funding:** plasmin test provided by Novo Ltd and Novo diagnostics
								PE Confirmed by: Not routinely screened for.	**Int:** 0 **Control:** 0 **p value:** None were clinically diagnosed during the study	
								Survival	**Int:** 74/74 **Control:** 85/85 **p value:** Not significant	

Mechanical vs Pharmacological prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Stannard et al., 1996[619]	RCT	+	**Total:** 75 Int 1: 25 Int 2: 25 Control: 25	**Type of surgery:** uncemented total hip arthroplasty **Duration of surgery:** Int1: mean 106 (85 - 128) mins; Int2: mean 113 (15 - 135) mins; Cont: mean 111 (87 - 140) mins; **Intervention 1:** Mean age: 68.7 (range 48-86) yrs M/F:not reported **Intervention 2:** Mean age: 65 (range 51-79) yrs M/F:not reported **Control:** Mean age: 69.7 (range 28-86) yrs M/F:not reported	**Intervention 1:** **Type:** Bilateral Foot pump + LDUH + aspirin **Dose:** FP 16hrs/day for first 3 days, then 12hrs/day; LDUH 5000U; Aspirin 325 mg **Intervention 2:** **Type:** Bilateral Foot pump 16hrs/day for first 3 days, then 12hrs/day **Timing:** FP begun immediately post-surgery and continued until end of study; LDUH begun 12hrs pre surgery and every 12hrs for first 3 days post-surgery, then aspirin 3x daily until end of study **Additional prophylaxis:** Spinal anaesthesia: 22/25	**Type:** LDUH + aspirin **Dose:** LDUH 5000U; Aspirin 325 mg **Timing:** LDUH begun 12hrs pre surgery and every 12hrs for first 3 days post-surgery, then aspirin 3x daily until end of study **Additional prophylaxis:** Spinal anaesthesia: 21/25	2 weeks postoperatively	**DVT** Confirmed by: Duplex US. Positive scans confirmed by venography	**Int1:** 0/25 **Int2:** 0/25 **Cont:** 5/25 **p value:** = 0.009	3/5 DVTs were symptomatic. 1 PE was symptomatic. 4/5 patients who developed DVT had spinal anaesthesia. Two patients reported as excluded from study due to abnormal pre-op US findings. Does not report to which group(s) they belonged **Not reported:** LoS, QoL, postthrombotic leg, proximal DVT **Funding:** Not reported
								PE Confirmed by: Not routinely screened for. No confirmatory tests reported	**Int1:** 0/25 **Int2:** 0/25 **Control:** 1/25 **p value:** **Not reported**	
								Bleeding related complications Surgical wound drainage - time taken for wound to seal (no of days post-op)	**Int1:** 5.9 **Int2:** 3.8 **Control:** 6.2 **p value:** = 0.05	
								Survival (specify)	**Int1:** 25/25 **Int2:** 25/25 **Control:** 25/25 **p value:** Not significant	

Mechanical vs Pharmacological prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Stone et al., 1996[627]	RCT	1+	**Total:** 50 Intervention: n= 25 Control: n= 25	**Type of surgery:** Total hip replacement **Intervention:** Mean age: 64 (range 42 – 83) yrs M/F:10/15 **Control:** Mean age: 64 (range 37-82) yrs M/F:8/15 **Pre-existing Risk Factors:** Not reported. Patients with known cancer were excluded.	**Type:** Calf length IPCD device. Worn on contralateral leg only during operation, and then bilaterally from the end of the procedure. **Timing:** Duration of device use not reported. **Additional non-comparative prophylaxis:** None	**Type:** LMWH **Dose:** 40 mg once daily **Timing:** Begun on the evening before surgery and continued until discharge (usually after 10 days). **Additional non-comparative prophylaxis:** None	**Both groups:** 6 weeks post-op.	**Proximal DVT:** Confirmed by: Colour duplex ultrasound, one week and six weeks post-operatively.	**At one week:** **Int:** 0/50 **Control:** 0/50 **p value:** n.s. **At six weeks:** **Int:** 1/50 **Control:** 1/50 **p value:** n.s.	**Comments:** Method of randomisation not reported. No mention of whether all included pts were assessed again at 6 weeks. **Not reported:** DVT (only proximal reported), PE, Post-thrombotic leg, major bleeding, QoL, survival, LoS. **Also reported:** Blood loss into drains, blood transfusion during and post-op, wound infection and haematoma.

Mechanical vs Pharmacological prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Warwick et al., 1998[675]	RCT	1+	**Total:** n = 290 **Intervention:** n = 147 **Control:** n = 143	**Type of surgery:** Patients undergoing total hip replacement **Intervention:** Mean age: 68±11 M/F:94/53 **Pre-existing risk factors:** Previous thromboembolism: Int: n = 2, control:n = 3	foot pump for 7days	Enoxaparin **Dose:** 40mg/dly for 7 days **Timing:** 7days **Additional prophylaxis:** Not reported	**Control:** 3mths **Int:** 3mths	**DVT (overall)** Confirmed by:venography on 6th, 7th & 8th day	**Int:** 24/136 **Control:** 18/138 (95%CI, -3.9 to +13.0%) **p value:** Not significant	**Comments:** 136 patients in the intervention and 138 in the comparison group completed both venography and the 3 month follow-up No patient died during follow-up **Not reported:** PTS, Bleeding related complications, QoL, Survival **Also reported:** Intraoperative blood loss, postop drainage, median no. of units transfused, oozing and bruising of thigh
								Proximal vein thrombosis	**Int:** 17/136 **Control:** 12/138 (95%CI, -3.5 to +11.1%) **p value:** Not significant	
								Distal vein thrombosis	**Int:** 7/136 **Control:** 6/138 (95%CI, -4.2 to +5.8%) **p value:** Not significant	
								Symptomatic PE Confirmed by ventilation perfusion scanning	**Int:** 1/136 **Control:** 0/138 **p value:** Not significant	
								Fatal PE Confirmed by:	**Int:** 0/136 **Control:** 0/138 **p value:** Not significant	
								Readmission to hospital because of DVT:	**Int:** 1/136 **Control:** 1/138 **p value:** Not significant	

Mechanical vs Pharmacological prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Warwick et al., 2002[676]			**Total:** 229 Intervention : n = 117 Control: n = 112	**Type of surgery:** Patients undergoing total knee replacement(TKR). All patients had stockings fitted below the knee before surgery **Intervention:** Mean age:73±9 M/F:43/74 **Control:** Mean age: 71±10 M/F:37/75 **Pre-existing risk factors:** Previous thomboembolism: Int: n = 7, control:n = 4, Smoking, varicose veins	A- V impulse foot pump **Additional non-comparative prophylaxis:** Not reported	Enoxaparin - LMWH	3 months	**DVT (overall)** Confirmed by: Ascending venography on 6th & 8th day	Analysis based on nos of pateints who completed venography **Int:** 57/99 **Control:** 48/89 **p value:** Not significant	Study concluded that there neither method provided superior prophylaxis. All patient completed follow-up but only 99 in the intervention and 89 in the control were available for venography 4 patients were said to have PE but paper did not state which groups they belonged **Not reported:** PTS, QoL, Survival
								Proximal vein thrombosis	**Int:** 4/99 **Control:** 0/89 **p value:** Not significant	
								Fatal PE Confirmed by:	**Int:** 2/99 **Control:** 0/89 **p value:** Not significant	
								Bleeding related complications	**Int:** 0/99 **Control:** 4/89 **p value:** Not significant	

Effectiveness - Double prophylaxis versus single prophylaxis

Evidence Table 38: GCS adjuvant

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Amaragiri and Lees, 2000[15] 8 RCTs included: 34,56,196,502,592, 640,691,693 6 of these studies were included in the guideline review 34,592,640,691,693	Systematic review	1+	**Total:** 16 studies, 9 with 1184 participants **Intervention:** GCS alone n = 589 **Control:** no stockings n = 595	General surgery, orthopaedics and medical patients Study with medical patients excluded. **Age:** > 16 years	Graduated compression stockings (thigh-length for 7 studies, not stated for 2 studies) **Timing:** Started either on day of admission or day of operation	No comparative prohylaxis **Additional non-comparative prophylaxis:** Dextran 70 (3 studies), subcutaneous heparin (3 studies), aspirin (2 studies), sequential compression (1 study)	Not stated	**DVT** Confirmed by: venogram, US, isotope studies	**Int:** 18/589 **Control:** 84/595 **p value:** <0.00001 (Significant)	**Not reported:** PEs, type of DVT, side effects, QoL and LoS. Event rates reported here are for all studies as published in the systematic review.

GCS adjuvant

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Kierkegaard et al., 1993[338] **Country of study:** Sweden **Study design:** RCT **List who was masked to interventions:** No one **Evidence level:** 1+/- **Duration of follow-up:** 8-10 days [Followed for at least 8 days or until they developed DVT or were discharged from the ward].	**Patient group:** Patients ≥ 70 years with acute Myocardial Infarction **Setting:** Coronary Care Unit **Inclusion criteria:** Patients ≥ 70 years with diagnosis of acute Myocardial Infarction established within the first 24 hours after admission. Definition of MI provided in the paper (new Q wave in Minnesota Code Category 1 on ECG at least 24 hrs after admission) **Exclusion criteria:** Refusal of consent, inability to give consent, treatment with anticoagulants, arthritis, inflammation, marked leg oedema, prominent varicose veins, signs of chronic venous insufficiency, leg lesions, Hemiplegia, acute stroke or death before entry into study [all patients admitted to the unit were considered for possible entry]. **<u>All patients</u>** **N:** 80 **Age (mean):** M: 77, F: 80 **M/F:** 45:35 **Additional risk factors:** 51 patients had CHF 25 patients had AF NB: Legs randomised (i.e. stocking on one leg only in all patients) **<u>Group 1</u>** **No. randomised:** 80 **No. of dropouts:** not clear from paper **<u>Group 2</u>** **No. randomised:** 80 **No. of dropouts:** not clear from paper	**Group 1** Kendal graduated compression stocking Start time: within 24 hrs of admission End time: At least 8 days Duration: continuous during study period Length and compression profile: Thigh length with profile of 18mmHg at ankle and 8mmHg at groin. (9 stocking sizes available – determined by the maximum circumference of the calf and the length from the gluteal fold to the plantar side of the heel). **Group 2** no intervention **Additional non-comparative prophylaxis:** All patients received 75-160mg Aspirin daily and received physiotherapy and active leg exercises	**Calf DVT, asymptomatic or symptomatic** (confirmed by: I^{25} Fibrinogen uptake [legs scanned on the second day and subsequently once every second day or every day when test results were positive. Eight points were scanned on each leg.]).	**Group1:** 0/80 **Group 2:** 8/80 **P value:** 0.003 NB: All DVTs found in the calf and seven of these were in women (p=0.02).	**Funding:** Grants from the Halmstad Hospital Foundation for Medical Research, the TRYGG-HANSA Foundation for Medical Research and the Faulty of Medicine, Lund University. Stockings supplied by The Kendall Health Care Products Co., Ins., USA. **Limitations:** Legs were randomised (not patients) and the method of randomisation is not stated. **Outcomes not reported:** All cause mortality by group, PE, bleeding, HIT, PTS, pulmonary hypertension, QoL, LoS **Additional outcomes reported:** Number of patients who had thrombolysis with streptokinase. Calf venous volume. Maximum calf venous outflow. **Notes:** Studied patients were confined to bed on admission. Patients used a bedside commode from the time of admission and spent increasing periods out of bed. On the 5th day all patients were allowed to walk freely in the bedroom if they were able to do so. None of the women used hormonal therapy.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
					Betaadrenoreceptor blockade was given as a routine procedure when tolerated. Furosemide was the diuretic of first choice in congestive cardiac failure. Nitrates were used in severe acute congestive heart failure and in the treatment of ischaemic pain.

GCS adjuvant

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Muir et al., 2000[466] **Country of study:** UK **Study design:** RCT **List who was masked to interventions:** Outcome assessment was masked **Evidence level:** 1+ **Duration of follow-up:** 7 days (+/- 2 days)	**Patient group:** Stroke patients within 72 hours of stroke onset **Setting:** Acute stroke unit **Inclusion criteria:** • Clinically diagnosed acute stroke not independently ambulant within 24hours of admission • Leg weakness of National Institutes of Health Stroke Scale (NIHSS) ≥ 1 **Exclusion criteria:** • Coma patients • Life threatening intercurrent illness • Critical lower-limb ischaemia • Severe dermatological conditions **<u>All patients</u>** **N:** 97 **Age (mean):** 76 **M/F:** NR **Additional risk factors:** ***For VTE*** Hypertension: 43/97 Ischaemic heart disease: 29/97 Previous stroke or TIA: 27/97 Smoker: 28/97 Diabetes: 8/97 Personal history of VTE: 4/97 Familial history of VTE: 1/97 ***Stroke categories: Oxford Community Stroke Project Scale (OCSP)*** Total Anterior Circulation Stroke: 29/97 Partial Anterior Circulation Stroke: 31/97 Lacunar Circulation Stroke: 21/97 Posterior Circulation Stroke: 8/97 **<u>Group 1</u>** **No. randomised:** 65 (37 Kendall TEDs + 28	**Group 1** Standard care + leg length graduated compression stockings. Either Kendall TED (37 patients) or Brevet TX (28 patients). Compression profiles not reported. Start time: NR End time: NR Duration: 7 days **Group 2** Standard care includes CT scanning or MRI, aspirin, IV fluids or those unable to swallow and early mobilisation within 24 hours of admission. Start time: NR End time: NR Duration: 7 days **Additional non-comparative prophylaxis:** Aspirin – dose not stated as standard stroke treatment	**All cause mortality** (study does not report how outcome was confirmed) **Pulmonary embolism, asymptomatic or symptomatic** (study does not report how outcome was confirmed) **DVT, asymptomatic or symptomatic detected within the first seven days** (confirmed by Acuson 128 colour-flow Doppler ultrasound with motion discrimination software)	**Group1:** 9/65 **Group 2:** 4/32 **P value:** NR in study but calculated by NCC-AC as p = 1.00 (Fishers exact test) **Group1:** 0/65 **Group 2:** 0/32 **P value** **Group1:** 7/65 **Group 2:** 7/32 **P value:** NR in study but calculated by NCC-AC as p = 0.21 (Fishers exact test)	**Funding:** Stroke Association **Outcomes not reported:** Fatal PE Symptomatic PE Symptomatic DVT Thigh DVT Calf DVT Fatal Bleeding Major Bleeding Neurological Bleeding Upper GI Bleeding Minor Bleeding Heparin induced thrombocytopaenia Post thrombotic syndrome Pulmonary hypertension Quality of life Length of stay **Additional outcomes reported:** ***Proximal DVT*** **Group1:** 3/65 **Group 2:** 2/32 DVT at 1st examination DVT at 2nd examination **Notes:** Computer generated randomisation with numbers placed in sealed envelopes (opacity of envelopes was not mentioned so possibly introducing selection bias). Power calculation

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Brevet TX) **No. of dropouts:** 19 (29%) [11 TX and 8 in TED] 3 patients were intolerant to stockings 4 withdrew for unstated reasons 2 protocol violations where stockings were not worn as intended **Age (mean):** 76 (TED) 73 (TX) **M/F:** NR **Additional risk factors:** ***For VTE*** Hypertension: 15/28 (TX) 14/37 (TED) Ischaemic heart disease: 9/28 (TX) 11/37 (TED) Previous stroke or TIA: 10/28 (TX) 8/37 (TED) Smoker: 10/28 (TX) 9/37 (TED) Diabetes: 2/28 (TX) 3/37 (TED) Personal history of VTE: 1/28 (TX) 3/37 (TED) Familial history of VTE: 1/28 (TX) 0/37 (TED) ***Stroke categories: Oxford Community Stroke Project Scale (OCSP)*** Total Anterior Circulation Stroke: 9/28 (TX) 9/37 (TED) Partial Anterior Circulation Stroke: 7/28 (TX) 13/37 (TED) Lacunar Circulation Stroke: 6/28 (TX) 10/37 (TED) Posterior Circulation Stroke: 4/28 (TX) 2/37 (TED) **<u>Group 2</u>** **No. randomised:** 32 **No. of dropouts:** 6 (19%) **Age (mean):** 76 **M/F:** NR **Additional risk factors:** ***For VTE*** Hypertension: 14/32 Ischaemic heart disease: 9/32 Previous stroke or TIA: 9/32				assuming 50% DVT incidence and 50% relative risk reduction. The study had 80% power to detect this difference at 5% significance with 100 patients randomised in a 2:1 ratio of stockings to standard treatment. 1070 screened for potential inclusion, 953 (89%) excluded and 19 (2%) non compliant. Reasons for exclusion: mobile / discharged 537, amputee 12, consent refused or unobtainable 77, coma / poor prognosis 66, peripheral vascular disease 4, dermatological (incl. MRSA) 19, non-stroke diagnosis 20, other clinical trial 59, technical / admin 17, already using stockings 34 and other 108. Of the 98 recruited one had 'clinically manifest DVT during the study period and was not included in the results.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Smoker: 9/32 Diabetes: 3/32 Personal history of VTE: 0/32 Familial history of VTE: 0/32 ***Stroke categories: Oxford Community Stroke Project Scale (OCSP)*** Total Anterior Circulation Stroke: 11/32 Partial Anterior Circulation Stroke: 11/32 Lacunar Circulation Stroke: 5/32 Posterior Circulation Stroke: 2/32 No significant difference in any demographic, stroke characteristics or drop out rates between the two groups.				

GCS adjuvant

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Roderick et al., 2005[557] Two RCTs included [330,440] All of these studies were included in the guideline review.	Systematic Review	1+	**Total:** 191	**Type of surgery:** General surgery 1 study, elective hip surgery 1 study	**Intervention :** **Type:** GCS + LMWH 1 study GCS + IPCD 1 study **Timing:** started preoperatively and continued until mobile or discharged	**Type:** LMWH 1 study IPCD 1 study **Timing:** started preoperatively and continued until mobile or discharged	8 to 12 days	**DVT** Confirmed by fibrinogen uptake test or venography	**Int:** 15/86 **Cont** 18/86 **p value:** 0.35	**Not reported:** LoS, QoL, or PTS.
								Pulmonary embolism	**Int: 2/32** **Control:** 3/32 **p value:** 0.50	
								Proximal DVT:	**Int:** 4/32 **Control:** 9/32 **p value:** 0.11	

Evidence Table 39: IPCD or FID devices adjuvant

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Dickinson et al., 1998[164]	RCT	1+	**Total**: 66 Int1: n= 21 Int 2: n=23 Control: n=22	**Type of surgery:** Neurosurgery for intracranial neoplasms **Intervention 1:** Mean age: 43 (28-61) yrs **Intervention 2:** Mean age: 50 (29-72) yrs **Control:** Mean age: 49 (20-72) **M/F numbers not reported** **Pre-existing Risk Factors:** Not reported **Ecluded patients:** history of DVT or PE, allergy to heparin or other anticoagulant agents, history of surgery or major trauma to the lower extremities, concurrent condition requiring anticoagulation therapy; cranial base neoplasms and pituitary adenomas	**Int 1**: LWMH (Enoxaparin) **Dose**: administered subcutaneously at a dose of 30mg in the anaesthesia holding room. He dose was continued at a dose of 30mg every 12 hours **Int 2**: Combination of Enoxaparin and SCD **Dose:** as before **Timing:**.started before induction of anaesthesia until discharge from Neurosurgery Service. **Additional non-comparative prophylaxis**: antiembolic stockings on lower extremities at time of admission to the hospital **Int 2**: Combination of LMWH and thigh high sequential compression device.	**Type**: Thigh high sequential compression device **Timing:** started before induction of anesthesia and continued postoperatively until patient was walking without assistance **Additional non-comparative prophylaxis**: antiembolic stockings on lower extremities at time of admission to the hospital	1 month	**DVT** Confirmed by: duplex imaging (on four occasions in the first 1 month after surgery)	**Int 1:** 1/21 **Control:** 3/22 **p value = 0.53** **Int 2:** 4/23 **Comp**: 3/22 **P**=0.90	**Comments:** Study terminated early when it was determined that the enoxaparin treated groups exhibited a greater incidence of postoperative neurological deficits secondary to intracranial haemorrhage. **Not reported:** Post thrombotic leg, length of stay. **Funding**: NR
								Symptomatic PE	**Int 1:** 0/21 **Int 2:** 0/23 **Comp:** 022	
								Bleeding related complications (intracerebral hemorrhage or epidural haematoma)	**Int 1:** 2/21 **Int 2:** 3/23 **Comp:** 0/22	
								Mortality	**Int 1:** 0/21 **Int 2:** 1/23 **Comp:** 122	

IPCD or FID devices adjuvant

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Goldhaber et al., 1995[226]	RCT	1+	**Total:** 344 Intervention: n = 172 Control: n = 172	**Type of surgery:** Coronary artery bypass Duration not reported **Intervention:** Mean age: 63.2 ± 9.7 yrs M/F:137/35 **Control:** Mean age: X±Y M/F:92/77 **Pre-existing risk factors:** Significantly greater proportion of patients in the comparison group had cancer	**Type:** Thigh-length IPCD device **Dose:** 30-45mm Hg **Timing:** First 98 patients started >24 hours postoperatively Patients 99 to 344 begun 4 -12 hrs post-surgery. Appeared to be worn until discharge **Additional non-comparative prophylaxis:** Graduated compression stocking (length unknown). Appears to be begun immediately post-op. Aspirin 325 mg/day (unless contraindicated)	Graduated compression stocking (length unknown). Appears to be begun immediately post-op. Aspirin 325 mg/day (unless contraindicated)	**Both groups:** followed up until discharge	**DVT** Confirmed by: bilateral doppler US on or after 4 post-op day	**Int:** 31/164 **Control:** 36/166 **p value:** 0.62	**Comments:** 14 participants dropped out after randomisation (8 IPCD + GCS; and 6 GCS). First 98 patients enrolled had delayed initiation of prophylaxis (outcome for these patients were not significantly different). Any interruption of prophylaxis > 3hrs was recorded. Significantly more non-compliance in the IPCD group. Difference between groups still Not significant when analysed with only those who's compliance had not been interrupted. Age was a significant predictors of DVT **Not reported:** PTS, QoL, bleeding **Funding:** not reported
								Proximal DVT Confirmed by: As above	**Int:** 5/164 **Control:** 6/166 **p value:** 0.98	
								PE Not routinely screened for. Non-fatal PE in control group confirmed by high probability V/Q scan	**Int:** 1/164 **Control:** 1/166 **p value:** 1.0000	
								Fatal PE Confirmed by: clinical evaluation (presumably). Patient underwent pulmonary emobolectomy procedure so diagnosis reliable	**Int:** 1 **Control:** 0/166 Patient had not received the intervention and is not included in any other analysis as no DVT measure had been obtained. (therefore 1/165)	
								Survival	**Int:** 2/164 **Control:** 0/166 **p value:** 0.2462	
								Length of Hospital Stay	**Int:** Median 9 **Control:** Median 9 **p value:** 0.36 Not significant	

IPCD or FID devices adjuvant

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Killewich et al., 2002[346]	RCT	1+	**Total:** 45 **Int1:** 13 **Int2:** 15 **Cont:** 16	Patients undergoing major abdominal surgery (35 bowel & 10 aortic reconstructions). Mean age: 67 M/F: 44:1	Intervention 1: IPCD (thigh-length) + unfractionated heparin (5000 units) subcutaneously twice a day **Timing:** Started with anaesthesia and continued until postoperative day 5 or discharge. Intervention 2: IPCD (thigh-length) during surgery and for the first 48 hrs after. **Additional non-comparative prophylaxis:** Patients undergoing aortic reconstruction also given systemic heparin during surgery which was reversed at end with protamine.	Unfractionated heparin (5000 units) subcutaneously twice a day **Timing:** Started with anaesthesia and continued until postoperative day 5 or discharge. **Additional non-comparative prophylaxis:** Patients undergoing aortic reconstruction also given systemic heparin during surgery which was reversed at end with protamine.	5 days or until day of discharge	**Proximal DVT** Confirmed by venous duplex US scan	**Int: 1:** 0/13 **Int 2:** 0/15 **Control:** 0/16 **P value:** not significant	It appears that the treatment was different to pts with aortic reconstructions. DVT prophylaxis was initiated in the operating room after induction of anaesthesia and continued until post op day 5 or discharge **Not reported:** PE, PTS, Bleeding-related complications, QoL, Survival

IPCD or FID devices adjuvant

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Lacut et al., 2005[369] **Country of study:** France **Study design:** RCT **List who was masked to interventions:** Outcome assessment was masked **Evidence level:** 1+ **Duration of follow-up:** 10, 30 and 90 days	**Patient group:** Hospitalised patients with stroke due to acute intracerebral haemorrhage (ICH) **Setting:** ICU or medical wards **Inclusion criteria:** • > 18 years • Traumatic or spontaneous ICH with or without subarachnoidal haemorrhage confirmed by CT or MRI **Exclusion criteria:** • Extra or subdural haematomas • Traumatic ICH due to polytrauma including lower limbs • Haemorrhagic transformation of ischaemic infarct & vasculitis • Consent refusal • DVT within previous 3 months • Lower limb arteriopathy with ankle-to-arm systolic pressure <0.7 • A venous graft • Lower limb ulceration • >24 hour delay since hospital admission • Do not resuscitate order **<u>All patients</u>** **N:** 151 **Age (mean):** NR Age group 1 = 59.9 ± 14.7 Age group 2 = 65.7 ± 12.7 **M/F:** 63/88 *Overall dropout as lost to follow-up =4/151 (2.6%) over both groups **Additional risk factors:** ***For ICH*** Hypertension: 62/151 Anticoagulants: 13/151 Antiplatelets: 31/151 Heavy alcohol drinkers: 43/151	**Group 1** Graduated Elastic Stockings (TED) + Intermittent Compression Device (IPCD) (SC response controller) 3 chamber device applied sequentially for 11 seconds with pressures of 45,40, 30 mmHg at ankle calf & thigh Start time: within 48 hours of admission **Duration:** Not clear **Group 2** Graduated Elastic Stockings Start time: within 48 hours of admission **Duration:** Not clear **Additional non-comparative prophylaxis:** NR	**All cause mortality - *total deaths at 90 days*** (confirmed by assessment of medical records in blinded fashion)	**Group 1:** 15/74 **Group2:** 24/77 **P value:** NR *p = 0.14 2-sided Fisher's exact test calculated by NCC-AC using ITT original numbers randomised*	**Funding:** Tyco – provider of elastic graduated stockings and IPCD **Limitations:** Duration of treatment was not clear. **Outcomes not reported:** Fatal PE Asymptomatic or symptomatic PE Symptomatic DVT Thigh DVT, Calf DVT Fatal Bleeding, Major Bleeding, Neurological Bleeding, Upper GI Bleeding, Minor Bleeding Heparin induced thrombocytopenia Post thrombotic syndrome Pulmonary hypertension Quality of life, Length of stay **Additional outcomes reported:** **Notes:** Computer generated randomisation and allocation concealment using opaque envelopes
			Symptomatic pulmonary embolism	**Group 1:** 0/64 **Group 2:** 0/69 **P value:** NA	
			DVT (asymptomatic or symptomatic) (screened by venous compression ultrasound (CUS) at day 10)	**Group 1:** 3/64 **Group 2:** 11/69 **P value:** 0.03 OR adjusted for differences in baseline variables age, hypertension & varicose veins = 0.31 (95% CI 0.08 – 1.22)	
			Proximal DVT (screened by venous compression ultrasound (CUS) at day 10)	**Group 1:** 0/64 **Group 2:** 3/69	
			Distal DVT (screened by venous compression ultrasound (CUS) at day 10)	**Group 1:** 3/64 **Group 2:** 8/69	
			Clinically overt DVT at 30 days (not stated how confirmed)	**Group 1:** 1/74 **Group 2:** 1/77	
			Clinically overt DVT at 30 days and 90 days (not stated how confirmed)	**Group 1:** 1/74 **Group 2:** 1/77	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	For VTE Cancer: 9/151 Personal history of VTE: 9/151 Familial history of VTE: 10/151 Varicose veins: 36/151 Previous hospitalisation: 9/151 **Group 1** **No. randomised:** 74 **No. of dropouts:** NR* 14 patients out stopped wearing IPCD after 5 days. **Group 2** **No. randomised:** 77 **No. of dropouts:** NR*				

IPCD or FID adjuvant

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Pambianco et al., 1995[509] **Country of study:** USA **Study design:** RCT **List who was masked to interventions:** No one **Evidence level:** 1+ /- ? **Duration of follow-up:** 28 days	**Patient group:** Stroke patients (not necessarily newly defined) **Setting:** Rehabilitation centre **Inclusion criteria:** All cases with a diagnosis of non-haemorrhagic stroke identified by CT scan in the referring hospital and who have a paralysed or severely weakened lower limb. **Exclusion criteria:** • Patients on anticoagulation therapy • haemorrhagic stroke • more than 10 weeks after stroke • active cancer • 'other medical contraindications' including dementia, amputation, stroke not identifying specific area • Contraindications to heparin • diabetic ulcers. **<u>All patients</u>** **N:** 360 randomised – overall baseline data provided for only those completing study **Age (mean):** 72.2 ± 9.5 **M/F:** 41/59 **Additional risk factors:** BMI: 26.1 ± 5.7 Time from stroke to admission: 24.2 days **<u>Group 1:</u>** <u>No prophylaxis</u> **No. randomised:** 115 **No. of dropouts:** 9 (8%) **<u>Group 2</u>** <u>(Heparin)</u> **No. randomised:** 120 **No. of dropouts:** 30 (25%)	**Group 1** No prophylaxis **Group 2** Standard Sodium Heparin (no brand name) Start time: 1st full day at centre End time: day 28 Duration: 28 days or discharge Dose and frequency: 5,000U every 8 hours, adjusted in 500U increments to maintain daily PTT between 30.0 – 39.9. Maximum dose 10,000U every 8 hours **Group 3** IPCD – Anti-thrombic pump (double lined stoking containing inflatable bladder) Start time: 1st full day at centre End time: day 28 Duration: 8 hours each night Length and compression profile: below knee. **Group 4** Mederomic Functional Electrical Stimulation Device (discontinued due to adverse events)	**All cause mortality** **DVT, asymptomatic or symptomatic** (screened for by: B-mode 2-dimensional imaging and pulsed doppler ultrasound at or above the popliteal vein twice a week until the completion of the study or discharge.)	**Group 1:** 0/115 **Group 2:** 0/120 **Group 3:** 0/117 **Group1:** 6/115 (completed study) **Group 2:** 5/120 (completed study) **Group 3:** 8/117 (completed study) **P value:** NR Grp 1 v Grp 2 = 0.76 Grp 1 v Grp 3 = 0.78 Grp 2 v Grp 3 = 0.41 *2-sided Fisher's exact test calculated by NCC-AC using ITT original numbers randomised*	**Funding:** US department of Education **Limitations:** - No details of randomisation provided - No blinding of analysts not mentioned - High patient drop out rates for heparin and IPCD group. **Outcomes not reported:** All cause mortality, PE (any type), Symptomatic DVT, Calf DVT, Thigh DVT, Bleeding (any type), HIT, PTS, Pulmonary Hyper tension, QoL, LoS **Additional outcomes reported:** Adverse events for heparin included: echymotic area over abdomen and areas distal to injection site. 10 point decrease in haematocrit level; nausea and vomiting with onset of heparin therapy, bleeding from the ear, haematochezia, haemepositive stools, blleding around tracheal stoma,

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 3 (IPCD) **No. randomised:** 117 **No. of dropouts:** 26 (22%) **Group 4** (Functional Electrical Simulation) **No. randomised:** 8 **No. of dropouts:** 6 (75%) Study arm discontinued	**Additional non-comparative prophylaxis:** All patients received bilateral below knee stockings (no compression).			thrombocytopaenia Adverse events for IPCD, bilateral skin changes **Notes:** High drop out rate in IPCD due to disruption of sleep. 21 patients were transferred to acute care for complications unrelated to study treatment

IPCD or FID devices adjuvant

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Ramos et al., 1996[544]	RCT	1+	**Total:** 2551 **Intervention:** n = 1355 **Control:** n = 1196	Patients who underwent cardiac surgery over a 10 year period **Intervention** M/F: 968/387 Mean age: 63±13 **Control** M/F: 814/382 Mean age: 65±11	**Type** Thigh-length IPCD + subcutaneous heparin (5000 units every 12 hours) Both started immediately after surgery and continued for 4 to 5 days or until the patient was ambulatory.	**Type:** UFH **Dose:** 5,000 U every 12hrs Started immediately after surgery and continued for 4 to 5 days or until the patient was ambulatory. **Additional non-comparative prophylaxis:** Not reported	4 to 5 days Study carried out during a 10 year period	**Symptomatic PE** 25 were confirmed by ventilation perfusion scan, 42 by pulmonary angiogram and 2 by autopsy	**Int:** 21/1355 **Control:** 48/1196 The frequency of concomitant use of bilateral PCS and SCH reduced the frequency of post-op PE in 62% in comparison to prophylaxis with SCH alone (95% CI, 47.2 to 71.3) **p value:** 0.01	Patients were excluded from either group for some of the following reasons: known DVT prior to surgery, bleeding complications, intra-operative death, intolerance to PCS or withdrawal of prophylaxis before full ambulation **Not reported:** DVT, PTS, Bleeding related complications, QoL, Survival
								Fatal PE Confirmed by autopsy	**2** (paper does not report to which groups they belong)	

IPCD or FID adjuvant

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Roderick et al., 2005[557] 7 RCTs included: [96,402,559,608,649,680] All of these studies were included in the guideline review.	Systematic Review	1+	8 studies (1 excluded: Pambianco 1995 as Medical not surgery) **Total:** 1005	**Type of surgery:** Orthopaedic: 2 studies Neurosurgery: 3 studies Mixed: 1 study General: 1 study **Timing:** Start time varied from preop to postop. End time varied from postop 3 days to 10 days/ambulant.	IPCD & GCS (4 studies) IPCD & Aspirin (1 study) IPCD & Heparin (1 study) IPCD & Dextran (1 study)	GCS (4 studies) Aspirin (1 study) Heprin (1 study) Dextran (1 study) **Additional non-comparative prophylaxis:** Not reported	Not reported	**DVT** confirmed by Doppler US, fibrinogen uptake, impedance phlethysmograph or venography	**Int:** 39/412 **Cont:** 54/416 **p value:** = 0.1234	**Notes:** Not all studies report total number of patients in each arm of study. **Not reported:** Major bleeds, QoL, hospital stay, PTS
								PE confirmed by angiography or scan	**Int:** 4/188 **Cont:** 7/176 (reported in 4 studies) **p value:** 0.3673	
								Proximal DVT	**Int:** 6/282 **Cont:** 8/277 (reported in 5 studies) **p value:** 0.5997	

IPCD or FID devices adjuvant

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Roderick et al., 2005[557] One RCT included [190]	Systematic Review	1+	**Total:** 84 Int: 42 Control: 42	**Type of surgery:** Orthopaedic surgery	**Intervention 1:** **Type:** Foot pump and GCS (Foot of operated leg) **Timing:** postoperative during sitting and bed rest	**Type:** GCS (Bilateral) **Timing:** Started postoperatively but not stated duration.	6-9 days postoperatively	**DVT** Confirmed by: venography	**Int1:** 4/39 **Cont** 16/40 **p value:** 0.0038	**Not reported:** PE, LoS, QoL, or PTS.
								Proximal DVT:	**Int1:** 2/39 **Control:** 13/40 **p value:** 0.0031	

IPCD or FID devices adjuvant

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Stranks et al., 1992[630]	RCT	1+	Total: 82 **Intervention**:n = 41 **Control**: n = 39	Patients undergoing surgery for fracture of the neck of femur (hemiarthroplasty) **Excluded**: Previous history of VTE, chronic venous insufficiency, presence of malignant tumour. **Intervention**: Mean age: 79.1 M/F: 6/35 **Control**: Mean age: 82 M/F: 9/30	Foot pump (A-V impulse system) + thigh-length graduated compression stockings Foot pump started immediately after the operation and used for 7 to 10 days while the patient was in bed or sitting at rest. Not stated whether applied to one or both feet. Stockings added to both legs before operation and used for 10 days. **Additional non-comparative prophylaxis**: Regional anaesthesia: 10/41	Thigh-length graduated compression stockings added to both legs before operation and used for 10 days. **Additional non-comparative prophylaxis**: Regional anaesthesia: 11/39	10 days	**Proximal DVT** Confirmed by:doppler US ---	**Int:** 0/40 **Control:** 9/39 **p value:** <0.01	**Not reported**: All DVT, PE, fatal PE, PTS, QoL, Survival
								Bleeding related complications	**Int:** 0/40 **Control:** 0/39 **p value:** Not significant	

IPCD or FID devices adjuvant

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Stannard et al., 1996[619]	RCT	+	**Total:** 75 Int 1: 25 Int 2: 25 Control: 25	**Type of surgery:** uncemented total hip arthroplasty **Duration of surgery:** Int1: mean 106 (85 - 128) mins; Int2: mean 113 (15 - 135) mins; Cont: mean 111 (87 - 140) mins; **Intervention 1:** Mean age: 68.7 (range 48-86) yrs M/F:not reported **Intervention 2:** Mean age: 65 (range 51-79) yrs M/F:not reported **Control:** Mean age: 69.7 (range 28-86) yrs M/F:not reported	**Intervention 1:** **Type:** Bilateral foot pump (PlexiPulse) + LDUH + aspirin **Dose:** FP 16hrs/day for first 3 days, then 12hrs/day; LDUH 5000U; Aspirin 325 mg **Intervention 2:** **Type:** Bilateral foot pump 16hrs/day for first 3 days, then 12hrs/day **Timing:** FP begun immediately post-surgery and continued until end of study; LDUH begun 12hrs pre surgery and every 12hrs for first 3 days post-surgery, then aspirin 3x daily until end of study **Additional prophylaxis:** Spinal anaesthesia: 22/25	**Type:** LDUH + aspirin **Dose:** LDUH 5000U; Aspirin 325 mg **Timing:** LDUH begun 12hrs pre surgery and every 12hrs for first 3 days post-surgery, then aspirin 3x daily until end of study **Additional prophylaxis:** Spinal anaesthesia: 21/25	2 weeks postoperatively	**DVT** Confirmed by: Duplex US. Positive scans confirmed by venography	**Int1:** 0/25 **Int2:** 0/25 **Cont:** 5/25 **p value:** = 0.009 (significant)	3/5 DVTs were symptomatic. 1 PE was symptomatic. 4/5 patients who developed DVT had spinal anaesthesia. Two patients reported as excluded from study due to abnormal pre-op US findings. Does not report to which group(s) they belonged **Not reported:** LoS, QoL, PTS, proximal DVT **Funding:** Not reported
								PE Confirmed by: Not routinely screened for. No confirmatory tests reported	**Int1:** 0/25 **Int2:** 0/25 **Control:** 1/25 **p value:** Not reported	
								Bleeding related complications Surgical wound drainage - time taken for wound to seal (no of days post-op)	**Int1:** 5.9/25 **Int2:** 3.8/25 **Control:** 6.2/25 **p value:** = 0.05 (Significant)	
								Survival (specify)	**Int1:** 25/25 **Int2:** 25/25 **Control:** 25/25 **p value:** Not significant	

Evidence Table 40: Fondaparinux adjuvant

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Fuji et al., 2008[201] **Country of study:** Japan **Study design:** RCT **List who was masked to interventions:** Paper states that study is double blind and that the endpoint assessors were blinded. **Evidence level:** 1+ **Duration of follow-up:** 11-17 days	**Patient group:** Study 1: Total knee replacement (TKR) Study 2: Total hip replacement (THR) **Setting:** Department of Orthopaedic Surgery **Inclusion criteria:** Patients of either gender if their age was 20 years or greater, and they were scheduled for TKR or THR surgery or revision surgery for TKR or THR **Exclusion criteria:** • Active, clinically significant bleeding • Bleeding tendency/disorder (e.g. ulcer of the digestive tract etc.) • Severe hepatic disorder • Hypersensitivity to UFH or LMWH • Requirement of an indwelling intrathecal or epidural catheter during the treatment period • Brain, spine or ophthalmologic surgery within 3 months preceding enrolment • Body weight <40kg • Severe renal disorder (serum creatinine concentration >2.0mg/dL) **Study 1 (TKR)** **All patients** **N:** 426 **No. of dropouts:** 29 (6.8%) **Age (mean):** 71.0 (sd = 8.0) **M/F:** 75: 351 **Additional risk factors:** BMI ≥ 30 kg/m² = 64 (15.0%) **Group 1** **No. randomised:** 84	**Study 1 (TKR)** **Group 1** Fondaparinux (Atrixa) Start time: 24hr ± 2 hrs after surgery Duration: 10-16 days Daily 2.5mg subcutaneous injections **Group 2** Placebo (0.25ml isotonic sodium chloride) Start time: 24hr ± 2 hrs after surgery Duration: 10-16 days Daily 2.5mg subcutaneous injections **Additional non-comparative prophylaxis:** More than 50% of patients received elastic stockings /bandages for part of the study. **Study 2 (THR)** **Group 3** Fondaparinux (Atrixa) Start time: 24hr ± 2 hrs after surgery Duration: 10-16 days Daily 2.5mg subcutaneous injections	**All cause mortality**	**Study 1 (TKR)** **Group1:** 0/84 **Group 2:** 0/87 **P value:** N/A **Study 2 (THR)** **Group3:** 0/81 **Group 4:** 0/82 **P value:** N/A	**Funding:** GlaxoSmithKlein, Sanovi-synthelabo and NV Organon **Limitations:** Method of randomisation not given. No details provided on allocation concealment. **Outcomes not reported:** DVT, PE, Heparin induced thrombocytopenia, post thrombotic syndrome, pulmonary hypertension, quality of life, length of stay **Additional outcomes reported:** Incidence of combined VTE was recorded Study 1 (TKR) Group 1: 16.2% Group 2: 65.3% P value: <0.05* Study 2 (THR) Group 3: 7.4% Group 4: 33.8% P value: <0.05* **Notes:** * calculated by NCC using fishers exact test. Study was a dose
			Fatal bleeding	**Study 1 (TKR)** **Group1:** 0/84 **Group 2:** 0/87 **P value:** N/A **Study 2 (THR)** **Group3:** 0/81 **Group 4:** 0/82 **P value:** N/A	
			Major bleeding (description: fatal bleeding; bleeding that was retroperitoneal, intracranial, or intraspinal or that involved any other critical organ; bleeding leading to reoperation; and overt bleeding with a bleeding index of 2 or more.)	**Study 1 (TKR)** **Group1:** 1/84 **Group 2:** 1/87 **P value:** 1.00* **Study 2 (THR)** **Group3:** 2/81 **Group 4:** 0/82 **P value:** 0.245*	
			Minor bleeding (description: not defined)	**Study 1 (TKR)** **Group1:** 2/84 **Group 2:** 3/87 **P value:** 1.00* **Study 2 (THR)** **Group3:** 4/81 **Group 4:** 0/82 **P value:** 0.059*	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 2 **No. randomised:** 87 **Study 2 (THR)** **All patients** **N:** 406 **No. of dropouts:** 25 (6.2%) **Age (mean):** 61.6 (sd = 10.9) **M/F:** 73: 333 **Additional risk factors:** BMI ≥ 30 kg/m^2 = 26 (6.4%) **Group 3** **No. randomised:** 81 **Group 4** **No. randomised:** 82	**Group 4** Placebo (0.25ml isotonic sodium chloride) Start time: 24hr ± 2 hrs after surgery Duration: 10-16 days Daily 2.5mg subcutaneous injections **Additional non-comparative prophylaxis:** More than 50% of patients received elastic stockings /bandages for part of the study.			ranging study with separate groups receiving 0.75, 1.5, 2.5 and 3.0mg fondaparinux. Only the group receiving 2.5 mg fondaparinux is analysed here as this is the licensed dose.

Fondaparinux adjuvant

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Turpie et al., 2007[645] **Country of study:** US **Study design:** RCT **List who was masked to interventions:** Double-blind placebo controlled trial **Evidence level:** 1+ **Duration of follow-up:** 32 days	**Patient group:** Patients undergoing abdominal surgery. **Setting:** Nov 2001 to Oct 2004, 50 US centres **Inclusion criteria:** Patients aged >40 years, weighing over 50 kg and scheduled to undergo abdominal surgery expected to last longer than 45 min. **Exclusion criteria:** ▪ Patients due to undergo vascular surgery, with evidence of leg ischemia caused by peripheral vascular disease, or unable to receive intermittent pneumatic compression or elastic stockings. ▪ Pregnant women and women of childbearing age not using effective contraception. ▪ Life-expectancy < 6 months ▪ clinical signs of deep vein thrombosis and/or history of venous thromboembolism within the previous 3 months; ▪ active bleeding; documented congenital or acquired bleeding disorder; ▪ active ulcerative gastrointestinal disease, unless it was the reason for the present surgery; ▪ hemorrhagic stroke or surgery on the brain, spine or eyes within the previous 3 months; bacterial endocarditis or other contraindication for anticoagulant therapy; ▪ planned indwelling intrathecal or epidural catheter for more than 6 h after surgical closure; unusual difficulty in achieving epidural or spinal anesthesia (e.g. more than two attempts); known ▪ hypersensitivity to fondaparinux or iodinated contrast medium; ▪ current addictive disorders; ▪ serum creatinine concentration above 2.0 mg dL^{-1} in a well-hydrated patient and	**Protocol:** **Group 1 Fondaparinux + IPCD** **Fondaparinux** 2.5 mg s.c. injection once-daily. Start: 6-8 h after surgery, provided that hemostasis was achieved, or 2hours after removal of intrathecal or epidural catheter 2nd injection: 16-28 h after 1st injection Duration: 5-9 days If the patient was discharged from hospital before completing the on-study-drug period, a visiting nurse administered the remaining trial infections. **IPCD:** Any type of device, except a foot pump, during the study period (5-9 days). "Duration" left to investigator's discretion. **Group 2 Placebo + IPCD** **Placebo** injections (isotonic saline) schedule same as above. **IPCD:** As above **Actual usage :** **Fondaparinux/placebo injections** Time to first postoperative injection, median (hours:min): Group 1 :6:42 Group 2 :6:45 < 6 h/ 6-8 h/ >8 hr , n (%): Group 1 :24 (3.6)/ 582 (91.5)/ 30 (4.7) Group 2 :25 (3.9)/ 593 (91.4)/ 31 (4.8) Duration of treatment n (%): <5 days/5-9days/>9 days Group 1: 55 (8.6)/ 577 (90.7)/ 4 (0.6)	**All cause mortality** (confirmed by: Causes of death were: PE (n=2, one in each group) and bleeding (see fatal bleeding) (n=3, all in the fondaparinux group). The other deaths (n=8, four in each group) were not related to VTE or bleeding. None of the deaths was considered to be related to study drug by the investigators **Fatal pulmonary embolism** (confirmed by: autopsy) **Symptomatic pulmonary embolism** (confirmed by: Clinically suspected pulmonary embolism was confirmed by a high-probability lung scan, by a non-high probability lung scan defect plus confirmed DVT, by pulmonary angiography, by helical computed tomography, or at autopsy) **Symptomatic DVT** (confirmed by: In hospital, patients were examined daily for signs and symptoms of VTE. Confirmation method not defined, but these were adjudicated)	Treatment period, up to Day 10 **Group 1;** 1/635 **Group 2:** 2/650 **P value:** NR Whole study period, up to Day 32 **Group 1 :**8/635 **Group 2 :**5/650 **P value** : 0.42 Treatment period, up to day 10 **Group 1;** 0/635 **Group 2:** 0/650 **P value:** NR Whole study period, up to Day 32 **Group 1 :**1/635 **Group 2 :**1/650 **P value:** NR Treatment period, up to day 10 **Group 1;** 1/635 **Group 2:** 1/650 **P value:** NR Whole study period, up to 32 days, **Group 1 :**2/635 **Group 2 :**4/650 **P value:** NR Treatment period, up to day 10 **Group 1;** 1/635 **Group 2:** 1/650 **P value:** NR	**Funding:** Funded initially by Sanofi-Synthelabo and then by GlaxoSmithKline. **Limitations:** ▪ >35% not evaluable for primary outcome. **Outcomes not reported:** Post thrombotic syndrome Pulmonary hypertension Quality of life **Additional outcomes reported:** Transfusions, thrombocytopenia, bleeding at surgical sites. **Notes:** Treatment period was defined as first injection up to 2 additional calendar days after last injection (>90% had injections up to day 9). Whole study period was up to day 32, patients followed up between day 28-32 After completion of study drug administration: Group 1 :1.4% (9/636) Group 2 :3.4% (22/649) Received extended prophylaxis with either heparins or vitamin K antagonist on the investigator's

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	platelet count below 100000mm^{-3}. ▪ Patients requiring anticoagulant therapy, or other pharmacologic prophylaxis besides intermittent pneumatic compression, according to the investigator. **All patients** **N:** 1309 randomised **Group 1 Fondaparinux + IPCD** **No. randomised:** 650 **No. of dropouts:** **Not evaluable for primary efficacy:** 226 /635 (35.6%) **Group 2 Placebo + IPCD** **No. randomised:** 659 **No. of dropouts:** **Not evaluable for primary efficacy:** 241/649 (37.1%) **Data for both groups**, based on n=636 in Group 1, n=649 in group 2 Age, median (range) (years): Group 1 :60 (40-93) Group 2 :59 (40-95) Gender, male/female: Group 1 :314/322 Group 2 :321/328 Weight, mean (SD) (kg): Group 1 :84.6 (20.4) Group 2 :84.6 (20.4) **Risk factor for VTE, no. (%):** Age >=75 years: Group 1: 90 (14.2) Group 2 :100 (15.4) Obesity (men with BMI >= 30 kg m^{-2}; women BMI >= 28.6 kg m^{-2}) Group 1 :269 (42.4) Group 2 :270 (41.7) History of VTE:	Group 2 :60 (9.2)/ 584 (90.0)/ 5 (0.8) **IPCD** Total receiving any IPCD Group 1: 634/636 (99.7) Group 2: 644/649 (99.2) Type, (%), duration, median (range): Knee-high Group 1: 312 (49.2), 4.0 (1-32) days Group 2; 319 (49.2), 4.0 (1-29) days Thigh high: Group 1: 322 (50.6), 4.0 (1-39) days Group 2: 325 (50.1), 4.0 (1-33) days **Additional non-comparative prophylaxis:** Elastic stockings, no. (%) Group 1 :316 (49.7) Group 2 :322 (49.6) Prohibited therapy (any type of anticoagulant agents, dextran), no. (%) Group 1 :12 (1.9) Group 2 :5 (0.8) Discouraged therapy (aspirin and non-steroidal anti-inflammatory agents), no (%): Group 1 :112 (17.6) Group 2 :122 (18.8) Physical therapy, no. (%) Group 1 :99 (15.6) Group 2 :116 (17.9)			initiative.
			DVT, asymptomatic or symptomatic (screened for by: In hospital, patients were examined daily for signs and symptoms of VTE. Patients were systematically examined for lower extremity DVT by bilateral ascending contrast venography between days 5 and 10, but no more than 1 calendar day after the last study drug injection)	Treatment period, up to day 10 **Group 1 :**7/424 (1.7) **Group 2 :**22/418 (5.3) **P value:** 0.004	
			Thigh DVT(screened for by: See above)	Treatment period, up to day 10 **Group 1 :**1/424 (0.2) **Group 2 :**7/417 (1.7) **P value:** 0.037	
			Only Calf DVT (screened for by: see above. Only included patients with only distal DVT and evaluable proximal DVT. Patients with distal DVT not counted if proximal was not evaluable)	Treatment period, up to day 10 **Group 1 :**6/424 (1.4) **Group 2 :**14/417 (3.4) **P value:** Not reported	
			Fatal bleeding (description: Two occurred 6 and 9 days after the study drug was discontinued. The other occurred 22 days after the study drug was discontinued in a patient who had repeated bleeding episodes starting on the first postoperative day)	Treatment period, up to day 10 **Group 1 :**0/635 **Group 2 :**0/650 Whole study period, up to Day 32 **Group 1 :**3/635 (0.2) **Group 2 :**0/650 (1.7) **P value:** 0.037	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 :16 (2.5) Group 2 :15 (2.3) Congestive heart failure (NYHA grade III or IV) Group 1 :22 (3.5) Group 2 :29 (4.5) Chronic obstructive pulmonary disease Group 1 :73 (11.5) Group 2 :83 (12.8) Inflammatory bowel disease: Group 1 :66 (10.4) Group 2 :58 (8.9) Cancer surgery: Group 1 :246 (38.7) Group 2 :262 (40.4) **≥ 2 risk factors for VTE, no. (%)** Group 1 :210/636 (33.0) Group 2 :224/649 (34.5) **Type of surgery, no (%):** GI: Group 1 :383 (60.2) Group 2 :389 (59.9) Gynecologic: Group 1 :62 (9.7) Group 2 :57 (8.8) Urologic: Group 1 :118 (18.6) Group 2 :112 (17.3) Other: Group 1 :255 (40.1) Group 2 :269 (41.4) **Type of anaesthesia, no. (%):** General only: Group 1 :626 (98.4) Group 2 :641 (98.8) Spinal epidural: Group 1 :10 (1.6) Group 2 :8 (1.2)		**Major bleeding** (description: Bleeding that was fatal, retroperitoneal, intracranial, or involved any other critical organ, led to intervention, or was associated with a bleeding index of 2.0 or more. The bleeding index was calculated as follows: (number of units of packed red blood cells or whole blood transfused) + [(prebleeding)-(postbleeding) haemoglobin (g dL^{-1}) values]	Treatment period, up to day 10 **Group 1 :**10/635 **Group 2 :**1/650 **P value** : 0.006	
			Minor bleeding (description: No details provided)	Treatment period, up to day 10 **Group 1 :**5/635 **Group 2 :**3/650 **P value: 0.50**	
				Data from text: During treatment period: **Platelet count below 100000mm^{-3}- n/N (%)** **Group 1 :**4/635 (0.7) **Group 2 :**7/650 (1.3) Decreased platelet count was reported by the investigators as an adverse event in : **Group 1 :**n=2 (0.3%) **Group 2 :**n=7(1.1%)	

Evidence Table 41: VKA adjuvant

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Roderick et al., 2005[557] 5 RCTs included [299,362,559,655,702] 4 of these studies were included in the guideline review [299,559,655,702]	Systematic review	1+	**Total: 688** 2 studies report total in both arms so unable to calculate totals for intervention and control.	Orthopaedic (3 studies), Mixed (1 study) and Neurosurgery (1 study)	OAC adjusted + GCS (2 studies) OAC-adjusted + Dextran OAC-adjusted + UFH OAC-adjusted + IPCD **Timing**: recovery room (1 study), admission, pre-op (2 studies) and day one post op (1 study). **Additional non-comparative prophylaxis**: Not reported	GCS (2 studies) Dextran (1 study) UFH (1 study) IPCD (1 study) Open studies: 4 Placebo: 1 **Additional non-comparative prophylaxis**: Not reported	Not reported	**DVT** confirmed by FUT, venography, Doppler US	**Int:** 20/165 **Cont:** 34/184 **p value:** 0.1057	**Not reported:** QoL, LoS and PTS. Event rates reported here are for all studies as published in the systematic review.
								PE confirmed by scan or post mortem for fatal	**Int:** 2/182 **Cont:** 6/199 **p value:** 0.2878	
								Major bleeds:	**Int:** 4/126 **Cont:** 1/141 **p value:** 0.1917	
								Proximal DVT	**Int:** 7/108 **Cont:** 11/119 **p value:** 0.4724	

Evidence Table 42: Aspirin +/- antiplatelet therapy adjuvant

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Antiplatelet Trialists' Collaboration, 1994[21] 3 out of 55 trials [188,406,713] All of these studies were included in the guideline review. One study reviewed separately in aspirin vs UFH tables below[666]	Systematic review	1+	273	**Type of surgery:** General surgery patients: 3 trials Elective orthopaedic surgery patients: 1 trials	Aspirin	No intervention	Majority 1, 2 or 3 week studies	**DVT** Confirmed by: fibrinogen uptake test or venography	**Int:** 21/127 **Control:** 31/131 **p value:** 0.11	Trials did not always what was considered a major bleed Reported pulmonary emboli but did not state how if they were confirmed. **Not reported:** QoL, survival, LoS, PTS, funding
					Additional non-comparative prophylaxis: heparin	**Additional non-comparative prophylaxis:** heparin		**Proximal DVT** Confirmed by: fibrinogen uptake test or venography	**Int:** 5/132 **Control:** 11/131 **p value:** 0.15	
								Major bleed	**Int:** 5/132 **Control:** 1/131 **p value:** 0.16	

Aspirin +/- antiplatelet therapy adjuvant

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Monreal et al., 1995[459]	RCT	1+	**Total:** 459 Int: 151 Control: 154 also group of 154receiving triflusal, data not extracted. No. of patients receiving correct prophylaxis: Int: 148 Cont: 153	**Type of surgery:** Hip fracture and elective hip replacement patients **Intervention:** Mean ±SD age: 75 ±14 yrs M/F:53/98 **Control:** Mean ±SD age: 72 ±15 yrs M/F:67/87 **Pre-existing risk factors:** Previous DVT: 10 intervention, 6 control Leg varicosities: 48 intervention, 45 control	**Type:** Aspirin **Dose:** 200mg 3 times daily with meals **Timing:** Elective hip replacement patients started evening before operation, hip fracture patients started immediately after operation. Both continued until 9th postoperative day **Additional non-comparative prophylaxis:** Unfractionated **heparin** 7500IU subcutaneously started 2 hours before surgery and continued at 12 hour intervals for 10 days.	**Type:** placebo 3 times daily with meals **Timing:** Elective hip replacement patients started evening before operation, hip fracture patients started immediately after operation. Both continued until 9th postoperative day **Additional non-comparative prophylaxis:** Unfractionated **heparin** 7500IU subcutaneously started 2 hours before surgery and continued at 12 hour intervals for 10 days.	8th postoperative day for scans followed up for 31 postoperative days	**DVT** Confirmed by: US scanning or venography	**Int:** 27/151 **Control:** 27/154 **p value:** 1.0000	**Comments:** **Not reported:** PTS, QoL, length of hospital stay **Also reported:** Mean red cell units transfused preoperatively and postoperatively **Funding:** not reported
								Proximal DVT Confirmed by: US scanning or venography	**Int:** 14/151 **Control:** 13/154 **p value:** 1.0000	
								Distal DVT Confirmed by: US scanning or venography	**Int:** 11/151 **Control:** 14/154 **p value:** 0.6775	
								Symptomatic PE Confirmed by: ventilation perfusion lung scan	**Int:** 8/151 **Control:** 8/154 **p value:** 1.000	
								Fatal PE Confirmed by: necropsy, ventilation perfusion lung scan before death or venographic documentation of DVT in lower limbs	**Int:** 2/151 **Control:** 1/154 **p value:** 0.6201	
								Number of patients receiving transfusion	**Int:** 58/151 **Control:** 47/154 **p value:** 0.1507	
								Number of people with overt bleeding	**Int:** 3/151 **Control:** 5/154 **p value:** 0.7230	

Aspirin +/- antiplatelet therapy adjuvant

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
PE Prevention (PEP) Trial Collaborative Group[541] Hip fracture patients	Multi-centre RCT covering 5 countries	1+	**Total:** 13,356 Intervention: 6679 Control: 6677 PEP trial also included elective arthroplasty patients. Total no. of patients in both parts of trail: 17,444 Intervention: n = 8726 Control: n = 8718	**Type of surgery:** Hip fracture patients Participants with a clear indication or contraindication to aspirin were excluded. Mean age: 79 years 79% women **Pre-existing risk factors:** none stated	**Type:** Aspirin **Dose:** 160mg daily **Timing:** 35 days started as soon as possible after admission and prior to surgery **Additional non-comparative prophylaxis:** UFH =1207 LMWH =1761 Stockings = 2026 Regional anaesthesia =2290 Aspirin or non-steriodal anti-inflammatory drugs within 48 hours before randomisation by 9% (figure for both groups, aspirin and placebo)	**Type:** Placebo matching aspirin in appearance **Timing:** 35 days started as soon as possible after admission and prior to surgery **Additional non-comparative prophylaxis:** UFH =1225 LMWH =1663 Stockings = 1969 Regional anaesthesia =2313 Aspirin or non-steriodal anti-inflammatory drugs within 48 hours before randomisation by 9% (figure for both groups, aspirin and placebo)	35 days for mortality or up to end of hospital stay for morbidity	**PE** Confirmed by (see comments)	**Int:** 46/6679 **Control:** 81/6677 **p value:** 0.02	**Comments:** * DVT data not routinely screened for, confirmed by venography or "other objective test". All PEs confirmed by: pulmonary angiogram, high probabliity ventilation-perfusion scan, intermediate probability scan with venographic evidence of DVT; or evidence of PE and necropsy. **Not reported:** PTS, QoL, screened DVT; length of hospital stay **Also reported:** Results for all venous thromboembolism by additional prophylaxis received. No spinal haematomas in patients receiving regional anaesthesia
								Fatal PE Confirmed by (see comments)	**Int:** 18/6679 **Control:** 43/6677 **p value:** 0.0013 result significant	
								Symptomatic* **DVT** Confirmed by venography or "other objective test"	**Int:** 69/6679 **Control:** 97/6677 **p value:** 0.0289	
								Any venous thromboembolism PE or symptomatic DVT confirmed by (see comments)	**Int:** 105/6679 **Control:** 165/6677 **p value:** 0.0002	
								Fatal bleeding	**Int:** 13/6679 **Control:** 15/6677 **p value:** 0.7107	
								Bleeding, requiring transfusion	**Int:** 198/6679 **Control:** 161/6677 **p value:** 0.0540	
								Evacuation of haematoma	**Int:** 24/6679 **Control:** 33/6677 **p value:**(0.2	
								Postoperative wound bleed ≥4 days not requiring transfusion	**Int:** 171/6679 **Control:** 141/6677 **p value:** 0.09	
								Haematemesis or melaena not requiring transfusion	**Int:** 182/6679 **Control:** 122/6677 **p value:** 0.0005	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
								Survival at day 35	**Int:** 6232/6679 **Control:** 6216/6677 **p value:** Not significant	**Funding:** Bayer AG and Sterling Winthrop donated calendar-packed aspirin and placebo
								Mortality day 36 to day 365	**Int:** 271/6679 **Control:** 291/6677 **p value:** 0.3891	

Aspirin +/- antiplatelet therapy adjuvant

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
PE Prevention (PEP) Trial Collaborative Group[541] Elective hip or knee arthroplasty	Multicentre RCT	1+	**Total:** 4088 Intervention: 2047 Control: 2041 PEP trial also included elective arthroplasty patients. Total no. of patients in both parts of trail: 17,444 Intervention: n = 8726 Control: n = 8718	**Type of surgery:** Elective hip or knee arthroplasty patients. Participants with a clear indication or contraindication to aspirin were excluded. Mean age: 67 years 53% women **Pre-existing risk factors:** none stated	**Type:** Aspirin **Dose:** 160mg daily **Timing:** 35 days started as soon as possible after admission and prior to surgery **Additional non-comparative prophylaxis:** Aspirin or non-steriodal anti-inflammatory drugs within 48 hours before randomisation =501 Proportion of participants taking additional prophylaxis across both arms: Non-study aspirin 27% Non-steriodal anti-inflammatory drugs 27% Unfractionated heparin 2% Low molecular weight heparin 35%	**Type:** Placebo matching aspirin in appearance **Timing:** 35 days started as soon as possible after admission and prior to surgery **Additional non-comparative prophylaxis:** Aspirin or non-steriodal anti-inflammatory drugs within 48 hours before randomisation =520 Proportion of participants taking additional prophylaxis across both arms: Non-study aspirin 27% Non-steriodal anti-inflammatory drugs 27% Unfractionated heparin 2% Low molecular weight heparin 35%	35 days for mortality or up to end of hospital stay for morbidity	**PE** Confirmed by (see comments)	**Int:** 9/2047 **Control:** 10/2041 **p value:** 0.8232	**Comments:** * DVT data not routinely screened for, confirmed by venography or "other objective test". All PEs confirmed by: pulmonary angiogram, high probabliity ventilation-perfusion scan, intermediate probability scan with venographic evidence of DVT; or evidence of PE and necropsy. **Not reported:** PTS, QoL, screened DVT; length of hospital stay **Funding:** Bayer AG and Sterling Winthrop donated calendar-packed aspirin and placebo
								Fatal PE Confirmed by (see comments)	**Int:** 1/2047 **Control:** 2/2041 **Hazard ratio (95% CI):** 0.50 (0.04-5.49)	
								Symptomatic* **DVT** Confirmed by venography or "other objective test"	**Int:** 15/2047 **Control:** 19/2041 **Hazard ratio (95% CI):** 0.78 (0.40-1.53)	
								Bleeding, requiring transfusion	**Int:** 64/2047 **Control:** 75/2041 **p value:** not significant	
								Evacuation of haematoma	**Int:** 16/2047 **Control:** 8/2041 **p value:** 0.10	
								Survival at day 35	**Int:** 2038/2047 **Control:** 2030/2041 **p value:** not significant	

Aspirin +/- antiplatelet therapy adjuvant

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Woolson et al., 1991[702]	RCT	1+	**Total:** 196 patients 217 operations Int 1: 69 patients and operations Int 2: 73 patients and 76 operations Cont: 70 patients 72 operations **(see comments)**	**Type of surgery:** Total hip replacement (primary or revision) **Intervention 1** average age: 67.9 M/F 31/38 **Intervention 1** average age: 66.3 M/F 27/66 **Control** average age: 62.3 M/F 35/35 **Pre-existing risk factors:** Intervention:history of DVT 10/69, varicose veins 9/69 Control: history of DVT 4/72, varicose veins 5/72	**Intervention 1: Type:** Warfarin + IPCD + GCS **Dose:** 7.5 or 10mg on evening before surgery, then adjusted to maintain prothrombin time between 14 and 16 seconds. **Intervention 2: Type:** Thigh-length Intermittent pneumatic compression and graduated elastic stockings. **Timing:** Warfarin started evening before surgery, IPCD and stockings started at surgery, both continued until discharge . **Additional non-comparative prophylaxis:** Not reported	**Type:**Aspirin + IPCD + GCS **Dose:** 650mg twice per day **Timing:** Started evening before surgery and until discharge .	Intervention until discharge, followed up for 3 months	**Proximal DVT** Confirmed by venography or ultrasonograpy	**Int 1:** 6/69 **Int 2:** 9/76 **Control:** 7/72 **p value:** not significant	Out of 196 patients, 20 had bilateral hip replacement, 1 had both procedures in the same operation, 18 had at least one week between procedures, 1 had bilateral procedure and a revision at a later date. All of these are included in the total to make 217 operations *DVT screened whilst in hospital, symptomatic PE followed for 3 months. **Not reported:** All DVTs, QoL, PTS, survival **Also reported:** Symptomatic DVTs by operation, prothrombin time **Funding:** reports: no commercial funding
								Symptomatic PE Confirmed by ventilation perfusion scan*	**Int 1:** 0/69 **Int 2:** 0/76 **Control:** 1/72 **p value:** not significant	
								Total blood loss (ml)	**Int 1:** 1564 (n = 69) **Int 2:** 1539 (n = 76) **Control:** 1595 (n = 72) **p value:** not significant	
								Total blood replacement (units)	**Int:** 2.8 (n = 69) **Int 2:** 2.7 (n = 76) **Control:** 2.9 (n = 72) **p value:** not significant	
								LoS (days)	**Int:** 9 (n = 69) **Int 2:** 10 (n = 76) **Control:** 9 (n = 72) **p value:** not significant	

Evidence Table 43: Aspirin + IPCD vs LMWH

<table>
<tr><th>Study details</th><th>Patients</th><th>Interventions</th><th>Outcome measures</th><th>Effect size</th><th>Comments</th></tr>
<tr>
<td>Gelfer et al., 2006[220]

Country of study:
Israel

Study design:
RCT

List who was masked to interventions:
Outcome assessors

Evidence level:
1+

Duration of follow-up:
5-8 postoperative day for DVT, 3 months for clinical VTE events</td>
<td>Patient group:
Hip and knee arthroplasty

Setting:
Unclear

Inclusion criteria:
All patients who were scheduled for unilateral primary Total hip or knee arthroplasty.

Exclusion criteria:
• Refusal of consent
• Long term anticoagulant therapy
• Treatment with antiaggregant medication for the last 10 days,
• Known hypersensitivity to contrast medium or aspiring on low molecular weight heparin
• Previously diagnosed VTE
• Concurrent thrombosis process
• Enrolment in another trial

<u>All patients</u>
N: 142 (136 randomised)
Baseline characteristics of 121 patients assessed for DVT
<table>
<tr><th></th><th>Gp1</th><th>Gp2</th></tr>
<tr><td>N</td><td>60</td><td>61</td></tr>
<tr><td>Age (mean):</td><td>67 (8.7)</td><td>68(10.4)</td></tr>
<tr><td>M/F:</td><td>23/37</td><td>21/40</td></tr>
</table>
Additional risk factors:
<table>
<tr><th></th><th>Gp1</th><th>Gp2</th></tr>
<tr><td>Procedure type (Hip)</td><td>40</td><td>33</td></tr>
<tr><td>Duodenal ulcer</td><td>7</td><td>5</td></tr>
<tr><td>Ischaemic heart disease</td><td>12</td><td>5</td></tr>
<tr><td>Hypertension</td><td>26</td><td>26</td></tr>
<tr><td>Diabetes</td><td>10</td><td>3</td></tr>
<tr><td>Malignancy</td><td>8</td><td>5</td></tr>
<tr><td>Other diseases</td><td>35</td><td>30</td></tr>
<tr><td>Smoking</td><td>6</td><td>10</td></tr>
<tr><td>BMI (mean)</td><td>29</td><td>28</td></tr>
</table>
</td>
<td>Group 1
LMWH
(Enoxaparin)
Start time: within 12 hours of operation
End time: unclear – until hospital discharge

Dose, and frequency: 40mg subcutaneously once daily

Group 2
Aspirin plus IPCD
<u>IPCD</u>
Start time: before surgery, immediately after induction of anaesthesia
End time: unclear – until hospital discharge

Length and compression profile:
Hip operation – calf length
Knee operations – foot pumps during operation and then calf length

<u>Aspirin</u>
Start time: within 12 hours of operation
End time: unclear – until hospital discharge

Dose and frequency: 100mg once daily

Additional non-</td>
<td>All cause mortality

Fatal pulmonary embolism

Symptomatic pulmonary embolism (confirmed by: ventilation-perfusion scan 1 month after operation)

DVT, asymptomatic or symptomatic (confirmed by: venography (n=107) or duplex ultrasonography (n=14))

Thigh DVT(confirmed by: venography or duplex ultrasonography)

Fatal bleeding

Major bleeding (description: Wound drainage of >500ml in 72 hours, ≥2 units of blood transfusion (patients transfused when Hb<9g/dL), platelets <100,000)

Length of stay</td>
<td>Group1: 0/68
Group 2: 0/68
P value: NS

Group1: 0/68
Group 2: 0/68
P value: NS

Group1: 1/68
Group 2: 0/ 68
P value: NS

Group1: 17/60
Group 2: 4/61
P value: 0.002*

Group1: 6/60
Group 2: 1/61
P value: 0.061*

Group1: 0/68
Group 2: 0/68
P value: NS

Group1: 43
Group 2: 52
P value: 0.134*

These are number of events, rather than number of patients with events

Group1: 9.1± 2.4 days
Group 2: 8.8 ± 1.9 days
P value: 0.4204#</td>
<td>Funding: No funds were received in support of this study

Limitations:
• Duration of treatment unclear
• Intention to treat analysis was not completed.
• IPCD group had more comorbidity than heparin group, but only reached significance for diabetes.
• Bleeding reported as number of events

Outcomes not reported:
Asymptomatic PE, calf DVT, minor bleeding, heparin induced thrombocytopaenia, post thrombotic syndrome, pulmonary hypertension, quality of life

Additional outcomes reported:
Soft tissue problems, gastrointestinal events, wound infection (no events) elevated temperature >38.5°C, Chest pain, arrhythmia, Dyspnea

Notes:
* Calculated by NCC team using Fisher's Exact test
Calculated by NCC team using unpaired t-test.</td>
</tr>
</table>

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 **No. randomised:** 68 **No. of dropouts:** 8 • 6 refused venography and Doppler scanning • 1 late information about previous VTE • 1 early dislocation requiring revision surgery. **Group 2** **No. randomised:** 68 **No. of dropouts:** 7 • 3 refused venography and Doppler scanning • 1 late information about previous VTE • 3 protocol violation (received enoxaparin and IPCD device)	**comparative prophylaxis:** None mentioned			

Evidence Table 44: UFH + IPCD vs LMWH

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Spinal Cord Injury Thromboprophylaxis Investigators, 2003[616] **Country of study:** Multi-centre study in 27 sites across US & Canada **Study design:** RCT **List who was masked to interventions:** Investigators blinded **Evidence level:** 1+ **Duration of follow-up:** 8 weeks	**Patient group:** Spinal Cord Injury (SCI) **Setting:** Acute SCI treatment unit **Inclusion criteria:** • Age 15 or older • Sustained traumatic SCI from spinal cord level C2 to T12 within previous 72 hours • American Spinal Injury Association (ASIA) classification of A (complete motor or sensory deficit) or B (complete motor and incomplete sensory deficit) or C (incomplete motor deficit and sensory deficit with > half muscles having strength grade <3) **Exclusion criteria:** • Objective evidence of bleeding around spinal cord • Intracranial bleeding • Uncontrolled bleeding at other sites or coagulopathy • GI bleeding within previous 2 weeks • Pregnancy • Conditions precluding use of bilateral IPCD, lower extremity ultrasound or contrast venography • Allergy to sulphating agents, heparin or contrast media • Uncontrolled hypertension • Serum creatinase >2 mg/dL • Requirement for anticoagulation as treatment • Spinal cord surgery planned for 2 weeks after injury • Planned use of aspirin or NSAIDs **<u>All patients</u>** **N:** 476 **Age (mean):** 36.9	**Group 1** Low Dose Heparin 5000 U subcutaneously every 8 hours + various IPCD to be used at least 22 hours/day Start time: within 72 hours of injury **Duration:** 2 weeks **Group 2** LMWH Enoxaparin 30 mg subcutaneously every 12 hours Start time: within 72 hours of injury **Duration:** 2 weeks **Additional non-comparative prophylaxis:** Not Applicable	**All cause mortality** (confirmed by: NR)	**Group1:** 2/246 **Group 2:** 2/230 **P value:**	**Funding:** Rhone-Poulenc Rorer/Aventis Pharmaceuticals manufacturers of enoxaparin **Limitations:** Over 3/4 of patients randomised were excluded from efficacy analysis because they either failed to receive adequate proximal and distal imaging, or discontinued study due to bleeding or platelet counts <100 x 10^9/L .Data collected for 107 (22.5%) patients remaining were reported with similar baseline characteristics. **Outcomes not reported:** Symptomatic PE Thigh DVT, Calf DVT Fatal bleeding, Neurological Bleeding Upper GI bleeding, HIT, Post thrombotic syndrome, Pulmonary hypertension Quality of life, Length of Stay **Additional outcomes reported:** Discontinuations due to bleeding Group 1: 9/246
			Fatal pulmonary embolism (confirmed by: ventilation-perfusion lung scan, spiral CT or pulmonary angiography at 2 weeks or 2 days after last dose)	**Group1:** 0/49 **Group 2:** 0/58 **P value:**	
			Pulmonary embolism, asymptomatic or symptomatic (confirmed by: ventilation-perfusion lung scan, spiral CT or pulmonary angiography at 2 weeks or 2 days after last dose)	**Group1:** 9/49 (18%) **Group 2:** 3/58 (5%) **P value:** 0.03	
			Symptomatic DVT (confirmed by: proximal and distal venography or proximal Doppler Ultrasound 2 weeks or 2 days after last dose)	**Group1:** 1/49 **Group 2:** 1/58 **P value:**	
			DVT, asymptomatic or symptomatic (confirmed by: proximal and distal venography or proximal Doppler Ultrasound 2 weeks or 2 days after last dose)	**Group1:** 22/49 (45%) **Group 2:** 35/58 (60%) **P value:** 0.11	
			Major bleeding (description:)	**Group1:** 13/246 **Group 2:** 6/230 **P value:** 0.14	
			Minor bleeding (description:)	**Group1:** 44/246 **Group 2:** 34/230 **P value:**	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	M/F: 389/87 **Additional risk factors:** ***BMI:*** *25.3 ± 4.9* ***Previous VTE:*** *3/476* ***Active Cancer:*** *3/476* ***Tetraplegia****: 277/476* ***Paraplegia****: 140/476* **Group 1** **No. randomised:** 246 **No. of dropouts:** 2 patients died during treatment phase. 9 discontinued due to bleeding. Dropouts due to other reasons NR **Group 2** **No. randomised:** 230 **No. of dropouts:** 2 patients died during treatment phase. 6 discontinued due to bleeding. Dropouts due to other reasons NR				Group 2: 6/230 Proximal DVT Group 1: 6/92 (7%) Group 2: 8/89 (9%) **Notes:** Randomisation by use of sequential sealed envelopes containing computer generated allocations

Effectivenss - Multiple prophylaxis versus multiple prophylaxis

Evidence Table 45: Fondaparinux adjuvant vs LMWH adjuvant

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Bauer et al., 2001[36]	RCT	1+	**Total:** 1049 **Interventio n** n: 526 **Control** n: 523 **Dropouts (not treated):** Int: 9 Comp: 6 **Dropouts (not available for analysis):** Int: 156 Comp: 154	**Type of surgery:** Patients undergoing elective major knee surgery. Duration of surgery: 128 mins, SD: ±42 **Intervention:** Mean age: 67.5, SD: ±10.7; M/F:204/313 **Control:** Mean age: 67.5, SD: ±10.2; M/F:223/294 **Pre-existing risk Factors:** History of VTE: **Intervention:** 23% **Control:** 28%. Orthopaedic surgery within the previous 12 months: **Intervention:** :87% **Control:**: 27%	2.5 mg of Fondaparinux sodium postoperatively once daily and a placebo once daily subcutaneously till day 5 to 9. Day of surgery is day 1. **Additional non-comparative prophylaxis:** The use of graduated compression stockings and physiotherapy was recommended No. patients receiving/using: GCS = 298/361 Anticoagulant/antiplat elet therapy (not aspirin) = 4/361 NSAIDs or aspirin= 44/361	30 mg of Enoxaparin twice daily postoperatively until day 5 to 9. Day of surgery is day 1. **Additional non-comparative prophylaxis:** The use of graduated compression stockings and physiotherapy was recommended No. patients receiving/using: GCS = 294/363 Anticoagulant/ant iplatelet therapy (not aspirin) = 11/363 NSAIDs or aspirin= 60/363	49 days	**DVT** Confirmed by: systematic bilateral ascending venography	**Int:** 45/361 **Control:** 98/361 **p value:** 0.001; RR: 54.1% (95% CI)	**Funding:** The authors have served as consultants to NV Organon and Sanofi-Synthelabo and the study supported by NVO & SS. ** defined as fatal bleeding; bleeding that was retroperitoneal, intracranial or intraspinal or that involved any other critical organ, bleeding that lead to reoperation; and overt bleeding with index of 2 or more.
								VTE	**Int:** 45/361 **Control:** 101/363 **p value:** <0.001 **Reduction in risk (95% CI)** 55.2 (36.2 to 70.2)	
								Symptomatic DVT	**Int:** 3/517 **Control:** 4/517 **p value:** 1.000	
								Proximal DVT Confirmed by: systematic bilateral ascending venography	**Int:** 9/368 **Control:** 20/372 **p value:** 0.06	
								Non-fatal PE Confirmed by: lung scan, pulmonary angiography or helical computed tomography or at autopsy	**Int:** 1/517 **Control:** 4/517 **p value:** 0.3738	
								Fatal PE Confirmed by:	**Int:** 0/517 **Control:** 0/517 **p value:** N/A	
								Major bleeding **	**Int:** 11/517 **Control:** 1/517 **p value:** 0.003	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
								Bleeding leading to re-operation	**Int:** 2/517 **Control:** 1/517 **p value:** 1.000	
								Other bleeding – number (%)	**Int:** 14/517 **Control:** 19/517 **p value:** 0.4797	
								Postoperative transfusions – number (%)	**Int:** 222/517 **Control:** 197/517 **p value:** 0.1284	
								Death from any cause - number (%) Up to day 11	**Int:** 1/517 **Control:** 2/517 **p value:** 1.0000	
								Death from any cause - number (%) Up to day 49	**Int:** 2/517 **Control:** 3/517 **p value:** 1.0000	

Fondaparinux adjuvant vs LMWH adjuvant

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Eriksson et al., 2001[175]	RCT	1+	Total: 1711 Intervention: 849 Control n: 862 **Dropouts (not treated):** Int: 18 Comp: 20 **Dropouts (not available for analysis):** Int: 205 Comp: 218	**Type of surgery:** Patients scheduled to undergo standard surgery for fracture of the upper third of femur, including femoral head and neck within 48 hours of admission. Duration of surgery: 104 mins, SD: ±44 **Intervention:** Mean age: 76.8, SD: ±12.3; M/F:187/644 **Control:** Mean age: 77.3, SD: ±12.6; M/F:224/698 **Pre-existing risk factors:** History of VTE: **Intervention:** 29 (3.5%) **Control:** 32 (3.8%). Orthopaedic surgery within the previous 12 months: **Intervention:** 33 (4.0%) **Control:**: 26 (3.1%)	2.5 mg of Fondaparinux sodium and a placebo. The first active dose was given 6±2 hrs postoperatively and the second 12 or more after the first. Treatment was scheduled to continue until day 5 to 9. Day of surgery is day 1. **Additional non-comparative prophylaxis:** The use of graduated compression stockings and physiotherapy was recommended No. patients receiving/using: GCS = 312/626 Anticoagulant/antiplatelet therapy (not aspirin = 23/626 NSAIDs or aspirin = 141/626	40 mg of Enoxaparin 1x/day and placebo. The first active dose was given 12±2 hrs preoperatively and the second 12 to 24 hours postoperatively. Treatment was scheduled to continue until day 5 to 9. Day of surgery is day 1. **Additional non-comparative prophylaxis:** The use of graduated compression stockings and physiotherapy was recommended No. patients receiving/using: GCS = 295/624 Anticoagulant/antiplatelet therapy (not aspirin) = 21/624 NSAIDs or aspirin = 126/624	49 days	**DVT** Confirmed by: systematic bilateral ascending venography	**Int:** 49/624 **Control:** 117/623 **p value:** <0.001; RR: 58.2% (95% CI)	**Funding:** The authors have served as consultants to NV Organon and Sanofi-Synthelabo and the study supported by NVO & SS. ** defined as fatal bleeding; bleeding that was retroperitoneal, intracranial or intraspinal or that involved any other critical organ, bleeding that lead to reoperation; and overt bleeding with index of 2 or more.
								VTE	**Int:** 52/626 **Control:** 119/624 **p value:** < 0.001 **Reduction in risk (95 % CI)** 56.4 (39.0 to 70.3)	
								Symptomatic DVT	**Int:** 1/831 **Control:** 1/840 **p value:** 1.000	
								Proximal DVT* Confirmed by: systematic bilateral ascending venography	**Int:** 6/650 **Control:** 28/646 **p value:** <0.001	
								Non fatal PE Confirmed by: lung scan, pulmonary angiography or helical computed tomography or at autopsy	**Int:** 1/831 **Control:** 1/840 **p value:** 1.000	
								Fatal PE Confirmed by:	**Int:** 2/831 **Control:** 2/840 **p value:** 1.000	
								Major bleeding **	**Int:** 18/831 **Control:** 119/842 **p value:** 0.52	
								Fatal bleeding	**Int:** 0/831 **Control:** 1/842 **p value:** 1.000	
								Bleeding leading	**Int:** 3/831	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
								to re-operation	**Control:** 2/842 **p value:** 0.6851	
								Minor bleeding – number (%)	**Int:** 34/831 **Control:** 18/842 **p value:** 0.0240	
								Postoperative transfusions – number (%)	**Int:** 421/831 **Control:** 422/842 **p value:** 0.8450	
								Death from any cause - number (%) Up to day 11	**Int:** 11/831 **Control:** 16/842 **p value:** 0.4386	
								Death from any cause - number (%) Up to day 49	**Int:** 38/831 **Control:** 42/842 **p value:** 0.7317	

Fondaparinux adjuvant vs LMWH adjuvant

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Lassen et al., 2002[377]	RCT	1+	**Total:** 2309 **Intervention** n: 1155 **Control** n: 1154 **Dropouts (not treated):** Int: 15 Comp: 21 **Dropouts (not available for analysis):** Int: 232 Comp: 214	**Type of surgery:** Patients scheduled for primary elective total hip-replacement surgery or revision of at least one component of a previously implanted total hip prosthesis. Duration of surgery: 2.4 hours, SD: ±0.83 **Intervention:** Mean age: 67, range: 30-90; M/F:396/512 **Control:** Mean age: 67, range: 24-97; M/F:402/517 **Pre-existing risk factors:** History of VTE: **Intervention:** 35 (4%) **Control:** 40 (4%). Orthopaedic surgery within the previous 12 months: **Intervention:** 85 (9%) **Control:** 84 (9%)	2.5 mg of Fondaparinux sodium and a placebo. The first active dose was given 6±2 hrs postoperatively and the second 12 or more after the first. Treatment was scheduled to continue until day 5 to 9. Day of surgery is day 1. **Additional non-comparative prophylaxis:** The use of graduated compression stockings and physiotherapy was recommended No. patients receiving/using: GCS = 649/908 Anticoagulant/antiplatelet therapy (not aspirin = 29/908 NSAIDs or aspirin: 483/908	40 mg of Enoxaparin 1x/day and placebo. The first active dose was given 12±2 hrs preoperatively and the second 12 to 24 hours postoperatively. Treatment was scheduled to continue until day 5 to 9. Day of surgery is day 1. **Additional non-comparative prophylaxis:** The use of graduated compression stockings and physiotherapy was recommended No. patients receiving/using: GCS = 654/919 Anticoagulant/antiplatelet therapy (not aspirin) = 30/919 NSAIDs or aspirin: 493/919	49 days study period 11 days	**DVT** Confirmed by: systematic bilateral ascending venography (number of events/ total number)	**Int:** 36/908 **Control:** 83/918 **p value:** <0.0001; RRR:- 56.1% (95% CI)	**Funding:** study supported by NV Organon and Sanofi-Synthelabo. * ** defined as fatal bleeding; bleeding that was retroperitoneal, intracranial or intraspinal or that involved any other critical organ, bleeding that lead to reoperation; and overt bleeding with index of 2 or more.
								VTE	**Int:** 37/908 **Control:** 85/919 **p value:** < 0.0001 **RRR (95 % CI) -** 55.9 (-72.8 to -33.1)	
								Symptomatic DVT	**Int:** 3/1129 **Control:** 1/1123 **p value:** 0.6247	
								Proximal DVT * Confirmed by: systematic bilateral ascending venography	**Int:** 6/922 **Control:** 23/927 **p value:** 0.002	
								Non fatal PE Confirmed by: lung scan, pulmonary angiography or helical computed tomography or at autopsy	**Int:** 2/1129 **Control:** 2/1123 **p value:** 1.000	
								Fatal PE Confirmed by:	**Int:** 0/1129 **Control:** 0/1123 **p value:** N/A	
								Major bleeding **	**Int:** 47/1140 **Control:** 32/1133 **p value:** 0.57	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
								Fatal bleeding	**Int:** 0/1140 **Control:** 0/1133 **p value:** N/A	
								Bleeding leading to re-operation	**Int:** 5/1140 **Control:** 3/1133 **p value:** 0.7261	
								other bleeding – number (%)	**Int:** 44/1140 **Control:** 38/1133 **p value:** 0.5743	
								Postoperative transfusions – number (%)	**Int:** 714/1140 **Control:** 690/1133 **p value:**	
								Death from any cause - number (%) Up to day 11	**Int:** 0/1140 **Control:** 2/1133 **p value:** 0.4122	
								Death from any cause - number (%) Up to day 49	**Int:** 2/1140 **Control:** 4/1133 **p value:** 0.4122	

Fondaparinux adjuvant vs LMWH adjuvant

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Turpie et al., 2002[651]	RCT	1+	**Total:** 2275 **Intervention** n: 1138 **Control** n: 1137 **Dropouts (not treated):** Int: 10 Comp: 8 **Dropouts (not available for analysis):** Int: 341 Comp: 332	**Type of surgery:** Patients scheduled for primary elective total hip-replacement surgery or revision of at least one component of a previously implanted total hip prosthesis. Duration of surgery: 2.42 hours, SD: ±0.98 **Intervention:** Mean age: 67, range: 26-92; M/F:386/401 **Control:** Mean age: 67, range: 19-91; M/F:375/422 **Pre-existing risk factors:** History of VTE: **Intervention:** 40 (5%) **Control:** 50 (6%). Orthopaedic surgery within the previous 12 months: **Intervention:** 99 (13%) **Control:** 84 (11%)	2.5 mg of Fondaparinux sodium and a placebo. The first active dose was given 4-8 hrs after surgery and the second 12 or more after the first. Treatment was scheduled to continue until day 5 to 9. Day of surgery is day 1. **Additional non-comparative prophylaxis:** The use of graduated compression stockings and physiotherapy was recommended No. patients receiving/using: GCS = 674/787 Anticoagulant/antiplatelet therapy (not aspirin) = 13/787 NSAIDs or aspirin = 107/787	30 mg of Enoxaparin twice daily. The first active dose was given 4-8 hrs after surgery and the second 12 or more after the first. Treatment was scheduled to continue until day 5 to 9. Day of surgery is day 1. **Additional non-comparative prophylaxis:** The use of graduated compression stockings and physiotherapy was recommended No. patients receiving/using: GCS = 676/797 Anticoagulant/antiplatelet therapy(not aspirin) = 11/797 NSAIDs or aspirin = 108/797	49 days study period 11 days	**DVT** Confirmed by: systematic bilateral ascending venography	**Int:** 44/784 **Control:** 65/796 **p value:** <0.047; RRR:- 31.3% (95% CI)	**Funding:** study supported by NV Organon and Sanofi-Synthelabo. ** defined as fatal bleeding; bleeding that was retroperitoneal, intracranial or intraspinal or that involved any other critical organ, bleeding that lead to reoperation; and overt bleeding with index of 2 or more.
								VTE	**Int:** 48/787 **Control:** 66/797 **p value:** 0.099 **RRR (95 % CI) -** 26.3 (-52.8 to -10.8)	
								Symptomatic DVT	**Int:** 5/1126 **Control:** 0/1128 **p value:** 0.0310	
								Proximal DVT* Confirmed by: systematic bilateral ascending venography	**Int:** 14/816 **Control:** 10/830 **p value:** 0.42	
								Non fatal PE Confirmed by: lung scan, pulmonary angiography or helical computed tomography or at autopsy	**Int:** 5/1126 **Control:** 0/1128 **p value:** 0.0310	
								Fatal PE Confirmed by:	**Int:** 0/1126 **Control:** 1/1128 **p value:** 1.0000	
								Major bleeding **	**Int:** 20/1128 **Control:** 11/1129 **p value:** 0.73	
								Fatal bleeding	**Int:** 0/1128 **Control:** 0/1129 **p value:** 1.0000	
								Bleeding leading	**Int:** 2/1128	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
								to re-operation	**Control:** 2/1129 **p value:** 1.0000	
								Other bleeding – number (%)	**Int:** 17/1128 **Control:** 24/1129 **p value:** 0.3447	
								Postoperative transfusions – number (%)	**Int:** 593/1128 **Control:** 555/1128 **p value:** 0.1192	
								Death from any cause - number (%) Up to day 11	**Int:** 3/1128 **Control:** 1/1129 **p value:** 0.3744	
								Death from any cause - number (%) Up to day 49	**Int:** 6/1128 **Control:** 3/1129 **p value:** 0.3427	

Evidence Table 46: LMWH adjuvant vs UFH adjuvant

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Farkas et al 1993[181]	RCT	1+	**Total:** 233 Intervention: n = 122 Control: n = 111 269 patients randomised, 36 excluded	**Type of surgery:** Vascular surgery – aortic or aortoiliac and aneurysmectomy; aorto-femoral bypass for atherosclerotic disease; and femoropopliteal or femorodistal bypass.	**Type:** LMWH (Enoxaparin) **Dose:** 2100 IU pre-op, then 4200 IU	**Type:** Unfractionated heparin **Dose:** 5000 units pre-op, 7500 units post-op	1 month	**DVT** Confirmed by: Duplex US, confirmed by venography on 7th-10th day post-op. Earlier if clinical suspicion	**Int:** 10/122 **Control:** 4/111 **p value:** Not significant)	**Comments:** Numbers in each group for baseline data do not tally with text. Arterial patency also assessed by duplex US scanning. No significant differences observed between groups in terms of development of post-op arterial thrombosis. **Thrombocytopenia** (which resolved spontaneously within 3 days) reported in 2 LMWH patients. **Not reported:** PVT, PTS, QoL, LoS, **Funding**: Trial supported by grant from Labaratoires Pharmuka, France.
				Mean duration of surgery: Intervention: 4.2±1.4 h Control: 4.2±1.5h	**Timing:** Begun day pre-op and repeatedly daily until 7th day post-op	**Timing:** Begun day pre-op and repeated twice daily until 7th day post-op		**PE** Confirmed by: Clinical suspicion investigated by angiogram	**Int:** 0/122 **Control:** 0/111 **p value:** N/A	
				Intervention: Mean age: 65±11 yrs M/F:101/25	**Additional non-comparative prophylaxis:** Intraoperative use of UFH (94.4%) or protamine (7.9%) was authorised in both groups	**Additional non-comparative prophylaxis:** Intraoperative use of UFH (97.4%) or protamine (9.4%) was authorised in both groups		**Preoperative red blood cell units**	**Int:** 3.91±2.79 units **Control:** 3.61±1.91 **p value:** Not significant	
				Control: Mean age: 64±11 yrs M/F:99/18				**Post-operative suction drain volume**	**Int:** 423±438ml **Control:** 408±455ml **p value:** Not significant	
				Pre-existing risk factors: Past history of VTE, age, obesity, varicose veins, COPD (no significant diffs between groups apart from COPD – more in LMWH group, p=0.02).				**Survival**	**Int:** 120 /122 **Control:** 111/111 **p value:** not reported	

LMWH adjuvant vs UFH adjuvant

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Faunø et al 1994[183]	RCT	1+	**Total:** 185 Intervention: n = 92 Control: n = 93 224 patients randomised. 39 excluded (16 LMWH, 23 UH)	**Type of surgery:** Unilateral knee replacement **Duration of operation:** Intervention: 102±24 min Control: 104±20 **Intervention:** Mean age: 70±10 yrs M/F:38/55 **Control:** Mean age: 71±11 M/F:35/57 **Pre-existing risk factors:** Not reported	**Type:** LMWH (Enoxaparin) **Dose:** 40 mg **Timing:** Begun evening pre-op and repeated daily until 7-10th day post-op. **Additional non-comparative prophylaxis:** Short compression stocking on involved limb and long compression stocking on uninvolved limb.	**Type:** UH **Dose:** 5000 IU **Timing:** Begun evening pre-op and repeated 3 times daily until 7-9th day post-op. **Additional non-comparative prophylaxis:** Short compression stocking on involved limb and long compression stocking on uninvolved limb.	2 months	**DVT** Confirmed by: bilateral ascending venography on 7-9th day post-op	**Int:** 21/92 **Control:** 25/93 **p value:** 0.6 Not significant	**Also reported:** total blood loss, decrease in haemoglobin levels, transfusion requirements
								PVT Confirmed by: bilateral ascending venography on 7-9th day post-op	**Int:** 3/92 **Control:** 5/93 **p value:** Not reported	
								PE Confirmed by: Not routinely assessed. Clinical suspicion investigated with V/Q scan	**Int:** 0/92 **Control:** 0/93	
								Wound haematoma	**Int:** 8/92 **Control:** 12/93 **p value:** 0.5	

LMWH adjuvant vs UFH adjuvant

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Goldhaber et al., 2002[225]	RCT	1+	**Total:** 150 Intervention : n = 75 (DVT assessed in) Control: n = 75 (DVT assessed in)	**Type of surgery:** Patients undergoing craniotomy with suspected or metastatic brain tumour Excluded people with a history of overt bleeding, heparin allergy or VTE within the prior 6 months **Intervention:** Mean age: 48.33 (±15.07) yrs M/F:39/36 **Control:** Mean age: 48.87 (±12.52) yrs M/F:40/35 **Pre-existing risk factors:** not reported	**Type:** LMWH (Enoxaparin) **Dose:** 40mg/ in the morning, placebo in the evening **Timing:** Begun morning of 1st postoperative day and continued until discharge or VTE diagnosed. **Additional non-comparative prophylaxis:** graduated compression stockings (73/75 participants) intermittent pneumatic compression devices (72/75 participants)	**Type:** UFH **Dose:** 5000 IU twice per day **Timing:** Begun morning of 1st postoperative day and continued until discharge or VTE diagnosed. **Additional non-comparative prophylaxis:** graduated compression stockings (72/75 participants) intermittent pneumatic compression devices (71/75 participants)	**30 days**	**DVT** Confirmed by duplex ultrasonography	**Int:** 9/75 **Control:** 5/75 **p value:** 0.401	Patients scanned one day prior to, or on day of discharge **Funding** Research grant from Aventis **Not reported:** PTS, QoL
								Symptomatic DVT Confirmed by duplex ultrasonography	**Int:** 0/75 **Control:** 0/75 **p value:** not sig	
								Proximal DVT Confirmed by duplex ultrasonography	**Int:** 2/75 **Control:** 2/75 **p value:** 1	
								Unilateral calf DVT Confirmed by duplex ultrasonography	**Int:** 6/75 **Control:** 2/75 **p value:** 0.276	
								Bilateral calf DVT Confirmed by duplex ultrasonography	**Int:** 1/75 **Control:** 1/75 **p value:** 1	
								Major postoperative bleeding complications	**Int:** 2/75 **Control:** 1/75 **p value:** 0.57	
								Length of stay	**Int:** 6.07 ±3.56 days **Control:** 5.75 ±3.24 days **p value:** 0.566	
								Mortality	**Int:** 0/75 **Control:** 0/75 **p value:** not sig	

LMWH v UFH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Haas et al., 2005[244]	RCT	1+	**Total:** 23,078 Intervention : n = 11,542 60 did not undergo surgery but were included in the analysis as part of an intention to treat analysis Control: n = 11,536 44 did not undergo surgery but were included in the analysis as part of an intention to treat analysis	**Type of surgery:** Mixed: patients over 40 undergoing surgery not less than 30 minutes between 1991 and 1996 at 67 centres in Germany, Austria and the Czech Republic Procedure: General: 17,057 Gynaecology: 2351 Traumatology: 1580 Orthopaedics: 1425 Urology: 402 Other: 159 No surgery: 104 Exclusion criteria: severe hypertension imparied renal or hepatic function; any haemostatic or bleeding disorder; previous inclusion in a trial within the preceding 4 weeks; pregnancy; lactation or known contraindication to heparin. **Age & Gender: Intervention:** Median age: 58 yrs M/F: 5021/6521	**Type:** LMWH (Centoparin) **Dose:** 3000 anti Xa IU subcutaneously once per day plus placebo injections **Timing:** Begun not less than 2 hours prior to surgery and continued for a minimum of 5 days and maximum of 20 days. **Additional non-comparative prophylaxis:** Other drugs known to alter blood coagulation were restricted and only prescribed if unavoidable. Treatments such as GCS and other types of physiotherapy were used according to normal practice at those centres. Spinal anaesthesia: 1153/11542 Epidural anaesthesia: 65/11542	**Type:** LDUH **Dose:** 5000 IU subcutaneously 3 times per day **Timing:** Begun not less than 2 hours prior to surgery and continued for a minimum of 5 days and maximum of 20 days. **Additional non-comparative prophylaxis:** Other drugs known to alter blood coagulation were restricted and only prescribed if unavoidable. Treatments such as GCS and other types of physiotherapy were used according to normal practice at those centres. Spinal anaesthesia: 1086/11536 Epidural anaesthesia: 63/11536	14 days	**Fatal pulmonary embolism*** confirmed by autopsy.	**Int:** 17/11,542 **Control:** 18/11,536 **p value:** 1.0	**Comments:** * PE regarded as primary cause of death if autopsy revealed obstruction of the pulmonary trunk or fesh emboli in either two pulmonary arteries or two lobar arteries. **Not reported:** DVT, Proximal DVT, symptomatic PE, PTS, QoL, LoS **Also reported:** incidence of fatal PE and death by surgical procedure; blood loss in drainage tubes; no. of patients requiring and volume of blood transfusion,
								Mortality	**Int:** 166/11,542 **Control:** 146/11,536 **p value:** 0.28	
								No. of deaths having an autopsy	**Int:** 114/166 (68.7%) **Control:** 105/146 (71.9%)	
								Thrombocytopenia (not stated how confirmed)	**Int:** 21/11,542 **Control:** 16/11,536 **p value:** not sig	
								Bleeding complications	**Intervention group:** Postop wound bleeding: 34 Haemorrhagic stroke: 10 Gastric bleeding: 2 Intestinal bleeding: 4 Abnormal uterine bleeding: 1 **Comparison group:** Postop wound bleeding: 35 Haemorrhagic stroke: 7 Gastric bleeding: 7 Intestinal bleeding: 3 Abnormal uterine bleeding: 2	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
				Control: Median age: 58 yrs M/F: 4995/6541						

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Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Haas et al., 2006[242] (ECHOS trial) **Country of study:** Multicentre study: Europe **Study design:** RCT **List who was masked to interventions:** Double-blind study **Evidence level:** 1+ **Duration of follow-up:** 6-8 weeks after discharge (9-10 weeks in a proportion of cases).	**Patient group:** Patients undergoing elective total hip *(THR)-68.3%* or knee replacement *(TKR)-31.7%* **Setting:** Multinational study **Inclusion criteria:** Patients ≥40 years undergoing THR or TKR, whose projected hospital stay was al least 11 days. **Exclusion criteria:** ▪ Previous history of VTE ≤ 6 months ▪ a positive D-dimer bedside test (SimpliRed) or any signs of acute thrombosis ▪ body weight of < 45 kg or > 100 kg ▪ known contraindications to heparin ▪ allergy to contrast media ▪ congenital or acquired hemorrhagic diathesis ▪ thrombocytopenia (platelets < 100000 per cubic milimiter) ▪ macroscopic haematuria ▪ myocardial infarction ▪ cerebrovascular stroke ▪ intracranial or intraocular bleeding within past 6 months ▪ active peptic ulcer, other gastro-duodenal bleeding within past 6 months ▪ active advanced malignant disease ▪ impaired liver or renal function; nephritic syndrome ▪ uncontrolled hypertension ▪ Taking anticoagulants, platelet aggregation inhibitors (except for aspirin < 300 mg per day) up to 8 days before surgery ▪ Pregnant, breastfeeding, <6 months postpartum ▪ Childbearing potential, not taking contraceptive precautions	**Group1:** **LMWH** Reviparin 4200 IU once daily + one placebo injection **Group 2:** **UFH** 7500 IU subcutaneous bd Start: Evening before surgery, administered the following day 6-8 h after surgery and given at 6-8 a.m. and 6-8 p.m. on subsequent days. Duration: 11 to 14 days, until venography was performed. **Additional non-comparative prophylaxis:** ▪ All thromboprophylactic medication was withdrawn before treatment initiation. Aspirin <300mg/day allowed ▪ Postopreative NSAIDS allowed ▪ Mechanical methods e.g. GCS, physiotherapy, early mobilization, were routinely provided. ▪ Additional thrombophrophylaxis (e.g. sequential intermittent pneumatic compression) was	**All cause mortality:**	Until Day 11-14 **Group 1;**2/813 **Group 2:** 2/815 **P value:** 1.00* (Two patients died of acute myocardial infarction (one in each group), one due to a fatal PE (UFH) and one due to sudden cardiac arrest (LMWH) Information from text (page 338)	**Funding:** Supported by Abbott GmbH & Co. KG, Ludwigshafen, Germany. **Limitations:** ▪ Reporting quality - discrepancy in numbers of deaths in table vs text **Outcomes not reported:** Symptomatic DVT Length of stay Quality of life Pulmonary hypertension Post thrombotic syndrome **Additional outcomes reported:** • % of patients using general vs regional anasthesia • Serious adverse events • Mean changes between baseline and discharge values for liver enzymes/ **Notes:** % of patients not evaluated for efficacy =19.2%
			Fatal pulmonary embolism (confirmed by: autopsy)	**Group 1;**0/813 **Group 2:** 1/815 **P value:** 1.00*	
			Symptomatic pulmonary embolism (confirmed by: Possible PE was assessed by ventilation- perfusion lung scan, pulmonary angiography, or by autopsy))	Events until day 11-14 **Group1:**1/813 (0.1%) **Group 2:** 1/815 (0.1%) **P value:** 1.00* "Three patients were confirmed to have PE between days 15 and 68 including two patients who had previously experienced a DVT"- treatment arm not stated	
			DVT, asymptomatic or symptomatic. Screened by systematic bilateral ascending contrast venography between days 11-14 after surgery or earlier if clinical signs of DVT occurred. VTE during follow-up was determined by clinical symptoms and confirmatory venography.	**All patients** **Group1:**200/813 (24.6%) **Group 2:** 204/815 (25%) **P value:** 0.86* **THR patients** **Group1:**87/494 **Group2:** 81/495 **P value:** 0.61* **TKA patients** **Group 1:** 113/319 **Group 2:** 124/320 **P value:** 0.41*	
			Thigh DVT(screened for by: Proximal DVT was defined as an intraluminal defect proximal to the knee joint space on venograms)	**Group1:**25/813 (3.1%) **Group 2:** 42/815 (5.2%) **P value:** 0.045* **THR patients** **Group1:**19/494 **Group2:** 31/495	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	▪ Drugs or alcohol abuse ▪ Participated in investigational drug studies within 4 weeks prior to study entry. **<u>All patients</u>** **N:** 2018 **THR:** 1233 **TKR:** 782 **<u>Group 1 ; LMWH</u>** **No. randomised:** 1013 **No. of dropouts:** n=1 not included in safety outcomes n=200 not evaluated for efficacy outcomes **THR (n):** 620 (61.3 %) **TKR (n):** 392 (38.7%) **General anesthesia (%):**61.3% **Cement prosthesis (n):** 678 (67%) **Duration of surgery (min)- median (range):** 85 (30-320) **Age mean (+/- SD):** 66.1 +/- 9.3 **Weight (kg):** 76.6 +/- 12.1 **Height (cm):** 165.8 +/- 8.3 **Female (n):** 676 (66.8%) **BMI (kg/m²):**27.8 +/- 3.8 **<u>Group 2: UFH up</u>** **No. randomised:** 1005 **No. of dropouts:** n=2 not included in safety outcomes n= 190 not evaluated for efficacy outcomes **THR (n):** 613 (61.1%) **TKR (n):** 390 (38.9%) **Duration of surgery (min)- median (range):** 85 (28-260) **General anaesthesia (%):** 60.9% **Cement prosthesis (n):** 692 (69%) **Age mean (+/- SD):** 66.9 +/- 9.8 **Weight (kg):**77 +/- 12.4 **Height (cm):**166.3 +/- 8.45 **Female (n):**655 (65.3%) **BMI (kg/m²):** 27.8 +/- 3.9	excluded.		**P value:** 0.11* **TKA patients** **Group 1:** 6/319 **Group 2:** 114/320 **P value:** 0.33*	
			Calf DVT (screened for by: systematic bilateral ascending contrast venography between days 11-14 after surgery or earlier if clinical signs of DVT occurred)	**Distal DVT:** **Group1:**175/813 (21.5%) **Group 2:** 162/815 (19.9%) **P value:** 0.43* **THR patients** **Group1:** 68/494 **Group2:** 50/495 **P value:** 0.08* **TKA patients** **Group 1:** 107/319 **Group 2:** 112/320 **P value:** 0.08*	
			Fatal bleeding (description: Bleedings and death reported but no mention of fatal bleeding)	**Group1:** 0/1012 **Group 2:** 0/1003 **P value:** 1.0*	
			Major bleeding (description: any severe overt bleeding; associated with a Hb drop ≥2g/dL within 24 h of the 1st postoperative day, transfusion of > 1500 mL of whole blood (except autologus transfusion); sero-sanguinous secretion at the wound site after day 6; hemorrhage requiring re-intervention and any retroperitoneal or intracranial haemorrhage or warranting permanent treatment cessation)	**Major bleeding (during treatment period day 1-14)** **Group1:**9/1012 (0.9%) **Group 2:** 12/1003 (1.2%) **P value:** 0.52*	
			Minor bleeding (description: small wound hematoma, wound oozing or hematoma not at the operation area,	**Group1:**38/1012 (3.8%) **Group 2:** 29/1003 (2.9%) **P value:** 0.32*	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
			decreases of postoperative Hb concentration in the expected range and transfusion requirements within the normal range)		
			Heparin induced thrombocytopaenia	**Group1:**0/1012 (0%) **Group 2:** 0/1003 (0%) **P value:** 1.00*	

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Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Kleber et al., 2003[350] (The PRINCE study) **Country of study:** Germany **Study design:** Multicentre RCT, open label study **List who was masked to interventions:** Open label study. Central reviewers of efficacy end points (interpreting the screening tests and assessment of venous thromboembolic events) were masked. **Evidence level:** 1+ **Duration of follow-up:** 10±2 days	**Patient group:** Heart failure (n=333)and respiratory disease(n=332) patients **Setting:** inpatient **Inclusion criteria:** ▪ Aged ≥18 ▪ Hospitalised for severe respiratory disease (based on lung function test or blood gas analyses outside normal range and at ≥1 of these: severe functional loss ≥2 lung segments, severe secondary pulmonary hypertension, pneumonia, interstitial lung disease, lung cancer and/or metatstases with life expectancy > 2 months, or exacerbation of COPD)or heart failure (class III or IV according to New York Heart Association classification) ▪ Confined to bed >2/3 of the time **Exclusion criteria:** ▪ Advanced acquired immunodeficiency syndrome ▪ Contraindication to LMWH or UFH ▪ Hypersensitivity to contrast media ▪ Severe hepatic, pancreatic or renal disease, arterial hypertension ▪ Intracranial bleeding or haemorrhagic stroke in the preceding 6 months ▪ Ocular ocr CNS surgery in the preceding 4 weeks ▪ Coagulation disorders ▪ Drug/alcohol abuse ▪ Acute signs of DVT or PE ▪ Gastrointestinal ulcer ▪ Immobilised for > 24 hours before enrolment ▪ Patients on anticoagulants or platelet inhibitors, or NSAIDs. However, heart failure patients allowed 100mg aspirin **<u>All patients</u>**	**Group 1** UFH 5000IU 3 times daily, subcutaneously **Group 2** Enoxaparin 40mg once daily, subcutaneously Start time: Day 1(on enrolment day) Duration: 10±2 days **Additional non-comparative prophylaxis:** ▪ Patients on anticoagulants or platelet inhibitors, or NSAIDs. However, heart failure patients allowed 100mg aspirin ▪ Compression stockings applied up to 20% of patients in each treatment group	**All cause mortality** (confirmed by:)	**Group1:** 15/333 **Group 2:** 9/ 332 **P value:**	**Funding:** Aventis Pharma **Limitations:** ▪ Open label study ▪ More patients with malignancy in the enoxaparin group **Outcomes not reported:** Symptomatic DVT Calf DVT Fatal bleeding Neurological bleeding Upper GI bleeding Heparin induced thrombocytopaenia PTS, Pulmonary hypertension QoL, LOS **Additional outcomes reported:** **Notes:**
			Fatal pulmonary embolism (confirmed by: Autopsy. 1 heart failure patient in UFH group had both PE and DVT)	**Group1:** 1/212 **Group 2:** 0/239 **P value:**	
			Symptomatic pulmonary embolism (confirmed by: perfusion scintigram)	**Group1:** 0/212 **Group 2:** 1/239 **P value:**	
			DVT, asymptomatic or symptomatic (confirmed by: patients with positive D dimmer or fibrin monomer test underwent bilateral venography. Autopsy) 1 heart failure patient in UFH group had both PE and DVT	**By D-dimer test** **Group1:** 86/212 **Group 2:** 84/236 **P value:** By Venography/autopsy, including venogram conducted >24 hours after last dose **Group1:** 28/235 **Group 2:** 26/264 **P value:** By Venography/autopsy, in primary efficacy population **Group1:** 22/212 **Group 2:** 19/239 **P value:** **<u>In heart failure patients:</u>** By Venography/autopsy **Group1:** 15/93 **Group 2:** 11/113 **P value:** **<u>In respiratory failure patients</u>** By Venography/autopsy **Group1:** 7/119 **Group 2:** 8/126 **P value**	
			Thigh (Proximal)DVT(confirmed by:)	**Group1:** 4/ 212 **Group 2:** 9/ 239 **P value:**	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No randomised: 668 (3 withdrawn before receiving any study medication) **No. of dropouts:** 214/665 **Age (mean):** 70±14 **Risk Factors** **Gp1** **Gp2** Immobilisation 332 333 Congestive heart failure 186 186 Age >70yr 185 187 COPD 134 142 Venous Disease 137 129 Overweight 104 98 Diabetes Mellitus 101 104 Severe infection 61 56 Pervious myocardial infarction 41 41 Pre-existing malignancy 25 16 Dehydration 15 23 History of DVT 20 19 **Group 1** **No. randomised: 333** **M/F:183/150** No evaluated: 212 Severe respiratory disease:164 Heart failure:169 **Group 2** **No. randomised: 332** **M/F:160/172** No evaluated: 239 Severe respiratory disease:168 Heart failure:164		**Major bleeding** (description: 1 urogenital –enoxaparin and 1 haemorrhoidal-UFH. Defined as retroperitoneal or intracranial bleeding, overt bleeding with Hb)	**Group1:** 1/333 **Group 2:** 1/332 **P value:**	
			Minor bleeding (description:)	**Group1:** 11/333 **Group 2:** 4/332 **P value:**	

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Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Macdonald et al., 2003[415]	RCT	1+	**Total:** 100 Intervention : n = 51 Control: n = 49	**Type of surgery:** Patients undergoing craniotomy for brain neoplasm, including trans-sphenoidal surgery, intracranial aneurysm, vascular malformation, infection, spontaneous intracranial hematoma, closed head injury or cortical resection for epilepsy. **Age & Gender:** **Intervention:** Mean age: 51 ±15 yrs M/F:23/28 **Control:** Mean age: 49 ±15 yrs M/F: 23/26	**Type:** LMWH (Dalteparin) **Dose:** 2500 IU once per day **Timing:** Begun at time of surgery and continued for 1 week **Additional non-comparative prophylaxis:** Thigh length intermittent pneumatic compression devices worn from time of admission until discharge or the patient was ambulatory for more than 3 hours per day.	**Type:** LDUH **Dose:** 5000 IU twice per day **Timing:** Begun at time of surgery and continued for 1 week **Additional non-comparative prophylaxis:** Thigh length intermittent pneumatic compression devices worn from time of admission until discharge or the patient was ambulatory for more than 3 hours per day.	1 month	**DVT** Confirmed by: Doppler US (on 7th post-op day?)	**Int:** 2/51 **Control:** 0/49 **p value:** 0.30	**Comments:** Excluded patients with VTE, thrombocytopenia, abnormal prothrombin time, abnormal partial thromboplastin time, abnormal bleeding time, history of hypersensitivity to heparin or pork products, penetrating head injury or pregnancy. **Not reported:** Proximal DVT, PTS, QoL, LoS **Also reported:** anaesthesia time; blood loss; no. of patients requiring intraoperative transfusion, surgeon's impression of haemostasis, no. of patients requiring erythrocyte transfusion
								Symptomatic pulmonary embolism confirmed by ventilation perfusion scan or spiral CT.	**Int:** 0/51 **Control:** 0/49 **p value:** not sig	
								Intracranial haemorrhage confirmed by CT scan and MRI	**Int:** 2/51 **Control:** 1/49 **p value:** 0.59	
								Thrombocytopenia	**Int:** 2/51 **Control:** 0/49 **p value:** 0.30	
								Mortality	**Int:** 0/51 **Control:** 1/49 **p value:** 0.48	

LMWH adjuvant vs UFH adjuvant

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Ward & Pradhan, 1998[670]	RCT	+	Total: 552 Intervention n:271 Control n: 281	**Type of surgery:** Women undergoing major gynaecological surgery. **Intervention:** Mean age: 55 ± 17 years **Control:** Mean age: 55 ± 16 years **Pre-existing risk factors:** Previous VTE: presence indicated but no figures are given Malignant disease: **Int:** n = 222 **Control:** n = 239 Radical surgery: **Int:** n = 208 **Control:** n = 222 Non radical surgery: **Int:** n = 63 **Control:** n = 59	**Type, dose and timing:** One dose daily of subcutaneous 5000 LMWH Reviparin (Fragmin) injection at a site distant from the surgical site. Treatment was begun 12 hrs prior to surgery and continued for 5 days or until full activity was resumed whichever was longer. **Additional non-comparative prophylaxis:** The use of compression stockings and intermittent calf compression devices used by small number of women with previous history of DVT or PE.	**Type, dose and timing:** Twice daily subcutaneous dose of 5000 U Sodium Heparin. Injection at a site distant from the surgical site. Treatment was begun 12 hrs prior to surgery and continued for 5 days or until full activity was resumed whichever was longer. **Additional non-comparative prophylaxis:** The use of compression stockings and intermittent calf compression devices used by small number of women with previous history of DVT or PE.	6 Weeks	**DVT** confirmed by Doppler US or Venography **PE** Confirmed by V/Q lung scan. **Blood transfusion**	**Int:** n = 0; **Control:** n = 1 **Int:** n = 5; **Control:** n = 1 **Int:** n = 57; **Control:** n = 39	

Evidence Table 47: LMWH adjuvant vs Aspirin adjuvant

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Westrich et al., 2006[686] **Country of study:** United States **Study design:** RCT **List who was masked to interventions:** Not stated **Evidence level:** 1+ **Duration of follow-up:** Up to 6 weeks	**Patient group:** Patients undergoing unilateral total knee arthroplasty (TKA) Anaesthesia method: spinal epidural **Setting:** Teaching hospital (Cornell University), September 2000 to February 2004 **Inclusion criteria:** Patient undergoing unilateral TKA **Exclusion criteria:** - Allergies to aspirin or hypersensitivity to enoxaparin sodium - Congenital or acquired bleeding disorders - Active ulcerative or angiodysplastic gastrointestinal disease - Multiple myeloma or other proteinaemias - Pheochromocytoma - Hyperthyroidism - Impaired renal function - Known hepatic disease - Past medical history of stroke - Recent brain, spinal or ophthalmologic surgery - Cardiac complications - Chronic heart failure - Severe peripheral vascular disease - Severe varicose veins - History of DVT or pulmonary embolism **All patients** **N:** 275 **Age (mean):** 69 (38-86 years) **M/F:** 99/176	**Group 1** Enoxaparin Dose: 30 mg twice daily, subcutaneously Start: 48 hours after surgery (within 2 hours of epidural catheter removal) Stop: Discharge *Followed by* Enoxaparin 40 mg once daily, subcutaneous injection for 3 weeks post discharge **Group 2** Aspirin, enteric coated Dose: 325mg, twice daily Start: Day 1 Stop: after week 4 Duration: 4 weeks post-operatively **Additional non-comparative prophylaxis:** Both arms received intermittent pneumatic compression pump (from ankle to knee), VenaFlow™ All patients received spinal epidural anaesthesia and continued using spinal epidural anaesthesia for about 48 hours post	**All cause mortality** (confirmed by: No deaths reported)	**Group1:** 0/139 **Group 2:** 0/136 **P value:** 1.0	**Funding:** Aventis **Limitations:** - Open label study – not certain whether technician performing scans were blinded **Outcomes not reported:** Neurological bleeding, Upper GI bleeding, Heparin induced thrombocytopaenia, Post thrombotic syndrome, Pulmonary hypertension, Quality of life **Additional outcomes reported:** - Compliance with enoxaparin post discharge - Compliance with pneumatic pump - Intraoperative blood loss - Post operative blood loss - Mean Length of stay, days (with DVT: 5.6days, Without DVT:5.4 days) **Notes:**
			Fatal pulmonary embolism (confirmed by: no deaths reported)	**Group1:** 0/139 **Group 2:** 0/136 **P value:** 1.0	
			Symptomatic pulmonary embolism (confirmed by: CT spiral)	**Group1:** 0/139 **Group 2:** 1/136 **P value:**	
			Pulmonary embolism, asymptomatic or symptomatic (screened for by: CT spiral)	**Group1:** 0/139 **Group 2:** 1/136 **P value:**	
			Symptomatic DVT (confirmed by: No mention of symptomatic DVTs)	**Group1:** 0/139 **Group 2:** 0/136 **P value:** 1.0	
			DVT, asymptomatic or symptomatic (screened for by: colour flow duplex ultrasound).	At discharge (Day 3 to 5) **Group1:** 17/135 **Group 2:** 18/129 **P value:**0.34 At follow up (4- 6 weeks after surgery) **Group1:** 2/99 **Group 2:** 5/92 **P value:** 0.21 Overall **Group1:** 19/135 **Group 2:** 23/129 **P value:** 0.27	
			Thigh DVT(screened for by: as above)	At discharge (Day 3 to 5) **Group1:** 5/135 **Group 2:** 2/129 **P value:**0.23 At follow up (4- 6 weeks after surgery) **Group1:** 0/99 **Group 2:** 1/92 **P value:** Overall **Group1:** 5/135 **Group 2:** 3/129 **P value:**	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No of dropouts: 11, 6 did not received ultrasound scan before discharge, or 5 did not receive correct study medication **Group 1** **No. randomised:** 139 **No. of dropouts:** 4 **Age:** 68.9±9.6 **Weight:**81.3±24.2 **Autologous blood donation (units):** 1.0±0.7 **Tourniquet time (min):**56.4±16.0 **Group 2** **No. randomised:** 136 **No. of dropouts:** 7 **Age:** 69.0±12.1 **Weight:** 77.8±26.1 **Autologous blood donation (units):**1.0±0.7 **Tourniquet time (min):** 54.5±16.8	operatively.	**Calf DVT** (screened for by: as above)	At discharge (Day 3 to 5) **Group1:** 12/135 **Group 2:** 16/129 **P value**:0.34 At follow up (4- 6 weeks after surgery) **Group1:** 2/99 **Group 2:** 4/92 **P value:** Overall **Group1:** 14/135 **Group 2:** 20/129 **P value:**	
			Fatal bleeding (description: None reported)	**Group1:** 0/139 **Group 2:** 0/136 **P value:** 1.0	
			Major bleeding (description: Non described, see minor bleeding)	**Group1:** 0/139 **Group 2:** 0/136 **P value**:1.0	
			Minor bleeding (description: 1 patient had an "internal bleeding complication")	**Group1:** 0/139 **Group 2:** 1/136 **P value:** 1.0	

Evidence Table 48: VKA + IPCD + GCS vs Aspirin + IPCD + GCS

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Woolson et al., 1991[702]	RCT	1+	**Total:** 196 patients 217 operations Int 1: 69 patients and operations Int 2: 73 patients and 76 operations Cont: 70 patients 72 operations **(see comments)**	**Type of surgery:** Total hip replacement (primary or revision) **Intervention 1** average age: 67.9 M/F 31/38 **Intervention 1** average age: 66.3 M/F 27/66 **Control** average age: 62.3 M/F 35/35 **Pre-existing risk factors:** Intervention: history of DVT 10/69, varicose veins 9/69 Control: history of DVT 4/72, varicose veins 5/72	**Intervention 1: Type:** Warfarin + IPCD + GCS **Dose:** 7.5 or 10mg on evening before surgery, then adjusted to maintain prothrombin time between 14 and 16 seconds. **Intervention 2: Type:** Thigh-length Intermittent pneumatic compression and graduated elastic stockings. **Timing:** Warfarin started evening before surgery, IPCD and stockings started at surgery, both continued until discharge.	**Type:** Aspirin + IPCD + GCS **Dose:** 650mg twice per day **Timing:** Started evening before surgery and until discharge. **Additional non-comparative prophylaxis:** Not reported	Intervention until discharge, followed up for 3 months	**Proximal DVT** Confirmed by venography or ultrasonograpy	**Int 1:** 6/69 **Int 2:** 9/76 **Control:** 7/72 not significant	Out of 196 patients, 20 had bilateral hip replacement, 1 had both procedures in the same operation, 18 had at least one week between procedures, 1 had bilateral procedure and a revision at a later date. All of these are included in the total to make 217 operations *DVT screened whilst in hospital, symptomatic PE followed for 3 months. **Not reported:** All DVTs, QoL, PTS, survival **Also reported:** Symptomatic DVTs by operation, prothrombin time **Funding:** reports: no commercial funding
								Symptomatic PE Confirmed by ventilation perfusion scan*	**Int 1:** 0/69 **Int 2:** 0/76 **Control:** 1/72 not significant	
								Total blood loss (ml)	**Int 1:** 1564 (n = 69) **Int 2:** 1539 (n = 76) **Control:** 1595 (n = 72) not significant	
								Total blood replacement (units)	**Int:** 2.8 (n = 69) **Int 2:** 2.7 (n = 76) **Control:** 2.9 (n = 72) not significant	
								LoS (days)	**Int:** 9 (n = 69) **Int 2:** 10 (n = 76) **Control:** 9 (n = 72) not significant	

Evidence Table 49: IPCD + GCS vs VKA + GCS

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Bailey et al., 1991[28]	RCT	1+	**Total** 95 Int: 50 Cont: 45	**Type of surgery:** total hip replacement Mean operating time Int: 184.5 min Cont: 208.5 min **Intervention:** Mean age: 65.3 (range: 41-88) yrs M/F:24/26 **Control:** Mean age: 64.4 (range: 45-50) M/F:22/23	sequential pneumatic compression device covering legs and thighs **Timing**: Applied after surgery in the recovery ward and worn continuously for the remainder of the study (except during bathing and physical therapy). **Additional non-comparative prophylaxis**: graded elastic compression stockings applied on admission and continued until after discharge.	low dose warfarin **Dose**: 10mg before surgery (7.5mg for women over 70 and patients with minor abnormalities of liver function tests). **Timing**: Evening before surgery and doses given after surgery adjusted to maintain a prothrombin time at 14-16 seconds. Prothrombin times routinely obtained by postoperative day 2 or 3. **Additional non-comparative prophylaxis:** graded elastic compression stockings applied before and after surgery	**Control**: 5 to 7 days (also day diagnostic test done for DVT) **Int**: 5 to 7 days (also day diagnostic test done for DVT)	**DVT** Confirmed by: venography (see comments)	**Int:** 3/50 **Control:** 12/45 **p value:** <0.006 (significant)	Weight was significantly greater in the warfarin group to the sequential compression group. There was no significant difference in weight between groups for those who developed DVT. Diagnosis of DVT for those where there was a lack of venous access: B-mode Doppler US and technecium-pyrophosphate red-cell labelled nuclear venogram with impedance plethysmography. **Funding**: Kendall Inc supplied the stockings (not under investigation). Unclear whether they provided any other support/materials
								Major bleeding (defined in the paper as "clinically important bleeding")	**Int:** 0/50 **Control:** 0/45 **p value:** N/A	

IPCD + GCS vs VKA + GCS

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Francis et al., 1992[193]	RCT	1+	**Total:** Intervention: n = 98 Control: n = 103	**Type of surgery:** Orthopaedic Total hip replacement Duration of surgery not reported **Intervention:** Mean age: 64±12 yrs M/F:43/55 **Control:** Mean age: 64±5 M/F:52/51 **Pre-existing risk factors:** 13 patients (Int 7, control 6 - Not significant difference) had prior history of VTE	**Type:** bilateral thigh-calf IPCD **Dose:** 35-55 mm Hg **Timing:** applied immediately prior to surgery. Continued until venography (6-8 day post-op). **Additional non-comparative prophylaxis:** bilateral thigh-high GCS. Patients moved from bed to chair on 2nd day post-op, began ambulation and physical therapy on 3rd day post-op	**Type:** Warfarin **Dose:** low intensity regimen, adjusted to achieve INR of 1.5 on day of surgery, and 2.5 post-operatively **Timing:** Begun 10-14 days pre-operatively. Continued until venography (6-8 day post-op). **Additional non-comparative prophylaxis:** bilateral thigh-high GCS. Patients moved from bed to chair on 2nd day post-op, began ambulation and physical therapy on 3rd day post-op	Intervention until venography (on average around day 9)	**DVT** Confirmed by: Venography 6-8 days post-op. Bilateral: Int. 87, control. 84. Operated-on leg only: int.11, control 19	**Int:** 26/98 **Control:** 32/103 **p value:** 0.5346	**Comments:** Of the initial 232 patients randomised, 220 received prophylaxis (all assessed for bleeding/arterial thrombotic complications), 201 were assessed for DVT with venography. Overall incidence of deep calf vein (distal) thrombi significantly lower in IPCD group. **Not reported:** PE, Fatal PE, PTS, QoL:
								Proximal DVT Confirmed by: venography (as above).	**Int:** 12/98 **Control:** 3/103 **p value:** <0.012	
								Length of Hospital Stay	Mean LoS 9 days (s.d. not reported). LoS not reported separately for each group	

IPCD + GCS vs VKA + GCS

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Rokito et al., 1996[559]	RCT	1+	**Total:** 110 Int: 35 Cont: 33 Also 42 patients randomised to a TED stocking only group. Results for this group are not presented here.	**Type of surgery:** Reconstructive spinal surgery **Intervention** Average age (range) 44 (22-70) years **Control** average age 45 (18-77) years **Pre-existing risk factors:** none reported	Pneumatic compression boots **Timing:** Started at surgery and continued until duplex dopplers were obtained. Mean ± SD duration of surgery: 286 ±127 mins (range: 97-750 mins) **Additional non-comparative prophylaxis:** Thigh high TED stockings	Coumadin: 10mg the evening before surgery the dose adjusted to maintain the prothrombin time level at 1.3 to 1.5 times the control. **Timing:** Started evening before surgery and continued until duplex dopplers were obtained. Mean ± SD duration of surgery: 232 ±89 mins (range: 95-575 mins) **Additional non-comparative prophylaxis:** Thigh high TED stockings	Intervention carried out until duplex doppler scan. Average of 5.3 days Patients followed for 1 year	**DVT** Confirmed by duplex doppler	**Int:** 0/35 **Control:** 0/33 **p value:** not significant	**Not reported:** proximal DVT, LoS, QoL, PTS, survival **Funding:** TED stockings and pneumatic compression boots provided by Kendall Healthcare Products
								PE (symptomatic)	**Int:** 0/35 **Control:** 0/33 **p value:** not significant	
								Mean ± SD (range) intraoperative blood loss	**Int:** 783 ±631 (100-2800) ml **Control:** 930 ±443 (200-2250) ml **p value:** (not reported)	

Evidence Table 50: IPCD + GCS vs LMWH + GCS

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Dickinson1998 [164]	RCT	1+	**Total:** 66 Int1: n= 21 Int 2: n=23 Control: n=22	**Type of surgery:** Neurosurgery for intracranial neoplasms **Intervention 1:** Mean age: 43 (28-61) yrs **Intervention 2:** Mean age: 50 (29-72) yrs **Control:** Mean age: 49 (20-72) **M/F numbers not reported** **Pre-existing Risk Factors:** Not reported **Ecluded patients:** history of DVT or PE, allergy to heparin or other anticoagulant agents, history of surgery or major trauma to the lower extremities, concurrent condition requiring anticoagulation therapy; cranial base neoplasms and pituitary adenomas	**Int 1:** LWMH (Enoxaparin) **Dose:** administered subcutaneously at a dose of 30mg in the anaesthesia holding room. He dose was continued at a dose of 30mg every 12 hours **Int 2:** Combination of Enoxaparin and SCD **Dose:** as before **Timing:**.started before induction of anaesthesia until discharge from Neurosurgery Service. **Additional non-comparative prophylaxis:** antiembolic stockings on lower extremities at time of admission to the hospital **Int 2:** Combination of LMWH and thigh high sequential compression device.	**Type:** Thigh high sequential compression device **Timing:** started before induction of anesthesia and continued postoperatively until patient was walking without assistance **Additional non-comparative prophylaxis:** antiembolic stockings on lower extremities at time of admission to the hospital	1 month	**DVT** Confirmed by: duplex imaging (on four occasions in the first 1 month after surgery)	**Int 1:** 1/21 **Control:** 3/22 **p value = 0.53** **Int 2:** 4/23 **Comp:** 3/22 **P**=0.90	**Comments:** Study terminated early when it was determined that the enoxaparin treated groups exhibited a greater incidence of postoperative neurological deficits secondary to intracranial haemorrhage. **Not reported:** Post thrombotic leg, length of stay. **Funding:** NR
								Symptomatic PE	**Int 1:** 0/21 **Int 2:** 0/23 **Comp:** 022	
								Bleeding related complications (intracerebral hemorrhage or epidural haematoma)	**Int 1:** 2/21 **Int 2:** 3/23 **Comp:** 0/22	
								Mortality	**Int 1:** 0/21 **Int 2:** 1/23 **Comp:** 122	

Evidence Table 51: IPCD + GCS vs UFH + GCS

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Mellbring and Palmer, 1986[440]	RCT	1+	**Total:** 114 Intervention: n = 54 Control: n = 54	**Type of surgery:** Major abdominal (cholecystectomy or more advanced) **Median operating time:** Int: 135 min (25 - 420) Control: 48 min (45 - 360) **Intervention:** Mean age: 67.8±7.8 yrs M/F:22/32 **Control:** Mean age: 64.2±7.8 M/F:29/25 **Pre-existing risk factors:** Not reported	**Type:** calf-length IPCD **Dose:** up to 40 mm Hg **Timing:** from anaesthetic until end of surgery **Additional non-comparative prophylaxis:** Thigh-length GCS applied to one leg (allocated randomly)	**Type:** Dihydroergotamine + LDUH **Dose:** 0.5 mg + 5000 IU **Timing:** Begun 2hrs pre-surgery and continued 2x/day until patient fully mobilised **Additional non-comparative prophylaxis:** Thigh-length GCS applied to one leg (allocated randomly)	**Both groups:** 9 days	**DVT** Confirmed by: I 125 FUT, started pre-op and then on days 1,3,5,7,9 post-op (daily if a positive reading found). Or until discharge if < 9 days	**Int:** 10/54 **Control:** 2/54 **p value:** <0.05 (	**Comments:** 6 patients excluded (4 intervention, 2 control). Both patients excluded from control due to post-operative bleeding requiring re-operation and dextran administration. All patients randomised to receive stocking on one leg. Subgroup analysis (heparin group only, or IPCD group only) to consider adjuvant effect of GCS not possible as results not amenable to analysis. Incidence of thrombosis did not differ significantly between stockinged and non-stockinged leg. **Not reported:** Proximal DVT, PE, QoL, LoS, PTS **Funding:**
								Bleeding related complications perioperative bleeding (ml) calculated from: amount of blood in suction drainage; and estimated content of blood in swabs	**Int:** mean 580, med 300, range minor - 3900 **Control:** mean 690, med 450, range minor - 2800 **p value:** Not significant	
								Survival (specify)	**Int:** 54/54 **Control:** 54/54 **p value:** Not significant	

IPCD + GCS vs UFH + GCS

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Pambianco et al., 1995[509] **Country of study:** USA **Study design:** RCT **List who was masked to interventions:** No one **Evidence level:** 1+ /- ? **Duration of follow-up:** 28 days	**Patient group:** Stroke patients (not necessarily newly defined) **Setting:** Rehabilitation centre **Inclusion criteria:** All cases with a diagnosis of non-haemorrhagic stroke identified by CT scan in the referring hospital and who have a paralysed or severely weakened lower limb. **Exclusion criteria:** • Patients on anticoagulation therapy • haemorrhagic stroke • more than 10 weeks after stroke • active cancer • 'other medical contraindications' including dementia, amputation, stroke not identifying specific area • Contraindications to heparin • diabetic ulcers. **<u>All patients</u>** **N:** 360 randomised – overall baseline data provided for only those completing study **Age (mean):** 72.2 ± 9.5 **M/F:** 41/59 **Additional risk factors:** BMI: 26.1 ± 5.7 Time from stroke to admission: 24.2 days **<u>Group 1:</u>** <u>No prophylaxis</u> **No. randomised:** 115 **No. of dropouts:** 9 (8%) **<u>Group 2</u>** <u>(Heparin)</u> **No. randomised:** 120 **No. of dropouts:** 30 (25%)	**Group 1** No prophylaxis **Group 2** Standard Sodium Heparin (no brand name) Start time: 1st full day at centre End time: day 28 Duration: 28 days or discharge Dose and frequency: 5,000U every 8 hours, adjusted in 500U increments to maintain daily PTT between 30.0 – 39.9. Maximum dose 10,000U every 8 hours **Group 3** IPCD – Anti-thrombic pump (double lined stoking containing inflatable bladder) Start time: 1st full day at centre End time: day 28 Duration: 8 hours each night Length and compression profile: below knee. **Group 4** Mederomic Functional Electrical Stimulation Device (discontinued due to adverse events)	**All cause mortality** **DVT, asymptomatic or symptomatic** (screened for by: B-mode 2-dimensional imaging and pulsed doppler ultrasound at or above the popliteal vein twice a week until the completion of the study or discharge.)	**Group 1:** 0/115 **Group 2:** 0/120 **Group 3:** 0/117 **Group1:** 6/115 (completed study) **Group 2:** 5/120 (completed study) **Group 3:** 8/117 (completed study) **P value:** NR Grp 1 v Grp 2 = 0.76 Grp 1 v Grp 3 = 0.78 Grp 2 v Grp 3 = 0.41 *2-sided Fisher's exact test calculated by NCC-AC using ITT original numbers randomised*	**Funding:** US department of Education **Limitations:** - No details of randomisation provided - No blinding of analysts not mentioned - High patient drop out rates for heparin and IPCD group. **Outcomes not reported:** All cause mortality, PE (any type), Symptomatic DVT, Calf DVT, Thigh DVT, Bleeding (any type), HIT, PTS, Pulmonary Hyper tension, QoL, LoS **Additional outcomes reported:** Adverse events for heparin included: echymotic area over abdomen and areas distal to injection site. 10 point decrease in haematocrit level; nausea and vomiting with onset of heparin therapy, bleeding from the ear, haematochezia, haemepositive stools, blleding around tracheal stoma,

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 3 (IPCD) **No. randomised:** 117 **No. of dropouts:** 26 (22%) **Group 4** (Functional Electrical Simulation) **No. randomised:** 8 **No. of dropouts:** 6 (75%) Study arm discontinued	**Additional non-comparative prophylaxis:** All patients received bilateral below knee stockings (no compression).			thrombocytopaenia Adverse events for IPCD, bilateral skin changes **Notes:** High drop out rate in IPCD due to disruption of sleep. 21 patients were transferred to acute care for complications unrelated to study treatment

IPCD + GCS vs UFH + GCS

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Santori et al., 1994[582]	RCT	1+	**Total:** n = 132 Intervention : n = 67 Control: n = 65	**Type of surgery:** Patients undergoing total hip replacement. All patients had compression stockings after operation **Excluded:** history of VTE, varicose veins, venous insufficiency in the legs, malignant neoplasm **Intervention:** Mean age: 72.4±6.65 M/F:19/48 **Control** Mean age: 69.8±6.22 M/F:15/50 **Pre-existing risk factors:** Not reported	Intermittent plantar foot pump (aka impulse group) on both feet immediately after the operation and used for 7 to 10 days. When patients started walking at postoperative day 4 or 5 the foot pump was only used when the patient was in bed. **Additional prophylaxis:** Graduated compression stockings on both legs after operation. Neither the length nor for how long they were worn was stated. Physiotherapy with mobilisation started on 2nd postoperative day. Walking began on 4th or 5th postoperative day	Calcium heparin. 5000 Units 3x per day for 10 days starting on the day before the operation **Additional prophylaxis:** Graduated compression stockings on both legs after operation. Neither the length nor for how long they were worn was stated. Physiotherapy with mobilisation started on 2nd postoperative day. Walking began on 4th or 5th postoperative day	Intervention for 8 to 10 days, follow-up 6 weeks	**DVT (overall)** Confirmed by: thermography and doppler US followed by phlebography	**Int:** 9/67 **Control:** 23/65 **p value:** <0.005	The paper did not report any dropouts 2 PEs (1 fatal) in the heparin group but not stated how confirmed **Not reported:** PTS, PE, QoL, Survival
								"Major" proximal DVTs	**Int:** 2/67 **Control:** 11/65 **p value:** : 0.0083	
								"Major" proximal & distal DVTs	**Int:** 0/67 **Control:** 2/65 **p value:** : 0.2406	
								Mean ±SD total blood loss (ml)	**Int:** 490 ±195.27 (n = 67) **Control:** 520 ±189.16 (n = 65) **P value:** not reported	
								Mean ±SD volume of blood transfused (ml)	**Int:** 308 ±289.15 (n = 67) **Control:** 300 ±267.7 (n = 65) **P value:** not reported	

Evidence Table 52: LMWH then FID + GCS vs LMWH + GCS

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Pitto et al., 2004[523]	RCT	1+	**Total:** 216 **Intervention:** n = 100 **Control:** n = 100	**Type of surgery:** Total hip replacement in patients with osteoarthritis **Intervention:** Mean age: 57.3±12 yrs M/F:30/70 Mean duration of surgery: 69±10 minutes **Control:** Mean age: 58.1±11 M/F:32/68 Mean duration of surgery: 65+11 minutes	**Type:** A-V Impulse System foot pump (slippers) and patient in Trendelenburg position (head-high, feet-low) **Cycle:** 130 mmHg for one second every 20 seconds **Timing:** (duration) started after surgery, not stated when stopped - could be used until discharge **Additional non-comparative prophylaxis:** Bilateral thigh-high anti-thromboembolic stockings. Physiotherapy and mobilisation with partial weight bearing usually started on postoperative day 2. Low molecular weight heparin (Fraxiparin) administered subcutaneously 12 hours preoperatively (dose adjusted to body weight, 0.2 to 0.6ml; 0.1ml = 950IU of anti Xa).	**Type:** Low molecular weight heparin (Fraxiparin) continued after surgery **Dose:** adjusted to body weight, 0.2 to 0.6ml; 0.1ml = 950IU of anti Xa. **Timing:** started postoperatively, not stated when stopped but could be until discharge. **Additional non-comparative prophylaxis:** Bilateral thigh-high anti-thromboembolic stockings. Physiotherapy and mobilisation with partial weight bearing usually started on postoperative day 2. Low molecular weight heparin (Fraxiparin) administered subcutaneously 12 hours	**Control:** 45 days **Int:** 45 days	**DVT** Confirmed by: serial bilateral duplex	**Int:** 3/97 **Control:** 6/94 **p value:** 0.30	**Comments:** Discrepancy with randomisation: computer generated numbers lead to 100 in each group but 216 were randomised. 16 dopped out of mechanical group because did not tolerate foot pump. Dropouts occurred between postoperative days 3 and 10. **Not reported:** PE, LoS, postthrombotic leg **Also reported:** Distal DVT, minor bleeding from wound; no. of hips without bruising at days 3 & 10, no. of hips without oozing at days 3 & 10 **Funding:** stated that authors have or will receive benefits from a commercial party directly related to the subject of this study. Does not
								Proximal DVT Confirmed by: serial bilateral duplex	**Int:** 0/97 **Control:** 2/94 **p value:** 0.29	
								Distal DVT Confirmed by: serial bilateral duplex	**Int:** 3/97 **Control:** 4/94 **p value:** 0.67 Not significant	
								Symptomatic DVT Confirmed by: serial bilateral duplex	**Int:** 1/100 **Control:** 1/100 Not significant	
								PE Confirmed by:	**Int:** 0/100 **Control:** 0/100	
								Fatal PE Confirmed by:	**Int:** 0/100 **Control:** 0/100	
								Major bleeding from wound	Int: 0/100 Control: 0/100	
								Major bleeding not related to wound	Int: 0/100 Control: 0/100	
								Heparin-induced thrombocytopenia	Int: 0/100 Control: 1/100 p value not reported	
								Survival	**Int:** 100/100 **Control:** 100/100	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
						preoperatively (dose adjusted to body weight, 0.2 to 0.6ml; 0.1ml = 950IU of anti Xa).				state who the commercial party is nor what the benefits are.

Evidence Table 53: IPCD/FID and delayed LMWH vs LMWH

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Eskander et al., 1997[177]	RCT	1+	**Total**: 45 **Interventio nn** = 21 **Control:** n = 24	**Type of surgery:** Patients with fractures of femoral neck Exclusion criteria: history of VTE, currently taking aspirin or warfarin, cancer, dementia. **Intervention**: Mean age: 78.7 (range 41-91) yrs M/F: Not reported **Control**: Mean age: 80.2 (range 41-90) yrs M/F: Not reported **In total population M/F :** 7/38	Intermittent calf compression garments (Flowtron DVT) then Enoxaparin (dose not specified) **Timing** Compression device started at the time of admission and continued for 48 hours after fracture. Then Enoxaparin given until postoperative day 7.	Enoxaparin (dose not specified) **Timing** Started at the time of admission and continued until postoperative day 7. **Additional non-comparative prophylaxis**: Not reported	7 days postoperati vely	**DVT** Confirmed by: Colour Duplex Doppler **PE** Confirmed by: Colour Duplex Doppler	**Int:** 2/21 **Control**: 4/24 **p value**: >0.49 **Int:** 1/21 **Control:** 0/24 **p value**: 0.45	**Not reported** proximal DVT, fatal PE, PTS, bleeding complications, QoL, survival, LoS **Funding:** not reported

IPCD/FID and delayed LMWH vs LMWH

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Stannard et al., 2006[620] [US] **Study design:** RCT **List who was masked to interventions:** NA **Evidence level:** 1+ **Duration of follow-up:** Mean 17 months (range 6 – 38months)	**Patient group:** Patients with recent blunt skeletal trauma (i.e. starting at admission) **Setting:** Hospital admission / ward **Inclusion criteria:** blunt trauma and at least one of the following – • An Abbreviated Injury score of 3 or more and a long bone fracture • Multiple (2 or more) long bone fractures • An age of more than 55 years and a long bone fracture. All patients were 18+ yrs, had no contraindication for anticoagulation and had been admitted to hospital less than 2 hours after time of trauma or had a negative magnetic resonance venogram prior to enrolment. **Exclusion criteria:** renal insufficiency, severe cranial or spinal cord injury; the use of anticoagulants; any contraindication to anticoagulation, including severe active bleeding; pregnancy; a history of venous thromboembolic disease; any contraindication to magnetic resonance venography; the presence of vena cava filters; and severe ocular trauma. **<u>All patients</u>** **N:** 200 **Age (mean):** 39.6 (range 19-80) **M/F:** NR	**Group 1** Enoxaparin (30mg administered subcutaneously twice a day) Start time: 24 – 48 hours after blunt trauma once severe bleeding associated with trauma had been controlled. Anyone not able to start within 72 hours excluded from study. **Group 2** Pulsatile foot pumps at time of admission (patients asked to use it for at least 12 hours per day) combined with enoxaparin on a delayed basis (5 days after admission) after all acute bleeding from blunt trauma had been resolved. NB: Prophylaxis was given for duration of hospital stay. If patients required a return to the operating theatre, the enoxaparin was discontinued on the	**All cause mortality**	**Group1:** 0/103 **Group 2:** 0/97 **P value:** NA	**Funding:** "In support of their research for or preparation of this manuscript one or more of the authors received grants or outside funding from Aventis Pharmaceutical Grant in Aid. No commercial entity paid or directed, or agreed to pay or direct, any benefits to any research fund, foundation, educational institution, or other charitable or non-profit organisation with which the authors are affiliated or associated". **Limitations:** unclear how patients were randomised. No intention to treat analysis (10.7% drop out rate). Lack of bleeding data. **Outcomes not reported:** Upper GI bleeding Major bleeding Minor bleeding Heparin induced thrombocytopaenia Post thrombotic syndrome Quality of life Pulmonary hypertension
			Fatal pulmonary embolism	**Group1:** 0/103 **Group 2:** 0/97 **P value:** NA	
			Symptomatic pulmonary embolism, (not stated how confirmed only states 'underwent test' to exclude)	**Group1:** 0/103 **Group 2:** 2/97 **P value:** 1.00 (Not Sig)	
			DVT, asymptomatic or symptomatic (confirmed by: bilateral magnetic resonance venography and ultrasonography within 24 hours before discharge or as soon as they developed signs or symptoms of DVT)	**Group1:** 9/103 **Group 2:** 13/97 **P value:** 0.2365 (Not Sig)	
			Symptomatic DVT (confirmed by: magnetic resonance venography and ultrasonography within 24 hours before discharge or as soon as they developed signs or symptoms of DVT)	**Group1:** 1/103 **Group 2:** 1/97 **P value:** NS	
			Fatal bleeding	**Group1:** 0/103 **Group 2:** 0/97 **P value:** NA	
			Neurological bleeding	**Group 1:** 1/103 **Group2:** 1/97 **P value:** 0.7362 (Not Sig)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Additional risk factors: Injury severity score (mean): 14.42 (range 4-57) Weight (mean): In kgs: 85.7 (range: 45.4 – 158.8) In lbs: 189 (range: 100 – 350) **Group 1** **No. randomised:** 103 **No. of dropouts:** 0 **Age (mean):** 41.0(range 19-80) **Additional risk factors**: Injury severity score (mean): 14.43 (range 4-41) Weight (mean): In kgs: 86.2 (range: 45.4 – 158.8) In lbs: 190 (range: 100 – 350) **Group 2** **No. randomised:** 97 **No. of dropouts:** 0 **Age (mean):** 38.2(range 19-75) **Additional risk factors**: Injury severity score (mean): 14.41 (range 8-57) Weight (mean): In kgs: 84.8 (range: 46.3 – 153.3) In lbs: 187 (range: 102 – 338) [NB: 24/224 (10.7%) did not complete the protocol and are excluded from the results, 5 because of erroneous discharge before studies were obtained, 5 because of claustrophobia in MRI scanner, **5 because of bleeding that required discontinuation of anticoagulants**, 4 withdrew from the study, 3 had errors in medication and two had other medical problems that required discontinuation of anticoagulants.]	night prior to surgery and resumed within 12 hours after surgery.	**Length of stay**	**Group 1:** 13.8 days (range: 3-68 days) **Group2:** 11.2 (range: 1-119 days) **P value**: NR (unable to calculate)	**Additional outcomes reported**: No. of DVTs that were occlusive (significantly more in Group 1 i.e. 11 compared to 3, p=0.025) Mean number of fractures per patient (by DVT vs. no DVT). % with acetabular fracture for DVT vs no DVT in each group. Mean duration of prophylaxis by DVT development. Mean duration of foot pump use (13.3 hrs per day, range 1-23 hrs) Time of prophylaxis initiation against DVT Mean number of surgical procedures per patient (by DVT vs. no DVT). No. of wound infections, wound hematomas at surgical site and other site, pseudoaneurysm, large hematoma. Prevalence of high risk skeletal injuries

Effectiveness - Dose or timing

Evidence Table 54: LMWH - comparing dose or timing

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Adolf et al., 1999[8]	RCT	1+	**Total:** 341 randomised **Intervention:** n = 169 **Control:** n = 172 (81 exclusions, 34 intervention, 47 control).	**Type of surgery:** Total hip replacement (& Duration of surgery)	**Type:** Increased dose LWMH (Certoparin) **Dose:** 5000 IU	**Type:** standard dose LMWH (Certoparin) **Dose:** 3000 IU	**Both groups:** 12-14 days post-op	**DVT** Confirmed by: Bilateral ascending venography on 12-14th post-op day (earlier if symptomatic)	**Intention to treat analysis:** **Int:** 16/169 **Control:** 17/172 **p value:** 0.9	**Comments:** Multi-centre trial.
				Randomised patients **Intervention:** Mean age: 67±11.7 yrs M/F:70/99	**Timing:** Begun at least 2 hours pre-op, then repeated daily until 12th-14th day post-op	**Timing:** Begun at least 2 hours pre-op, then repeated daily until 12th-14th day post-op		**Proximal DVT** Confirmed by: venography	**Intention to treat:** **Int:** 4/169 **Control:** 2/172 **p value:** 0.4456	**Not reported:** PTS, QoL, LoS, funding
				Randomised patients **Control:** Mean age: 69±9.5 M/F:64/108	**Additional non-comparative prophylaxis:** none reported	**Additional non-comparative prophylaxis:** none reported		**Symptomatic PE** Confirmed by: Supposed to be by V/Q scan but appears not to be case.	**Int:** 2/169 **Control:** 2/172 **p value:** 1.0000	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
				Pre-existing risk factors: Smoking 44/341 Previous DVT 29/341 Previous PE 5/341 Varicose veins 133/341 (no significant difference between groups).				**Bleeding related complications:** - Transfusion volumes - Cell saver volumes - Drain loss - Haematoma formation	**Transfusion volumes:** **Int:** Mean 1004±478 ml **Control:** 950±517 ml **p value:** Not significant **Cell saver vol:** **Int:** 475±186 ml **Control:** 770±136 **p value:** <0.001 (Significant) **Drain loss:** **Int:** 752±351 **Control:** 790±374 **p value:** Not significant **Haematoma formation:** **Int:** 28/169 **Control:** 26/172 **p value:** Not significant	**Funding:**

LMWH comparing dose or timing

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Bergqvist et al., 1995[48]	Multicentre RCT	1+	**Total:** 2070 Int: 1036 Cont: 1034	**Type of surgery:** Elective general abdominal surgery.	**Type:** LMWH (dalteparin) 5000 units daily	**Type:** LMWH (dalteparin) 2500 units daily	7 postoperative days for intervention, followed up at 30 postoperative days	**DVT** Confirmed by: FUT.	**Int:** 65/981 **Control:** 124/976 **p value:** <0.001	**Comments:** 20 patients dropped out after randomisation mainly due to operation cancellation. None developed evidence of DVT or PE No additional prophylaxis used.
				Intervention: Median (range) age: 70 (40-90) yrs M/F: 513/523 Median (range) duration of surgery: 125 (15-525) minutes	**Timing:** Started at 22 hours the day before surgery for 7 days postoperatively.	**Timing:** Started at 22 hours the day before surgery for 7 days postoperatively.		**Total no bleeding episodes**	**Int:** 49/1036 **Control:** 28/1034 **p value:** 0.02	
								Major bleeding episodes	**Int:** 13/1036 **Control:** 3/1034 **p value:** 0.0208	
				Control: Median age: 69 (40-95) yrs M/F: 472/562 Median (range) duration of surgery: 129 (19-470) minutes	**Additional non-comparative prophylaxis:** none reported	**Additional non-comparative prophylaxis:** none reported		**Minor bleeding episodes**	**Int:** 36/1036 **Control:** 25/1034 **p value:** 0.1543	**Other outcomes reported:** PE (not all confirmed by accepted diagnostic test), 1 fatal PE in each arm confirmed by autopsy but not all deaths received imaging or autopsy.
								Median (range) intraoperative blood loss ml	**Int:** 300 (0-7800) ml **Control:** 300 (0-30,000) **p value:** not reported	
				Pre-existing risk factors: Past history of DVT or PE Int: 62/1036 Control: 60/1034 Excluded: past history of bleeding diathesis; oral anticoagulant or dextran treatment within previous 14 days				**Mortality (confirmed by autopsy)**	**Int:** 32(15)/1036 **Control:** 35(12)/1034 **p value:**	**Not reported:** Proximal and distal DVT, PTS, QoL, length of hospital stay.
										Funding: not reported

LMWH comparing dose or timing

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Colwell et al., 1994[129]	Multicentre RCT	1+	**Total:** 610 Multicentre study involving 32 institutions Int A: 195 In B: 203 Int C: 209	**Type of surgery:** Hip replacement surgery, including primary and revision procedures, in patients 40 years or older	**Int A:** Enoxaparin 30mg every 12 hours	**Int B:** Enoxaparin 40mg once daily	**Study period:** 7 days	**DVT** Confirmed by: bilateral contrast venography	**Int A:** 8 (n = 136) **Int B:** 28 (n = 136) **Int C:** 21 (n = 142) **p value not reported**	**Comments:** Only 67.9% of patients evaluated for DVT. Multicentre study, not all centres used a valid diagnostic technique (same numbers in each group). An intention to treat analysis was followed. Results are available for patients diagnosed by valid test alone as well as all patients.
						Int C: 5000 units UFH every 8 hours		**Proximal DVT** Confirmed by: bilateral contrast venography	**Int A:** 4 (n = 136) **Int B:** 8 (n = 136) **Int C:** 10 (n = 142) **p value not reported**	
				Intervention A: Mean age: 65.6±10.97 yrs M/F:98/97	**Timing:** Administered within 24 hours after surgery and continued for a maximum of 7 days.	**Timing:** Administered within 24 hours after surgery and continued for a maximum of 7 days.		**Distal DVT** Confirmed by: bilateral contrast venography	**Int A:** 4 (n = 136) **Int B:** 20 (n = 136) **Int C:** 11 (n = 142) **p value not reported**	
				Intervention B: Mean age: 65.0±11.31 yrs M/F:99/104				**PEs (symptomatic)** (not reported how confirmed)	**Int A:** 0 (n = 195) **Int B:** 1 (n = 203) **Int C:** 3 (n = 209) **p value:** not reported	
				Intervention C: Mean age: 65.6±10.65 yrs M/F:101/108	**Additional non-comparative prophylaxis:** No. patients receiving epidural/spinal anaesthesia: Int A: 64/195	**Additional non-comparative prophylaxis:** No. patients receiving epidural/spinal anaesthesia: Int B: 72/203 Int C: 72/209		**Major bleeding episodes**	**Int A:** 8 (n = 195) **Int B:** 3 (n = 203) **Int C:** 13 (n = 209) **p value:** not reported	**Other outcomes reported:** Total proximal and distal DVTs (i.e. confirmed by venography, supportive non-invasive vascular examinations or other clinical evidence of treatment failure.) haemoglobin levels, minor bleeding
				Pre-existing risk factors: Excluded patients include: a history of DVT, PE or both and heparin associated thrombocytopenia.				**Moderate thrombocytopenia episodes** ($20x10^9$/L to $100x10^9$/L. In no case was the count $<50x10^9$/L).	**Int A:**7 (n = 195) **Int B:** 3 (n = 203) **Int C:** 5 (n = 209) **p value:** not reported	
								Mortality during study not due to sudden death by PE	**Int A:** 1 (n = 136) **Int B:** 0 (n = 136) **Int C:** 2 (n = 142) **p value not reported**	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
								Adverse events (no. of patients, none completed the study)	**Int A:** 7 (n = 136) **Int B:** 5 (n = 136) **Int C:** 12 (n = 142) **p value not reported**	**Not reported:** PEs in hospital PTS, QoL,
								No. of patients rehospitalised (due to symptomatic DVT or PE).	**Int A:** 3 (n = 136) **Int B:** 1 (n = 136) **Int C:** 4 (n = 142) **p value not reported**	**Funding:** Rhone Poulenc Pharmaceuticals

LMWH comparing dose or timing

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Hauch et al., 1988[264]	RCT	1+	**Total:** 35 Int: n = 19 Control: n = 16	**Type of surgery:** Major abdominal (& Duration of surgery)	**Type:** LMWH **Dose:** 3500 IU	**Type:** LMWH **Dose:** 2500 IU	1 month	**DVT** Confirmed by: ^{125}I FUT on 1st, 3rd, 5th and 7th post-op day (positive result confirmed by venography)	**Int:** 0/19 **Control:** 2/16 **p value:** 0.20	**Not reported:** QoL, survival, LoS, PTS, funding **Also reported:** 3rd arm investigating a dose of 50 IU per kg of body weight.
			42 patients randomised Int: n = 20 Control n = 22	**Intervention:** Median age 72 (range 40-88) yrs M/F:8/11	**Timing:** started 2 hours preoperatively and administered once daily until postoperative day 7 or discharge	**Timing:** started 2 hours preoperatively and administered once daily until postoperative day 7 or discharge				
				Control: Median age 68 (range 41-85) M/F:5/11				**Symptomatic PE** (confirmation not reported)	**Int:** 0/19 **Control:** 0/16 **p value:** N/A	
				Pre-existing risk factors: No. of patients with predisposing risk factors (malignant disease, varicose veins, previous thromboembolism, myocardial infarction): Int: 13 Cont: 7	**Additional non-comparative prophylaxis:** none reported	**Additional non-comparative prophylaxis:** none reported		**Fatal PE** Autopsy:	**Int:** 0/19 **Control:** 0/16 **p value:** N/A	
								Major bleeds	**Int:** 1/19 **Control:** 0/16 **p value:** 0.54	

LMWH comparing dose or timing

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Marlovits et al., 2007[425] **Country of study:** Austria **Study design:** RCT **List who was masked to interventions:** The operator conducting diagnosis was blinded to patient group. The paper states it was double blind and did use placebo as the control arm, however, no information about blinding was provided. **Evidence level:** 1+ **Duration of follow-up:** 23-28 days after surgery	**Patient group:** Patients who underwent arthroscopic surgery of the anterior cruciate ligament. **Setting:** University Teaching Hospital **Inclusion criteria:** Patients aged 19-55 years with a maximum weight of 100kg, who were admitted to the hospital for arthroscopic ACL surgery. **Exclusion criteria:** • Participated in another trial in the 4 weeks prior to this trial, • Diagnosis of DVT confirmed by magnetic resonance venography on admission • Were receiving oral anticoagulant therapy (not including non-steroidal anti-inflammatory drugs) or were allergic to heparin • Presence of haemophilia or other blood disorders • Presence of bleeding disorders (e.g. haemorrhagic injury, acute intracranial bleeding, peptic ulcer, gastrointestinal tract bleeding, and lung bleeding) • Pregnancy • Presence of other serious illness such as proliferative diabetic retinopathy, liver or pancreatic illness, multiple trauma, uncontrollable hypertension or endocarditis lenta. **<u>All patients</u>** **N:** 175 **Gp1** **Gp2** **Age (mean):** 29.9 ± 7.4 30.2 ± 6.9 **M/F:** 55/32 53/35 **Additional risk factors:** (140 patients included in ITT analysis)	**Group 1** LMWH (Enoxaparin) Start time: 12-18 hrs pre-operatively End time: 3-8 days in hospital and then 20 days post discharge Duration: No average prophylaxis period provided in paper Dose, and frequency: 40mg subcutaneously once daily. **Group 2** LMWH (Enoxaparin) and then placebo Start time: 12-18 hrs pre-operatively End time: 3-8 days in-hospital after surgery And then Placebo for 20 days post discharge Dose and frequency: 40mg subcutaneously once daily whilst in hospital And then Placebo injections once daily post discharge. **Additional non-comparative prophylaxis:**	**All cause mortality**	**Group1:** 0/87 **Group 2:** 0/88 **P value:** NS	**Funding:** Supported by an unrestricted grant from Sanofi-Aventis. **Limitations:** ▪ The randomisation method and allocation concealment was not mentioned in the paper ▪ Inconsistency within paper of the number of patients randomised (87and 88 in text; 79 and 80 in figure 1). Difference due to those who did not undergo ACL operations. ▪ Paper reports an intention to treat analysis but excludes patients who did not follow the study protocol ▪ Differences in reasons for drop outs between the two studies are not discussed. **Outcomes not reported:** Asymptomatic and symptomatic PE, Heparin induced thrombocytopaenia, pulmonary hypertension, post thrombotic syndrome quality of life, length of stay.
			Fatal pulmonary embolism (confirmed by: N/A)	**Group1:** 0/87 **Group 2:** 0/88 **P value:** NS	
			Symptomatic pulmonary embolism (confirmed by: lung scan)	**Group1:** 0/87 **Group 2:** 0/88 **P value:** NS	
			Symptomatic DVT (confirmed by: venography)	**Group1:** 0/87 **Group 2:** 3/88 **P value:** 0.246*	
			DVT, asymptomatic or symptomatic (confirmed by: Magnetic Resonance Venograpy at 23-28 days)	**Group1:** 2/72 **Group 2:** 28/68 **P value:** <0.001	
			Thigh DVT(confirmed by: Magnetic Resonance Venograpy at 23-28 days)	**Popliteal and Femoral** **Group1:** 3/72 **Group 2:** 18/68 **P value:** <0.001* **Popliteal** **Group1:** 2/72 **Group 2:** 12/68 **P value:** 0.003 **Femoral** **Group1:** 1/72 **Group 2:** 6/68 **P value:** 0.044	
			Calf DVT (confirmed by: Magnetic Resonance Venograpy at 23-28 days)	**Group1:** 2/72 **Group 2:** 28/68 **P value:** <0.001	
			Fatal bleeding	**Group1:** 0/ 87 **Group 2:** 0/ 88 **P value:** NS	
			Major bleeding (description: bleeding that was retroperitoneal, intracranial, intraspinal, or involving any other critical organ; bleeding	**Group1:** 0/87 **Group 2:** 0/88 **P value:** NS	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	<table><tr><th></th><th>Gp1</th><th>Gp2</th></tr><tr><td>Aged>30yr</td><td>30</td><td>28</td></tr><tr><td>Smoker</td><td>24</td><td>32</td></tr><tr><td>Immobile before surgery</td><td>21</td><td>16</td></tr><tr><td>Immobilisation >4days</td><td>15</td><td>11</td></tr><tr><td>Ischaemia during operation</td><td>49</td><td>39</td></tr><tr><td>Length of operation >2hrs</td><td>36</td><td>34</td></tr></table> **Group 1** **No. randomised:** 87 **No. of dropouts:** 15 (17%) **Group 2** **No. randomised:** 88 **No. of dropouts:** 20 (22%) Reasons for dropouts (not listed for each group individually) Arthroscopy but not anterior cruciate ligament (n=16) Noncompliance (n=11) No MRV due to technical reasons (n=4) Lost to follow-up (n=2) Withdrawal (n=1) Adverse events (n=1)	None stated in paper	leading to reoperation; transfusion of 2 units of packed red blood cells or whole blood; or overt bleeding with a bleeding index of two or more.) **Minor bleeding** (description: All other bleeding not defined in fatal or major bleeding)	 **Group1:** 13/87 **Group 2:** 10/88 **P value:** 0.595	**Additional outcomes reported:** Adverse events – no information. **Notes:** * calculated by Fisher's Exact Test

LMWH comparing dose or timing

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Palareti et al 1996[508]	RCT	1+	**Total:** 180 randomised (outcome for 131) **Intervention:** n = 91 (65 assessed for VTE) **Control:** n = 89 (66 assessed for VTE)	**Type of surgery:** Elective hip replacement	**Type:** LMWH (nadroparin) begun pre-operatively **Dose:** 7500 IU, 10000 IU	**Type:** LMWH (nadroparin) begun post-operatively **Dose:** 7500 IU, 10000 IU	**Both groups:** 4-6 weeks post-op	**DVT** Confirmed by: Bilateral ascending venography on 10th-15th post-op day, or earlier if symptomatic	**Int:** 27/65 **Control:** 24/66 **p value:** Not significant	**Comments:** Multi-centre study involving 7 orthopaedic departments. Across the whole study group, age was a significant risk factor for developing DVT. * intracranial, ocular (with reduction of viscous), articular, retroperitoneal, and/or associated with reduction of haemoglobin ≥ 2g/dl or a need to transfuse ≥ 2 U of blood
				Duration of surgery: **Int:** 84.6±29.4 min **Cont:** 80.0±28.4 min	**Timing:** 7500 units begun 12hrs pre-op and repeated daily until 3rd day post-op. Then 10000 units daily until for 14 days or until discharge.	**Timing:** Placebo 12hrs pre-op, and then LMWH 7500 units begun eve post-op and repeated daily until 3rd day post-op. Then 10000 units daily until discharge or for 14 days.		**Proximal DVT** Confirmed by: Bilateral ascending venography on 10th-15th post-op day, or earlier if symptomatic	**Int:** 7/65 **Control:** 4/66 **p value:** Not significant	
				Intervention: Mean age: 62.3±6.8 yrs M/F:26/65				**PE** Confirmed by: Not routinely assessed. Clinical suspicion investigated with V/Q scan	**Int:** 0/90 **Control:** 0/89 **p value:** N/A	
				Control: Mean age: 61.3±7.6 yrs M/F:29/60	**Additional non-comparative prophylaxis:** Early mobilisation, graduated compression stockings, physical exercise	**Additional non-comparative prophylaxis:** Early mobilisation, graduated compression stockings, physical exercise		**Bleeding related complications**	**Safety analysis** (179 patients. 1 patient excluded - wrong intervention)	
				Pre-existing risk factors: age, obesity, varicose veins, previous VTE (no significant differences between groups).				**Major haemorrhage**	**Int:** 2/90 **Control:** 3/89 **p value:** Not significant	**Not reported:** PTS, QoL, LoS, survival, funding
								Minor haemorrhage: clinically evident but without *	**Int:** 14/90 **Control:** 11/89 **p value:** Not significant	

LMWH comparing dose or timing

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Samama et al., 1999[579] MEDENOX study **Country of study:** International: 60 centres in 9 countries **Study design:** RCT **List who was masked to interventions:** Double-blind: Patients and investigators of VTE **Evidence level:** 1+ **Duration of follow-up:** 3 months	**Patient group:** Acutely ill medical patients **Setting:** General medical ward (most patients were not in an intensive care unit) **Inclusion criteria:** Medical patients older than 40 years, whose projected stay in hospital was at least six days and not immobilised for more than three days. Patients had to have congestive heart failure (CHF) (New York Association class III or IV), acute respiratory failure that did not require ventilatory support, or one of the following conditions if it was associated with at least one additional risk factor for VT: acute infection with septic shock, acute rheumatic disorders, acute arthritis of the legs, or an acute episode of rheumatoid arthritis in the legs; or an episode of inflammatory bowel disease. The additional risk factors were age >75 years, cancer, previous VT, obesity (BMI >=30 for men and >=28 for women), varicose veins, hormone therapy (antiandrogen or estrogen, except for postmenopausal hormone-replacement therapy) and chronic heart or respiratory failure. **Exclusion criteria:** Women of childbearing age if pregnant, breast-feeding or not using contraception. Other exclusions were: stroke or major surgery within the previous three months, contraindications to use of iodinated contrast medium; known thrombofilia; a serum creatinine concentration >1.7 mg/dl, intubation, HIV, uncontrolled arterial hypertension, active peptic ulcer, bacterial endocarditis, or other conditions that could increase the risk of hemorrhage; hypersensitivity to heparin or heparin-	**Group 1** LMWH (20 mg Enoxaparin) 20 mg of enoxaparin (Lovenox, Clexane or Klexane, Rhone-Poulenc Rorer, Antony, France) subcutaneously once daily. 20 mg of enoxaparin in 0.2 ml of water for injectable preparations Start time: within 24 after randomisation End time: Treatment scheduled to last 6 to 14 days in the hospital **Group 2** LMWH (40 mg Enoxaparin) 40 mg of enoxaparin (Lovenox, Clexane or Klexane, Rhone-Poulenc Rorer, Antony, France) subcutaneously once daily. 40 mg of enoxaparin in 0.2 ml of water for injectable preparations Start time: within 24 after randomisation End time: Treatment scheduled to last 6 to 14 days in the hospital **Group 3** (Placebo) Placebo (0.2 ml of isotonic water) Start time: within 24 after randomisation End time: Treatment scheduled to last 6 to 14 days in the hospital **Additional non-**	**All cause mortality** (confirmed by:)	**Treatment period (days 1-14)** **Group 1:** 15/351 **Group 2:** 12/360 **Group 3:** 16/362 P: NR **Study period (days 1-110)** **Group 1:** 51/351 **Group 2:** 41/360 **Group 3:** 50/362 **RR (95% CI)** as compared with placebo: Group 1: 1.05 (0.71-1.56) p= 0.80 Group 2: 0.83 (0.56-1.21) p=0.31	**Funding:** Supported by grant from Rhone-Poulenc Rorer (France) **Limitations:** A number of patients were not included in the analyses for primary and secondary outcomes. Reasons below **Outcomes not reported:** pulmonary hypertension, heparin-induced thrombocytopenia; post thrombotic syndrome, quality of life, length of stay **Additional outcomes reported:** Local reaction at injection site (hematoma>5 cm in diameter); any thrombocytopaenia **Notes:** * (description: If bleeding was overt and was associated with the need for transfusion of two or more units of packed red cells or whole blood or with a decrease in the hemoglobin concentration of 2.0 g per decilitre or more from baseline or if bleeding was retroperitoneal, intracranial, or fatal)
			Fatal pulmonary embolism (confirmed by autopsy)	**Primary outcome (VT between days 1-14)** **Group 1:** 0/287 **Group 2:** 0/291 **Group 3** 0/288 P: NR **Secondary outcome (VT between days 1-110)** **Group 1:** 1/263 **Group 2:** 2/272 **Group 3:** 1/263 **P value:** NR	
			Symptomatic pulmonary embolism (confirmed by: not reported)	**Reported in text: by day 14** **Group 1:** 1/287 **Group 2:** 0/291 **Group 3:** 3/288 **P value:** NR	
			Pulmonary embolism, asymptomatic or symptomatic (confirmed by high-probability lung scanning, pulmonary angiography, or helical computed tomography or at autopsy)	**Primary outcome (VT between days 1-14)** **Group 1:** 1/287 **Group 2:** 0/291 **Group 3** 3/288 **P value:** NR **Secondary outcome (VT between days 1-110)** **Group 1:** 1/263 **Group 2:** 0/272 **Group 3:** 3/263 **P value:** NR	
			Symptomatic DVT (confirmed by: not reported)	**Primary outcome (VT between days 1-14)** **Group 1:** 3/287 **Group 2: :** 1/291 **Group 3:** 2/288 **Secondary outcome (VT between days 1-110)** **Group 1:** 6/263	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	induced thrombocytopenia; or platelet count < 100,000/mm^3 a prolonged activated partial-thromboplastin time, a prothrombin ratio of less than 50 percent, or an international normalized ratio of more than 1.2. Patients who required anticoagulant therapy and those who received any type of anticoagulant therapy for more than 48 hours. **All patients** **N:** 1,102 **No. of dropouts:** There were 236 patients not evaluated for the primary outcome (VT defined as DVT, PE, or both between days 1 and 14) and 71 patients were not evaluated for the secondary outcome (VT between days 1 and 110) reasons included in table 1. **Group 1** (20 mg Enoxaparin) **No. randomised:** 364 **No. of dropouts** No. evaluated for primary outcome: Evaluated: 287 (78.8%) Not evaluated: 77 (21.2%) No. evaluated for secondary outcome: Evaluated: 263 (72.3%) Not evaluated: 25 (6.9%) **Age (mean +/- SD):** 72.9 +/- 10.1 **M/F:** 187/176 **Reasons for hospitalisation-no. (%):** NYHA class III CHF: 76 (20.9) NYHA class IV CHF: 44 (12.1) Acute respiratory failure: 192 (52.9) Acute infectious disease: 194 (53.4) Acute rheumatic disorder: 40 (11.0) Inflammatory bowel disease: 1 (0.3) **Additional risk factors- no. (%):** Age>75 yr: 172 (47.4) Cancer (previous or current): 56 (15.4) History of VT: 35 (9.6) Obesity: 79 (21.8) Varicose veins: 88 (24.2)	**comparative prophylaxis:** Elastic bandages or support stockings, and physiotherapy were used according to the usual practice at each centre. Throught the treatment period, intramuscular injections and treatment with nephrotoxic substances, particularly nephrotoxic antibiotics, were not permitted. Centres were advised to avoid giving patients nonsteroidal anti-inflammatory drugs		**Group 2: :** 3/272 **Group 3:** 4/263	Reasons for patients not evaluated for primary outcome, analysis of VTE at 14 days: death 28/236; patient's refusal 62/236, investigator's decision 62/236, venography technically unfeasible 12/236, venogram could not be evaluated 72/236, unknown, venography not performed 10/236 Reasons for patients not evaluated for secondary outcome, analysis of VTE at 110 days: death 61/71; loss to follow up or scheduled visit before 90 days 10/71
			DVT, asymptomatic or symptomatic (confirmed by systematic ascending contract venography of the legs between days 6 and 14, or earlier if thrombosis was clinically suspected. If venography was infeasible venous ultrasonography was performed.)	**Primary outcome (VT between days 1-14)** **Group 1:** 42/287 **Group 2: :** 16/291 **Group 3:** 41/288 **RR (95% CI)** as compared with placebo: Group 1: 1.05 (0.71-1.57) p= 0.81 Group 2: 0.40 (0.23-0.69) p<0.001 **Secondary outcome (VT between days 1-110)** **Group 1:** 44/263 **Group 2: :** 17/272 **Group 3:** 42/263 **RR (95% CI)** as compared with placebo: Group 1: 1.07 (0.73-1.58) p= 0.81 Group 2: 0.40 (0.23-0.69) p<0.001	
			Thigh DVT Reported in table described as proximal deep-vein thrombosis. Confirmed by see above	**Primary outcome (VT between days 1-14)** **Group 1:** 13/287 **Group 2:** 5/291 **Group 3:** 14/288 **RR (95% CI)** as compared with placebo: Group 1: 0.93 (0.45-1.94) p=0 1 Group 2: 0.35 (0.13-0.97) p=0.04 **Secondary outcome (VT between days 1-110)** **Group 1:**14/263 **Group 2:** 6/272 **Group 3:** 17/263 **RR (95% CI)** as compared with placebo: Group 1: 0.83 (0.42-1.64) p= 0.71 Group 2: 0.34 (0.14-0.86) p=0.02	
			Calf DVT Reported in table described as distal deep-vein thrombosis. Confirmed by see above	**Primary outcome (VT between days 1-14)** **Group 1:** 30/287 **Group 2: :** 11/291 **Group 3:** 27/288 G **Secondary outcome (VT between days 1-110)** **Group 1:** 31/263 **Group 2:** 12/272 **Group 3:** 27/263	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Hormone therapy: 8 (2.2) Chronic heart failure: 106 (29.2) Chronic respiratory failure: 197 (54.3) >=2 Risk factors 241 (66.4) **Group 2** (40 mg Enoxaparin) **No. randomised:** 367 **No. of dropouts:** No. evaluated for primary outcome: Evaluated: 291 (79.3) Not evaluated 76 (20.7%) No. evaluated for secondary outcome: Evaluated: 272 (74.1%) Not evaluated: 20 (5.4%) **Age (mean):** 73.1 +/- 10.8 **M/F:** 171/196 **Reasons for hospitalisation-no. (%):** NYHA class III CHF: 103 (28.1) NYHA class IV CHF: 26 (7.1) Acute respiratory failure: 195 (53.1) Acute infectious disease: 197 (53.7) Acute rheumatic disorder: 28 (7.6) Inflammatory bowel disease: 3 (0.8) **Additional risk factors- no. (%):** Age>75 yr: 185 (50.4) Cancer (previous or current): 45 (12.3) History of VT: 30 (8.2) Obesity: 72 (19.6) Varicose veins: 98 (26.7) Hormone therapy: 5 (1.4) Chronic heart failure: 123 (33.5) Chronic respiratory failure: 195 (53.1) >=2 Risk factors: 245 (66.8) **Group 3** (Placebo) **No. randomised:** 371 **No. of dropouts:** No. evaluated for primary outcome: Evaluated: 288 (77.6 %) Not evaluated: 83 (22.4%)		**Fatal bleeding** (description:)	**Treatment period (days 1-14)** **Group 1:** 0/351 **Group 2:** 1/360 **Group 3:** 0/362 P value not reported Study reports NS difference between groups **Study period (days 1-110)** **Group 1:** 1/351 **Group 2: :** 2/360 **Group 3:** 0/362 P value not reported Study reports NS difference between groups	
			Major bleeding *	**Treatment period (days 1-14)** **Group 1:** 1/351 **Group 2:** 6/360 **Group 3:** 4/362 P value not reported Study reports difference NS **Study period (days 1-110)** **Group 1:** 4/351 **Group 2:** 12/360 **Group 3:** 7/362 P value not reported Study reports difference NS	
			Minor bleeding (description: Overt but did not meet the other criteria for major bleeding)	**Treatment period (days 1-14)** **Group 1:** 40/351 **Group 2:** 39/360 **Group 3:** 27/362 P value not reported Study reports difference NS **Study period (days 1-110)** **Group 1:** 57/351 **Group 2:** 51/360 **Group 3:** 45/362 P value not reported Study reports difference NS	
			Venous thromboembolic events (defined as DVT, PE or both)	**Primary outcome (VT between days 1-14)** **Group 1:** 43/287 **Group 2:** 16/291 **Group 3:** 43/288 **RR (95% CI)** as compared with placebo: Group 1: 1.02 (0.70-1.51) p= 0.90 Group 2: 0.37 (0.22-0.63) p<0.001 **Secondary outcome (VT between days 1-110)** **Group 1** (20 mg Enoxaparin):46/263	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No. evaluated for secondary outcome: Evaluated: 263 (70.9%) Not evaluated: 26 (7.0 %) **Age (mean):** 74.1 +/- 10.6 **M/F:** 192/178 **Reasons for hospitalisation-no. (%):** NYHA class III CHF: 95 (25.7) NYHA class IV CHF: 32 (8.6) Acute respiratory failure: 202 (54.6) Acute infectious disease: 193 (52.2) Acute rheumatic disorder: 32 (8.6) Inflammatory bowel disease: 1 (0.3) **Additional risk factors- no. (%):** Age>75 yr: 197 (53.2) Cancer (previous or current): 56 (15.1) History of VT: 39 (10.5) Obesity: 71 (19.2) Varicose veins: 93 (25.1) Hormone therapy: 9 (2.4) Chronic heart failure: 124 (33.5) Chronic respiratory failure: 197 (53.2) >=2 Risk factors: 247 (66.8)			**Group 2:** 19/272 **Group 3:** 45/263 **RR (95% CI)** as compared with placebo: Group 1: 1.02 (0.70-1.49) p= 0.91 Group 2: 0.41 (0.25-0.68) p<0.001	
			DVT and PE	**Primary outcome (VT between days 1-14)** **Group 1:** 1/287 **Group 2:** 0/291 **Group 3** (Placebo): 1/288 **Secondary outcome (VT between days 1-110)** **Group 1:** 1/263 **Group 2:** 0/272 **Group 3:** 1/263	
			Thrombocytopaenia (Thrombocytopenia was defined as a decrease in the platelet count of less than 100,000/mm^3. Thrombocytopenia was considered severe if the platelet count was less than 50,000/mm^3	**Treatment period (days 1-14)** **Group 1:** 10/351 (4 related to treatment) **Group 2:** 8/360 (2 related to treatment) **Group 3:** 3/362 (8 related to treatment) P value not reported Study reports NS difference **Severe thrombocytopenia:** **Group 1:** 0/351 **Group 2:** 0/360 **Group 3:** 3/362 **Study period (days 1-110)** **Thrombocyotpenia:** **Group 1:** 10/351 **Group 2:** 8/360 **Group 3:** 13/362 **Severe thrombocytopenia:** **Group 1:** 0/351 **Group 2:** 0/360 **Group 3:** 3/362 P value not reported Study reports NS difference	

LMWH comparing dose or timing

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Spiro et al., 1994[618]	Multicentre RCT	1+	**Total:** 572 Multicentre study involving 32 institutions Int A: 210 In B: 201 Int C: 161 (see comments)	**Type of surgery:** Hip replacement surgery, including primary and revision procedures, in patients 31 years or older	**Int A:** Enoxaparin 30mg every 12 hours	**Int B:** Enoxaparin 40mg once daily	**Study period:** 7 days, or earlier if indicated, or on day of discharge. Follow up mentioned but no period given.	**DVT** Confirmed by: bilateral contrast venography	**Int A:** 16/143 **Int B:** 21/149 **Int C:** 36/116 **p value:** A to B >0.2; C to B =0.005; C to A <0.001	**Comments:** Int C was stopped because of the high incidence of treatment failure Only 71.3% of patients evaluated for DVT. Multicentre study, not all centres used a valid diagnostic technique (same numbers in each group). An intention to treat analysis was followed. Results are available for patients diagnosed by valid test alone as well as all patients. **Other outcomes reported:** Total proximal and distal DVTs (i.e. confirmed by venography, supportive non-invasive vascular examinations or other clinical evidence of treatment failure.) thrombocytosis, haemoglobin levels, alanine aminiotransferase, minor bleeding
				Intervention: Mean age: 65.2±10.6 yrs M/F:124/84		**Int C:** 3rd arm Enoxaparin 10mg once daily		**Proximal DVT** Confirmed by: bilateral contrast venography	**Int A:** 8/143 **Int B:** 9/149 **Int C:** 16/116 **p value:** not reported	
				Control: Mean age: 64.8±10.3 yrs M/F:127/72	**Timing:** Administered within 24 hours after surgery and continued for as long as 7 days. **Additional non-comparative prophylaxis:** Not reported	**Timing:** administered within 24 hours after surgery and continued for as long as 7 days.		**Distal DVT** Confirmed by: bilateral contrast venography	**Int A:** 8/143 **Int B:** 12/149 **Int C:** 20/116 **p value:** not reported	
				3rd discontinued arm: Mean age: 63.9±10.5 yrs M/F:107/54				**PE** Confirmed by clinical evidence in patients subsequent to confirmation of DVT	**Int A:** 0/143 **Int B:** 1/149 **Int C:** 1/116 **p value:** not reported	
				Pre-existing risk factors: Excluded patients include: a history of DVT, PE or both and heparin associated thrombocytopenia.				**Major bleeding episodes**	**Int A:** 11/208 **Int B:** 7/199 **Int C:** 3/161 **p value:** not reported	
								Mild thrombocytopenia episodes (>100x10^9/L and < lower limit of normal)	**Int A:** 28/208) **Int B:** 23/199) **Int C:** 17/161) **p value:** A to B not given ; A to C >0.2; B to C >0.2	
								Moderate thrombocytopenia episodes	**Int A:** 1/208 **Int B:** 2/199 **Int C:** 1/161	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
								(20x10^9/L to 100x10^9/L. In no case was the count <50x10^9/L).	**p value:** A to B not given; A to C >0.2; B to C >0.2	**Not reported:** PTS, QoL **Funding:** Rhone Poulenc Pharmaceuticals
								Mortality	**Int A:** 0/208 **Int B:** 2/199 **Int C:** 0/161 **p value:** not reported	
								Adverse events (no. of patients)	**Int A:** 10/208 **Int B:** 16/199 **Int C:** 13/161 **p value:** not reported	
								No. of patients rehospitalised	**Int A:** 2/208 **Int B:** 2/199 **Int C:** 2/161 **p value:** not reported	

Evidence Table 55: Unfractioned Heparin - comparing dose or timing

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Cade et al 1983[91]	RCT	1+	**Total:** 100 Intervention: n = 51 Control: n = 49	**Type of surgery:** Major thoracic (incl. lobectomy, pneumonectomy, oesophagogastrectomy, thoracotomy) (& Duration of surgery)	**Type:** LDUH **Dose:** 7500 IU	**Type:** LDUH **Dose:** 5000 IU	10 days or until the patient was fully ambulant (at least 5 days).	**DVT** Confirmed by: FUT daily until patient fully ambulant or 10th post-op day	**Int:** 11/51 **Control:** 11/49 **p value:** > 0.2	**Comments:** DVT significantly more common in male than female patients.
				Intervention: Mean age: 60 (range 46-77) yrs M/F:42/9	**Timing:** Begun 1-2 hrs pre-op then repeated twice daily until patient fully ambulated	**Timing:** Begun 1-2 hrs pre-op then repeated twice daily until patient fully ambulated		**Bleeding related complications** Postoperative bleeding: measured blood loss from thoracic drain tubes and post-operative transfusion needs	**Actual values not reported.** No excessive bleeding was reported and there was no clinically detectable difference in bleeding between the two groups	**Not reported:** PVT, PE, PTS, QoL, Survival, and LoS.
				Control: Mean age: 61 (range 44-86) yrs M/F:38/11	**Additional non-comparative prophylaxis:** Electrical calf muscle stimulation during surgery	**Additional non-comparative prophylaxis:** Electrical calf muscle stimulation during surgery				

Evidence Table 56: Vitamin K antagonists - comparing dose or timing

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Bern et al., 2002[58]	RCT	1+	**Total:** 98 (20 excluded) Intervention : n = 43 Control: n = 35	**Type of surgery:** Unilateral total hip replacement (for degenerative disease). **Intervention: (49 patients randomised)** Mean age: 61.9 Range: 31-91 yrs M/F:25/24 **Control: (49 patients randomised)** Mean age: 65.3 Range: 29-84 yrs M/F:30/19 **Pre-existing risk factors:**	**Type:** adjusted dose warfarin **Dose:** 5mg pre-op, then PT 1.3 – 1.5 x normal **Timing:** 5 mg eve pre-op, then adjusted dose until 6th week **Additional non-comparative prophylaxis:** stockings. 23/49 originally randomised received dextran intraoperatively	**Type:** fixed low-dose warfarin **Dose:** 1 mg **Timing:** begun 7 days pre-op and continued until 6th week **Additional non-comparative prophylaxis:** stockings. 29/49 originally randomised received dextran intraoperatively	**Both groups:** 6 weeks post-op	**DVT** Confirmed by: Doppler duplex US at discharge or 7 days post-op. Repeated at 6 week FU	**Int:** 0/43 **Control:** 0/35 **p value:** 1.0000	**Comments:** 6 patients excluded from adjusted dose and 14 from fixed dose group. Difference in withdrawals due to 8 patients. 1 withdrawal from each group developed DVT. **Not reported:** Proximal DVT, PTS, QoL, Survival, LoS **Funding:** Study supported by donations to the Foundation for Haematology Research, and residual funds from previous grant from Dupont Pharmaceuticals Company (Wilmington, DE)
								PE Confirmed by: Not routinely assessed. Clinical suspicion investigated with V/Q and angiogram	**Int:** 0/43 **Control:** 0/35 **p value:** 1.0000	
								Bleeding related complications Estimated perioperative blood loss (mL) Transfusion requirements (units)	**Perioperative blood loss** mean (range) **Int:** 625 (200 – 2,250) **Control:** 557 (200 – 1400) **p value:** Not significant **Transfusions given** mean (range) **Int:** 2.4 (0-5) **Control:** 2.3 (0-5) **p value:** Not significant	

VKA - comparing dose or timing

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Francis et al., 1996[194]	RCT	1+	**Total:** 220 **Intervention:** 110 **Control:** 110 110 randomised into each arm but 24 excluded from analysis of DVT and 12 excluded from analysis of bleeding*	**Type of surgery:** Elective knee replacement **Intervention** mean ±SD age: 69 ±10 years (n = 95) **Control** mean ±SD age: 69 ± years (n = 101) **Pre-existing risk factors:** History of venous thromboembolism Int: 15 (n = 95) Cont: 21 (n = 101)	Warfarin: Preoperatively 2.5mg alternating with 5mg daily. **Dose**: adjusted to achieve and INR of approximately 1.5 on day of surgery. Post-operatively dose adjusted to achieve a target INR of 2.2 **Timing:** Started 10-14 days preoperatively and continued until venography between postoperative day 5 and 9 **Additional non-comparative prophylaxis:** Thigh-high GCS on both legs (all patients) Continuous passive motion in recovery room (most patients) Regional Anaesthesia: 75 (n = 95)	Warfarin: Initial dose based on weight, subsequent daily doses adjusted to achieve a INR of 2.2 **Timing:** Started the night before surgery and continued until venography between postoperative day 5 and 9 **Additional non-comparative prophylaxis:** Thigh-high GCS on both legs (all patients) Continuous passive motion in recovery room (most patients) Regional Anaesthesia 82 (n = 101)	Postoperatively between day 5 and 9	**DVT** Confirmed by bilateral or unilateral venography	**Int:** 37/95 **Cont:** 38/101 **p value:** not significant	**Comments:** **Not reported:** PE, LoS, QoL, PTS, **Also reported:** DVT confined to calf veins, thrombosis of the minor veins, lowest postoperative haematocrit count **Exclusions** No surgery or prophylaxis: **Intervention:** 7 **Control:** 5 No venography **Intervention:** 8 **Control:** 4 **Funding:** National Heart, Lung and Blood Institute, National Institutes of Health.
								Proximal DVT Confirmed by venography	**Int:** 5/95 **Cont:** 7/101 **p value:** not significant	
								PE (symptomatic)	**Int:** 0/95 **Cont:** 0/101 not significant	
								Major bleeding complications	**Int:** 5/103 **Cont:** 2/105 **p value:** (not reported)	
								Total bleeding complications	**Int:** 11/103 **Cont:** 9/105 **p value:** (not reported)	
								Mean ± SD units of blood transfused	**Int:** 1.33 ±1.26 (n = 103) **Cont:** 0.95 ±1.22 (n = 105) **p value:** <0.05	

VKA - comparing dose or timing

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Roderick et al., 2005[557] 2 RCTs included: [184,530] All of these studies were included in the guideline review.	Systematic review	1+	Total: 267 Int: 135 Cont: 132	**Type of surgery:** Orthopaedic (1 study) Gynaecological (1 study)	**OAC-adjusted** **1st study:** warfarin adjusted INR 2-4 **Timing:** Night pre-op to day 3 post-op (fixed) than adjuvant **2nd study:** Nic adjusted INR 2.4 **Timing:** 5 day pre-op to discharge **Additional non-comparative prophylaxis:** Not reported	**OAC-fixed** **Warfarin 1 mg** **Timing:** 1st study night pre-op to 14 days post op. 2nd study mean 20d pre-op to discharge. **Additional non-comparative prophylaxis:** Not reported	NR	**DVT** confirmed by venography or fibrinogen uptake/Doppler US	**Int:** 17/133 **Cont:** 33/129 **p value:** 0.0114	**Not reported:** LoS, QoL, PTS
								PE (scan)	**Int:** 1/98 **Cont:** 0/97 (reported in 1 study) **p value:** 1.0000	
								Major bleeds	**Int:** 8/135 **Cont:** 6/132 **p value:** 0.7850	
								Proximal DVT	**Int:** 4/98 **Cont:** 11/97 (reported in 1 study) **p value:** 0.0650	

VKA - comparing dose or timing

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Swierstra et al., 1988[632]	RCT	1+	**Total:** 101 Intervention: n = 50 Control: n = 51	**Type of surgery:** Total hip replacement **Mean duration of surgery:** (mins) **Intervention:** 178 ± 34 **Control:** 175 ± 27 **Intervention:** Mean age: 66±11 yrs M/F:13/37 **Control:** Mean age: 66±10 yrs M/F:7/44 **Pre-existing risk factors:** previous history of VTE, varicosis.	**Type:** Acenocoumarol starting 4 days pre-op **Dose:** 3mg pre-op then INR 2.1. **Timing:** Begun 4 days pre-op. 3mg daily on 4th and 3rd day pre-op, then adjusted dose aiming for INR of 1.5-1.6 during surgery. Post-op adjusted dose, INR 2.1 until discharge. **Additional non-comparative prophylaxis:** None reported	**Type:** Acenocoumarol **Dose:** 3mg pre-op then INR 2.1. **Timing:** 3mg 1 day pre-op and day of op, then adjusted dose INR 2.1 until discharge. **Additional non-comparative prophylaxis:** None reported	**Both groups:** to discharge	**Proximal DVT** Confirmed by: Venography (99mTc plasmin), 10 days post-op	**Int:** 12/50 **Control:** 11/51 **p value:** Not significant	**Comments:** Unclear how many patients were randomised and how many of these were excluded. 17 intervention and 22 control patients used NSAIDs. Analysis showed no relationship between NSAID use and development of Proximal DVT **Not reported:** Calf vein thrombi, PE, PTS, QoL, LoS, survival, funding
								Bleeding related complications Perioperative blood loss – amount of blood in suction apparatus, weight of gauzes Post-operative blood loss – contents of drain bottles No of blood transfusions	**Perioperative blood loss:** **Int:** 1.11± 0.52 L **Control:** 1.2. ± 0.62 L **p value:** Not significant. **Postoperative blood loss:** **Int:** 0.6 ± 0.41 L **Control:** 0.58 ± 0.33L **p value:** Not significant	

Evidence Table 57: Aspirin – comparing dose or timing

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Antiplatelet Trialists' Collaboration, 1994[21] 3 out of 55 trials [12,259,436] All of these studies were included in the guideline review.	Systematic review	1+	184	**Type of surgery:** Elective orthopaedic	Higher dose aspirin	Lower dose aspirin	Majority 1 or 2 week studies	**DVT** Confirmed by: fibrinogen uptake test or venography	**Int:** 32/93 **Control:** 34/91 **p value:** 0.65 (3 studies)	Not stated what was considered a major bleed Reported pulmonary emboli but did not state how if they were confirmed. **Not reported:** QoL, survival, LoS, PTS, funding
					Additional non-comparative prophylaxis: None reported	**Additional non-comparative prophylaxis:** None reported		**Major bleed**	**Int: 0**/43 **Control:** 1/41 **p value:** 0.43 (2 studies)	

Effectiveness - Extended duration or post discharge prophylaxis

Evidence Table 58: Fondaparinux - extended duration or post discharge prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Cohen et al., 2007[122] **Country of study:** Brazil, HK, UK, Spain **Study design:** Randomised single blinded study, multicentre **List who was masked to interventions:** Ultrasonographers **Evidence level:** 1+ **Duration of follow-up:** 35-49 days	**Patient group:** Hip Surgery – fracture and elective **Setting:** A multinational Phase III study **Inclusion criteria:** - Minimum age 18 years - Primary of revision total hip replacement - Surgery for fracture of the proximal third of the femur **Exclusion criteria:** - Bilateral joint surgery - Multiple trauma - Delay >24 hours between trauma and admission - Conditions precluding use of graduated compression stockings - Leg oedema - Peripheral vascular disease - Peripheral neuropathy - Marked leg deformity - Conditions that increase the risk of bleeding - Pregnant/lactacting women or those of child bearing age taking inadequate contraceptive precautions. **All patients** **N recruited:** 874 **N randomised:** 856 **N evaluable:** 795	**Group 1:** **GCS + fondaparinux** Type: Thigh length worn by 266/389 (68%). Shorter length if "not permitted by circumference of thigh"), Start : Pre-operative End : Last day of follow up Duration: 35-49 days for GCS Actual usage: mean 42 days, median 44 days, range 1-86 days Continuous use in hospital: 323/380 (85%) Continuous use post discharge: 252/330 (76%) **Group 2** **Fondaparinux only** **Additional non-comparative prophylaxis:** Timing and dose for fondaparinux (Group 1 and Group 2) Dose: 2.5mg daily Start time: 6 hours after wound closure. The 2nd dose 18 to 24 hours later. Subsequent doses were administered daily at a	**All cause mortality** (confirmed by: no autopsy reported)	**Group1:** 1/430 **Group 2:** 3/426 **P value:** NS Noted as unrelated to VTE. Cause s of death were: cardiac failure, haemoptysis, ischaemic heart disease and myocardial infarction.	**Funding:** The sponsor of the study was not stated. "One or more of the authors have received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this article" **Limitations:** - Study was concluded early. Authors reasoned that it would be "futile" to continue when difference between arms were small. The study was stopped early, therefore study is underpowered as the total sample size needed according to calculations was 1072 and there were 856 patients randomised - Method for PE assessment or confirmation not stated - Study reported VTE as the primary outcome.
			Fatal pulmonary embolism (confirmed by: No autopsy reported. Defined as "sudden death"	**Group1:** 0/430 **Group 2:** 0426 **P value:** NS	
			Symptomatic pulmonary embolism (confirmed by: "sudden death". No mention of objective confirmation method)	**Group1:** 0/430 **Group 2:** 0426 **P value:** NS	
			Symptomatic DVT (confirmed by: ultrasound or venography) All distal DVTS	**Group1:** 4/395 **Group 2:** 4/400 **P value:** NS	
			DVT, asymptomatic or symptomatic (reported as VTE, defined as: Symptomatic or asymptomatic proximal, symptomatic distal, PE or fatal PE. DUS scheduled within a week of Day 42)	**Group1:** 19/395 **Group 2:** 22/400 **P value:** NS Distal asymptomatic DVT not reported	
			Thigh DVT(screened for by: DUS scheduled within a week of Day 42, asymptomatic)	**Group1:** 16/395 **Group 2:** 19/400 **P value:** NS	
			Calf DVT (screened for by: only the symptomatic ones)	**Group1:** 4/395 **Group 2:** 4/400 **P value:**	
			Fatal bleeding (description:)	**Group1:** 0/430 **Group 2:** 1/426 **P value:** NS	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 **No. randomised:** 430 **N evaluable:** 395 **No. of dropouts:** 35 did not receive study medication **Group 2** **No. randomised:** 426 **N evaluable:** 400 **No. of dropouts:** 26 did not receive study medication **Surgery types:** **Elective total hip replacement:** 756/795 **Primary/ Revision** Group 1: 352/23 Group 2: 362/19 **Hip Fracture:** 39/795 **Standard/ cervical/trochanteric:** Group 1: 16/9/7 Group 2: 23/17/6 **Additional risk factors:** **Age** [mean (range)]: Group 1: 65 (18 to 97) Group 2: 65 (23 to 99) **Gender- M/F** (% Female): Group 1: 163/228 (58) Group 2: 179/224 (56) **BMI** , mean (range): Group 1: 28 (15.0 to 44.6) Group 2: 28 (16.9 to 50.1) **Obesity** (%): Group 1: : 75/388 (19) Group 2: 85 /402 (21) **History of VTE** (%): Group 1: 11/390(2.8) Group 2: 13 /403(3.2) **Family history of VTE** (%):	median interval of 22 to 26 hours for between 5 and 9 days. Duration: 5-9 days, Mean: 7 days (range 1-9 days in both groups)	**Major bleeding** (description: fatal bleeding, bleeding into critical organs or reoperation required, clinically overt bleeding leading to Hb level dropped ≥2 g/dl, transfusion ≥2 units)	**Group1:** 0/391 **Group 2:** 1/404 **P value:** NS	Distal DVT only reported if symptomatic **Outcomes not reported:** PE, symptomatic or asymptomatic, Calf DVT (asymptomatic) , Neurological and GI bleeding, HIT, PTS syndrome, Pulmonary hypertension, Length of Stay **Additional outcomes reported:** - Rates of VTE in long vs short stockings: 14/251 (5.6%) vs 5/118 (4.1%) - Need for transfusion - Anaemia - Wound secretion - Haemoglobin decreased **Notes:** Details of patients withdrawn from the study provided in text and flow chart The number of patients wearing compression stockings fell with time. * Calculated by NCC team using Fisher's Exact test
		Minor bleeding (description:)	**Group1:** 25/391 **Group 2:** 29/404 **P value:** NS	
		Quality of life (as measured by: EQ-5D) **Health states, median, (range), n** Screening Last day of treatment Follow up Screening Last day of treatment Follow up **Overall (visual analogue scale)** Screening Last day of treatment Follow up Screening Last day of treatment Follow up	**Group 1** 0.16(-0.59 to 1.00), 377 0.59(-0.43 to 1.00), 345 0.71(-0.09 to 1.00), 330 **Group 2** 0.21(-0.59 to 1.00), 394 0.59(-0.59 to 1.00), 344 0.76(-0.17 to 1.00), 328 **Group 1** 60 (0 to 100), 369 70(6 to 100), 341 80(3 to 100), 333 **Group 2** 65(0 to 100), 389 70(20 to 100),339 90(0 to 100),325	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1: 16/390 (4.1) Group 2: 12/403(2.9) **History of cancer** (%): Group 1 : 18/390 (4.6) Group 2: 29/403 (7.2) **Varicose veins and/or chronic venous insufficiency** (%): Group 1: 37/390(9.5) Group 2: 26/403 (6.5) **Previous ischaemic heart disease** (%) Group 1: 20 /390(5.1) Group 2: 14/403 (3.4) **Previous stroke** (%): Group 1: 3/390 (0.8) Group 2: 7/403 (1.7) **Chronic heart failure** (%): Group 2: 3/403 (0.7) Group 1 : 4/390 (1.0) **Chronic respiratory failure** (%): Group 1: 2/390 (0.5) Group 2: 7/403 (1.7) **History of thrombophilia** (%): Group 1 : 1/390 (0.3) Group 2: 0/403 (0) **Oestrogen use** (%): Group 1: 16/390(4.0) Group 2: 13/403 (3.2) **Hip replacement ≤ 12 months** (%): Group 1 : 16/390 (4.1) Group 2: 22/403 (5.4) **Knee replacement ≤12 months** (%): Group 1 : 0/390 (0) Group 2 : 0/403 (0) **Hip fracture ≤ 12 months** (%): Group 1: 1/390 (0.2) Group 2: 2/403 (0.5)				

Fondaparinux – extended duration or post discharge prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Eriksson & Lassen, 2003[176]	RCT	1+	**Total:** 656 **Intervention** n: 326 **Control** n: 330 Treatment compliance verified: **Intervention:** 307/326 **Control:** 305/330 I patient from placebo group received Fondaparinux by mistake.	**Type of surgery:** Patients undergoing standard surgery for fracture of the upper third of femur, including femoral head & neck were included if surgery was planned within 48 hours after admission. **Intervention:** Median age: 79 (range, 23-94 years; M/F:92/235 **Control:** Median age: 79 (range, 28-96 years; M/F:98/231	2.5 mg of Fondaparinux sodium in 0.5ml water once daily subcutaneously till day 6 to 8. Day of surgery is day 1. After this open label period pts were randomised to receive either 2.5 mg of Fondaparinux sodium or placebo once daily subcutaneously till day 25 to 31. The first dose was given less than 2 hours after randomisation. **Additional non-comparative prophylaxis:** The use of graduated elastic stockings was permitted and early mobilisation was strongly recommended. Graduated compression stockings: 92/208 No. patients using anticoagulation or antiplatelet therapy other than aspirin: 6/208 No. patients using NSAIDs: 42/208	2.5 mg of Fondaparinux sodium in 0.5ml water once daily subcutaneously till day 6 to 8. Day of surgery is day 1. After this open label period pts were randomised to receive either 2.5 mg of Fondaparinux sodium or placebo 0.5ml of isotonic sodium chloride solution once daily subcutaneously till day 25 to 31. The first dose was given less than 2 hours after randomisation. **Additional non-comparative prophylaxis:** The use of graduated elastic stockings was permitted and early mobilisation was strongly recommended. Graduated compression stockings:	31 days or 32 days?	**DVT** Confirmed by: systematic ascending bilateral contrast venography	**Int:** 3/208 **Control:** 74/218 **p value:** < 0.001	No. of patients available for Proximal DVT analysis was more than DVT as the patient was considered if both proximal veins were visualised regardless of whether the distal vein was visualised or not. Around a third of patients in each arm (int: 118/326, control: 110/330) were not included in the analysis because they had no VTE assessment or inadequate VTE assessment. **Funding:** Grant from Sanofi-synthelabo, Paris, France and NV Organon, Oss, The Netherlands. **Not reported:**
								Proximal DVT* Confirmed by: systematic ascending bilateral contrast venography	**Int: 2**/221 **Control:** 35/222 **p value:** < 0.001	
								Symptomatic PE Confirmed by: high – probability lung scanning, pulmonary angiography, spiral computed tomography or at autopsy	**Int:** 1/326 **Control:** 9/330 **p value:** 0.02	
								VTE	**Int:** 3/208 (1.4%) **Control:** 77/220 (35%) **p value:** < 0.001	
								Bleeding leading to reopertion	**Int:** 2/327 **Control:** 2/329 **p value:** 1.0000	
								Overt bleeding	**Int:** 6/327 **Control:** 0/329 **p value:** 0.0150	
								Minor bleeding	**Int:** 5 **Control:** 2/329 **p value:**	
								Transfusion	**Int:** 29 **Control:** 20/329 **p value:**	
								Death from any cause	**Int:** 6 **Control:** 8	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
						107/220 No. patients using anticoagulation or antiplatelet therapy other than aspirin: 5/220 No. patients using NSAIDs: 34/220			**p value:**	

Evidence Table 59: LMWH – extended duration or post discharge prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Bergqvist et al., 1996[47]	RCT	1+	Total: 262 Intervention n: 131 Control n: 131	**Type of surgery:** Patients scheduled for Total hip replacement surgery. Surgery was performed expeditiously with a mean duration of 1.9 hours (range 1.0 to 5.0). **Intervention:** Mean age: 70 (range: 44 - 87 years) M/F:56/75 **Control:** Mean age: 70 (Range: 44 – 87 years) M/F:57/74 **Pre-existing risk factors:** Previous VTE: **Int:** n = 8 **Control:** n = 12 Varicose veins: **Int:** n = 27 **Control:** n = 31 Leg ulcer: **Int:** n = 2 **Control:** n = 3	**Type, dose and timing:** 40 mg of Enoxaparin injected subcutaneously into abdomen once daily. The first active dose was given 12±2 hrs preoperatively until day 21 **Additional non-comparative prophylaxis:** Not reported	**Type, dose and timing:** Placebo or Single dose of 0.4 ml saline.	3 months	**DVT** confirmed by bilateral ascending phlebography	**Int:** 21/117 **Control:** 43/116 **p value:** 0.0012	
								PE Confirmed by ventilation – perfusion lung scan or a pulmonary angiography.	**Int:** 0/117 **Control:** 2/116 **p value:** 0.2468	

LMWH – extended duration or post discharge prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Bergqvist et al., 2002[46]	RCT	1+	**Total:** Results for 332 **Intervention:** n = 165 **Control:** n = 167 501 randomised **Int:** 253 **Control:** 248 Outcome not obtained/not interpretable for 88 int. and 81 cont. patients	**Type of surgery:** Abdominal (curative surgery for abdominal/pelvic cancer) Patients excluded from randomisation if had objectively confirmed VTE or major bleeding. **Duration of surgery:** **Int:** Median: 3hr 3min (range 23 min – 9hr 35min). **Cont:** Median: 3hr 5 min (range 45 min – 11hr). **Age and gender:** **Intervention:** Median age: 66, range 40-90 M/F: 96/69 **Control:** Median age: 65, range 30-87 M/F: 104/63 **Pre-existing risk factors:** All patients had malignant cancer. Patients with history of VTE within previous 3 mo. excluded.	**Type:** Extended (4 wk) LMWH (Enoxaparin) **Dose:** 40 mg **Timing:** begun 10-14 hrs pre-op then once daily for 25-31 days **Additional non-comparative prophylaxis:** Not reported	**Type:** LMWH (1wk) (Enoxaparin) then placebo **Dose:** 40mg **Timing:** begun 10-14 hrs pre-op then once daily for 6-10 days. Placebo for further 19-21 days.	**Both groups:** 3 months ± 10 days	**DVT** Confirmed by: bilateral venography within 3 days of final injection (days 25-31 post-op).	**Int:** 8/165 **Control:** 20/167 **p value:** 0.02	**Comments:** Patients randomised after initial treatment with LMWH for 6-10 days. Multi-centre trial at 37 centres across 8 European countries. Randomisation stratified by country where institution located. Between site differences not considered. At 3 mo. FU a further 4 DVTs (1 int. 3 cont.) were clinically suspected. Results also reported for haemorrhage during double-blind and FU periods separately. No significant difference between groups for any outcome. * denominator is total no of patients randomised **Not reported:** QoL, LoS **Funding:**
								Proximal DVT Confirmed by: bilateral venography within 3 days of final injection (days 25-31 post-op).	**Int:** 1/165 **Control:** 3/167 **p value:** 0.6228	
								Symptomatic PE Confirmed by: V/Q scan or angiogram	**Int:** 0/165 **Control:** 1/167 **p value:** 1.000 Patient with PE also had distal DVT	
								Fatal PE Confirmed by: autopsy	**Int:** 0/165 **Control:** 1/167 **p value:** 1.000 Fatal PE occurred during 3 mo. FU period	
								Major haemorrhage (at 3 mo FU)*	**Int:** 3/253 **Control:** 1/248 **p value:** 0.62	
								Minor haemorrhage (at 3 mo FU)*	**Int:** 12/253 **Control:** 9/248 **p value:** 0.66	
								Total haemorrhage (at 3 mo FU)*	**Int:** 11/253 **Control:** 18/248 **p value:** 0.20	
								Survival	**Int:** 250/253 **Control:** 249/248 **p value:** Not reported	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
										Sponsored by Aventis pharmaceuticals. Two company representatives were involved in statistical analysis and writing of manuscript.

LMWH – extended duration or post discharge prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Heit et al., 2000[272]	Multi-centre RCT	1+	**Total:** Intervention: n= 607 Control: n= 588	**Type of surgery:** Orthopaedic (total hip or knee replacement) (& Duration of surgery) **Intervention:** Mean age: 65±11 yrs M/F:265/342 **Control:** Mean age: 66±11 M/F:275/313 **Pre-existing Risk Factors:** Not reported	**Type:** Extended (6 week) LMWH (ardeparin sodium) **Dose:** 50 IU/kg body weight twice daily to discharge, then 100 IU/kg once daily. **Timing:** Begun with 24 hours post-op. Continued until 6 weeks post-op. **Additional non-comparative prophylaxis:** Not reported	**Type:** LMWH (ardeparin sodium), then placebo **Dose:** 50 IU/kg body weight twice daily **Timing:** Begun within 24 hours of surgery and continued until discharge (4-10 days). Placebo as per intervention schedule. **Additional non-comparative prophylaxis:** Not reported	**Both:** 6 weeks	**Symptomatic DVT** Confirmed by: Venous duplex ultrasonography or venography	**Int:** 4/607 **Control:** 8/588 **OR: 0.5 (0.1-1.6)** **p value:** >0.2	**Comments:** Multicentre trial conducted ay 33 clinical centres. Patients randomised after initial treatment with LMWH for 4-10 days. Results reported from after patients randomised after initial treatment. **Not reported:** Asymptomatic DVT, proximal DVT, post thrombotic leg, **Funding:** Wyth-Ayerst Research, Philadelphia
								Symptomatic PE Confirmed by: ventilation perfusion lung scanning or pulmonary angiography.	**Int:** 3/607 **Control:** 2/588 **p value: >0.2** **OR: 1.5 (0.2-8.7)**	
								Thrombocytopenia	**Int:** 2/607 **Cont:** 0/588	
								Major bleeding *defined as overt bleeding with a haemoglobin decrement of at least 20g/L or transfusion of at least 2 units of blood or any intracranial, retroperitoneal, intraocular or mediastinal bleeding that occurred after at least one does of drug	**Int:** 2/607 **Control:** 3/588 **OR: 0.6 (0.1-3.9)** **p value: ≥0.2**	

LMWH – extended duration or post discharge prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Hull et al., 2001[294] 6 RCTs [47,132,142,295,378,526] All of these studies were included in the guideline review.	Systematic Review	1+	**Total:** 1953 **Int:** 1091 **Cont:** 862	**Type of surgery:** Orthopaedic	**Extended post-hospital LMWH** Enoxaparin (3 studies) Dalteparin (3 studies) **Timing**: preoperatively in four studies and postoperatively in one study. The remaining study included separate randomly assigned groups for preoperative and postoperative imitation of therapy. **Additional non-comparative prophylaxis:** GCS – some patients used in four studies.	**Out of hospital placebo** Five studies had LMWH prophylaxis in hospital followed by out of hospital placebo. The remaining study had a comparator group that received in hospital warfarin followed by out of hospital placebo. **Additional non-comparative prophylaxis:** GCS – some patients used in four studies	In hospital prophylaxis ranged from 6-14 days. Extended out of hospital duration ranged from 18-29 days.	**DVT** confirmed by venography	**Int:** 105/1006 **Cont:** 187/810 **p value:** 0.000	**Not reported:** QoL, funding, PTS or LoS. **Notes:** Review used hip replacement data only for Hull 2000a trial –the knee replacement data has been included.
								PE	**Int:** 0/899 **Cont:** 8/884 **p value:** 0.8139	
								Proximal DVT	**Int:** 40/1042 **Cont:** 92/837 **p value:** 0.0000	
								Thrombocytopenia	**Int:** 5/1091 [0.46%(CI, 0.15% to 1.07%)] **Cont:** 3/862 [0.34% (CI, 0.07% - 1.01%)] **p value:** 1.000	

LMWH – extended duration or post discharge prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Kolb et al., 2003[357]	RCT	1+	**Total:** 310 randomised Intervention: n = 146 Control: n = 127 15 withdrawn from int. and 22 from cont. groups.	**Type of surgery:** Hip arthroplasty, knee arthroplasty, hip fracture surgery	**Type:** Extended (6wk) LWMH (certoparin) **Dose:** 3000 U	**Type:** LMWH (certoparin) + placebo **Dose:** 3000 U	**Both groups:** 42 days post-op	**DVT** Confirmed by: Duplex US performed weekly between days 14 and 42 post-op.	**Int:** 7/146 **Control:** 17/127 **p value:** 0.0172 **Intention-to-treat:** **Int:** 7/161 **Control:** 17/149 **p value:** 0.0316	**Comments:** Coagulation parameters (fibrin monomers, D-dimers) also measured. Multi-centre trial across 13 centres in Germany and Czech Republic. Patients were randomised after the initial, 14 day, open-label period. 25 patients (6.9%) excluded prior to randomisation due to thromboembolic complications.
				Intervention: Mean age: 78.1±8.4 yrs M/F:25/136	**Timing:** begun perioperatively and repeated daily until 42nd day post-op **Additional non-comparative prophylaxis:** Not reported	**Timing:** begun perioperatively and repeated daily until 14th day post-op. Then placebo for 28 days.		**PVT** Confirmed by: Duplex US performed weekly between days 14 and 42 post-op.	**Int:** 2/146 **Control:** 17/147 (11 of which also had a distal VT) **p value:** 0.0005 Per-protocol analysis **p value:** (Significant/Not significant) ITT analysis **P value:**	
				Control: Mean age: 75.8±8.4 M/F:29/120				**PE** Confirmed by: Not routinely assessed. Clinical suspicion investigated with angiography, spiral CT or V/Q scan	**Int:** 0/147 **Control:** 2/127 **p value:** 0.2139	**Not reported:** Bleeding, QoL, LoS
								Fatal PE Confirmed by: autopsy	**Int:** 0/161 **Control:** 0/149 **p value:** N/A	**Funding:** Study partly sponsored by Novartis.

LMWH – extended duration or post discharge prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Lausen et al., 1998[384]	RCT	1+	**Total:** 176 randomised (data for 118) Intervention : n = 58 Control: n = 60 (58 excluded, 29 from each group)	**Type of surgery:** Major general surgery (major elective abdominal or non-cardiothoracic operations) **Duration of surgery:** Intervention: Median 3hr (range 0.5-8.5), control: Median 3.25 hr (range 0.75-6) **Age and gender: Intervention:** Median age: 68 yrs (range 37-84) M/F:31/27 **Control:** Median age: 68.6 yrs (range29-87) M/F:33/27 **Pre-existing risk factors:** varicose veins, HRT (no significant differences between groups), malignancy.	**Type:** Extended duration LMWH (tinzaparin) **Dose:** 3500 IU	**Type:** LMWH (tinzaparin) **Dose:** 3500 IU	**Both groups:** 28 days	**DVT** Confirmed by: Bilateral ascending venography of 28th post-op day	**Int:** 3/58 **Control:** 6/60 **p value:** 0.49	**Comments:** Patients randomised 7days post-op. Clinical suspicion of PE in two patients (but not verified by objective methods). **Not reported:** PE, PTS, QoL **Funding:** Supported by grants from Bispebjerg University Hospital, the Beckett Foundation, Novo Nordisk A/S, Bruel and Kjaer DK, Schering Denmark.
					Timing: : Begun pre-op and repeated once daily for 4 weeks	**Timing:** Begun pre-op and repeated once daily until 7th post-op day		**Proximal DVT** Confirmed by: Bilateral ascending venography of 28th post-op day	**Int:** 0/58 **Control:** 0/60 **p value:** N/A	
					Additional non-comparative prophylaxis: Thigh-length stockings during 1st week post-op	**Additional non-comparative prophylaxis:** Thigh-length stockings during 1st week post-op		**Intraoperative blood loss**	**Int:** Mean 900 ml (range 0-900) **Control:** 600 ml (range 0-3500 **p value:** not reported	
								Intraoperative transfusion requirements	**Int:** Mean 1.4 units (range 0-12) **Control:** Mean 0.9 units (range 0-9) **p value:** not reported	
								Post-operative transfusion requirements	**Int:** Mean 1.2 (range 0-8) **Control:** Mean (0-8) **p value:** Not reported	
								Length of Hospital Stay	**Int:** Median 15 dys **Control:** 14 days **p value:** Not reported	
								Survival (Denominator is no. of patients randomised).	**Int:** 81/87 **Control:** 84/89 **p value:** 0.7651	

LMWH – extended duration or post discharge prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Rasmussen et al., 2006[547] **Country of study:** Denmark and Norway **Study design:** RCT, open label, multicentre **List who was masked to interventions:** Radiologists (2) who evaluated the venograms **Evidence level:** 1+ **Duration of follow-up:** Up to 3 months	**Patient group:** Major abdominal surgery **Setting:** University and large community hospitals **Inclusion criteria:** - Hospitalised for major abdominal surgery ie open abdominal surgical intervention in the gastric tract, the biliary system, pancreas, or intestine as well as explorative laparotomy - Duration of surgery > 1 hour - >18 years old **Exclusion criteria:** - Severe peripheral arterial insufficiency (absence of palpable pulsation in the dorsalis pedis artery) - Pregnancy - Allergy to radiographic contrasts medium, acid sulphite or LMWH - Hepatic insufficiency - Acute stroke within the last 3 months - Gastrointestinal bleeding within the last month - Haemorrhagic diathesis - Anticoagulation treatment (including heparin, vitamin K antagonists, but not antiplatelet treatment) - Treatment with dextran - Psychosis or dementia - Simultaneous participation in another clinical study, or previous participation in present study **<u>All patients</u>** **N:** 427 **Age (mean):** **M/F:** 209/218 **<u>Group 1 (Prolonged)</u>** **No. randomised:** 205	**Group 1 (prolonged)** Dalteparin 5000U once daily Start: Day before surgery End: Day 28 Duration: 28 days **Group 2 (short term)** Dalteparin 5000U once daily Start: Day before surgery End: Day 7 Duration: 7 days For both arms, 1st dose may be given the evening before surgery; or 2500U was administered 2 hours before surgery, followed by another 2500U 12 hour later. **Additional non-comparative prophylaxis:** All patients wore graduated compression stockings for 7 days.	**All cause mortality**	During study period (Day 7-28) **Group1:** 16/205 **Group 2:** 10/222 **P value:** 0.16# Up to 3 months: **Group1:** 20/205 **Group 2:** 17/222 **P value:**0.49#	**Funding:** Grants from Pfizer and 9 other Danish foundations. **Limitations:** - Open label study, with block randomisation - Efficacy outcomes did not include data from first 7 days post surgery - Point of randomisation not clear (within 7 days after surgery) - Patients not likely to have been scanned before entering the study - Baseline characteristics of patients who dropped out were provided. They were more likely to be female ($p<0.05$) and of had lower body weight ($p<0.05$) **Outcomes not reported:** Symptomatic DVT DVT, asymptomatic or symptomatic, Thigh DVT, Calf DVT, Fatal bleeding, Major bleeding, Neurological bleeding, Upper GI bleeding, Minor bleeding, Heparin induced thrombocytopaenia, Post thrombotic syndrome, Pulmonary hypertension, Quality of life, Length of stay **Additional outcomes reported:** Causes of death
			Fatal pulmonary embolism (confirmed by:)	**Group1:** 0/205 **Group 2:** 0/222 **P value:**1.0#	
			Symptomatic pulmonary embolism (confirmed by: 2 by ventilation perfusion scan, 1 case by CT scan)	**Group1:** 0/205 **Group 2:** 3/222 **P value:** 0.25#	
			Symptomatic DVT (confirmed by: detected during autopsy)	**Group1:** 0/205 **Group 2:** 1/222 **P value:** 1.00#	
			DVT, asymptomatic or symptomatic (screened for by: bilateral venography at day 28)	**Group1:** 12/165 **Group 2:** 26/175 **P value:** 0.027	
			Thigh DVT(screened for by: as for DVT)	**Group1:** 3/165 **Group 2:** 14/175 **P value:** 0.009	
			Calf DVT (screened for by: as for DVT)	**Group1:** 9/165 **Group 2:** 13/175 **P value:** 0.28	
			Fatal bleeding (description: "none of the deaths were considered as related to treatment")	**Group1:** 0/205 **Group 2:** 0/222 **P value:**1.00#	
			Major bleeding (description: Criteria: resulted in death, fall in haemoglobin≥2g/dl, transfusion ≥2 units of blood, retroperitoneal, intracranial, intraocular, resulted in life threatening event, or surgical/medical intervention required to stop it .)	**Group1:** 1/205 **Group 2:** 4/222 **P value:** 0.37# All were gastrointestinal bleeding	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No. of dropouts: 40 **Intention to treat population:** 165 Age (years), median (range): 67(25-91) M/F: 79/86 Weight (kg), median (range): 71(40-124) Previous VTE, n (%): 6(3.6) Previous cancer, n (%): 11(6.7) Surgery types: - Colorectal: 111(67.3) - Gastric, biliary: 24(14.5) - Pancreatic: 4(2.4) - Other abdominal: 26(15.8) For malignancy: 56%, 67% was curative **Group 2 (Short term)** **No. randomised:** 222 **No. of dropouts:** 44 **Intention to treat population:** 178 Age (years), median (range): 67(22-93) M/F: 95/83 Weight (kg), median (range): 72(40-124) Previous VTE, n (%): 9(5.1) Previous cancer, n (%): 14(7.9) Surgery types: - Colorectal: 121(68.0) - Gastric, biliary: 20(11.2) - Pancreatic: 3(1.7) - Other abdominal: 34 (19.1) For malignancy: 60%, 71% was curative		**Upper GI bleeding** (diagnosed by endoscopy)	**Group1:** 1/205 **Group 2:** 4/222 **P value:**	**Notes:** Compliance (included in protocol, but was not reported in results) Patients in prolonged prophylaxis arm were taught self-injection techniques by staff nurses. Injections were self administered (n=120), administered by a family member (n=4), a visiting nurse (n=32), or a staff nurse (n=9).
			Minor bleeding (description: Over or clinical important feature, not meeting major bleeding criteria)	**Group1:** 3/205 **Group 2:** 2/222 **P value:**0.68#	
			Length of stay (median), range not stated	**Group1:** 9 days **Group 2:** 9 days **P value:** NR	
			# *P values calculated by NCC-AC team using Fishers' exact test*		

LMWH – extended duration or post discharge prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Tincani et al., 2005[637] **Country of study:** Italy or Canada **Study design:** RCT, open label, multicentre **List who was masked to interventions:** Radiologists (2) who evaluated the venograms **Evidence level:** 1+ **Duration of follow-up:** Up to 3 months	**Patient group:** Video assisted laparoscopic surgery **Setting:** Hospital supervised out of hospital prohylaxis **Inclusion criteria:** - >18 years old **Exclusion criteria:** - Renal or hepatic failure - Active peptic ulcer - Chronic use of warfarin - Known hypersensitivity to LMWH - Surgery for abdominal cancer **All patients** **N:** 209 **Age (mean):** **M/F:** 97/112 **Group 1 ()** **No. randomised:** 104 **No. of dropouts:** 0 **Intention to treat population:** 104 **Age (SD):** 57.5 ±14.4 **M/F:** 49/55 **Group 2 (Short term)** **No. randomised:** 105 **No. of dropouts:** 0 **Intention to treat population:** 105 **Age (SD):** 56.5 ±14.2 **M/F:** 49/56	**Group 1 (prolonged)** Dalteparin 5000U once daily for high risk patients, Dalteparin 2500 IU once daily for moderate risk Start: Day at discharge End: 1 week post discharge Duration: 7 days **Group 2 (short term)** No prophylaxis Start: Day at discharge End: 1 week post discharge Duration: 7 days Both arms received either Dalteparin 5000U once daily (high risk patients), Dalteparin 2500 IU once daily (moderate risk patients) up to discharge. Patients then randomised to either continue LMWH or stop prophylaxis **Additional non-comparative prophylaxis:** Elasticated stockings may have been used on the day of operation.	**DVT, asymptomatic or symptomatic** (screened for by: duplex ultrasound 4 weeks after discharge) **Symptomatic pulmonary embolism** **Major bleeding** (description: Criteria: resulted in death, fall in haemoglobin≥1.25mmol/L, transfusion ≥2 units of blood, retroperitoneal, intracranial, intraocular, resulted in life threatening event, or surgical/medical intervention required to stop it .)	**Group1:** 0/104 **Group 2:** 1/105 **P value:** 1.00 **Group1:** 0/104 **Group 2:** 0/105 **P value:**1.0 **Group1:** 1/205 **Group 2:** 4/222 **P value:** 0.37# All were gastrointestinal bleeding	**Funding:** Research scholarship from the Canadian Institutes of Health Research. **Limitations:** - Open label study, with block randomisation - Study stopped at about 28% predicted sample size because investigators believed they had underestimated the number of participants required to show a difference. The study estimate of 760 would not have shown one. - Patients not likely to have been scanned before entering the study **Outcomes not reported:** Mortality (although no one was lost to follow up so probably 0 events) Symptomatic DVT, Heparin induced thrombocytopaenia, Post thrombotic syndrome, Pulmonary hypertension, Quality of life, Length of stay **Notes:**

Evidence Table 60: UFH – extended duration or post discharge prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Manganelli et al., 1998[420]	RCT	1+	**Total:** 79 randomised **Intervention:** n = 33 **Control:** n = 28 18 withdrawals (8 intervention, 10 control).	**Type of surgery:** Elective total hip replacement	**Type:** Extended duration unfractionated heparin **Dose:** 5000 IU **Timing:** 5000 IU from 1 day pre-op, every 8hrs for 30 days **Additional non-comparative prophylaxis:** Not reported	**Type:** unfractionated heparin **Dose:** 5000 IU **Timing:** 5000 IU from 1 day pre-op, every 8hrs until discharge.	**Both groups:** 45 days post-op	**DVT** Confirmed by: unilateral ascending venography on 45th day post-op (earlier if symptomatic)	**Int:** 4/33 **Control:** 6/28 **p value:** 0.48	**Comments:** Patients randomised at discharge. 2 patients had objectively confirmed PE, but the paper does not report the study group these patients were in. **Not reported:** PE, PTS, QoL, Survival, funding
				Intervention: Mean age: 65±8.2 yrs M/F:10/23				**Proximal DVT** Confirmed by: unilateral ascending venography on 45th day post-op (earlier if symptomatic)	**Int:** 1/33 **Control:** 5/28 **p value:** 0.08	
				Control: Mean age: 66.2±11.5 M/F:15/23				**Major haemorrhage** clinically overt and associated with a decrease in haemoglobin values of 2g/dl or more, compared with the last post-op value, or a need for blood transfusion, or if it was retroperitoneal or intracranial	**Int:** 0/33 **Control:** 0/33 **p value:** N/A	
				Pre-existing risk factors: Obesity (no significant differences between groups)				**Length of Hospital Stay**	**Int:** 12±2 dys **Control:** 12±3 dys **p value:** Not significant	

Evidence Table 61: VKA – extended duration or post discharge prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Prandon et al., 2002[534]	RCT	1+	**Total:** 360 Intervention: n = 184 Control: n = 176	**Type of surgery:** Total hip arthroplasty. Duration of surgery not reported **Intervention:** Median age: 68 range: 48 - 82 yrs M/F:83/101 **Control:** Median age: 69 range: 44 - 87 yrs M/F:79/97	**Type:** Extended warfarin **Dose:** 5mg pre-op then adjusted dose INR 2.0 – 3.0 **Timing:** 5mg 2nd day pre-op then adjusted dose INR 2.0 – 3.0 continued for 4 weeks **Additional non-comparative prophylaxis:** Not reported	**Type:** Warfarin **Dose:** 5mg pre-op then adjusted dose INR 2.0 – 3.0 **Timing:** 5mg 2nd day pre-op then adjusted dose INR 2.0 – 3.0 until discharge (mean 9 days) **Additional non-comparative prophylaxis:** Not reported	**Both groups:** 4 weeks. Patients observed for further 2 months.	**Proximal DVT** Confirmed by: Bilateral Doppler US of proximal venous system at 1, 2, and 4 weeks post-op	**Int:** 1/184 **Control:** 8/176 (3 symptomatic) **p value:** not reported. RR of developing VTE statistically significant	**Comments:** Study prematurely terminated after 360 patients because of statistically significant and clinically relevant superiority of extended over short-term prophylaxis observed. 3 patients from each group violated protocol, but ITT analysis performed. In the following 2 months 2 symptomatic VTE events occurred in intervention group. **Not reported:** Distal DVT, PTS, QoS, LoS, funding
								PE Not routinely assessed. Symptomatic PE confirmed by V/Q, spiral CT or angiography	**Int:** 0/184 **Control:** 1/176 **p value:** not reported. RR of developing VTE statistically significant	
								Fatal PE Confirmed by: autopsy or where PE could not be ruled out	**Int:** 0/184 **Control:** 0/176 **p value:** Not reported	
								Major bleeding. Defined as 1. clinically overt and associated with either a decrease in haemoglobin of at least 2.0 g/dL or requiring transfusion of 2 or more units of red blood cells 2. Intracranial or retroperitoneal 3. resulted in permanent discontinuation of anticoagulation	**Int:** 1/184 **Control:** 0/176 **RR and statistical significance:** Not reported	

Patient views

Evidence Table 62: Patient views on mechanical prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Barker and Hollingsworth, 2004[33]	Survey	3	**Total**: 218	**Type of surgery:** Mixed surgical patients from 16 wards in one hospital	**Type:** Graduated compression stockings (GCS) Survey of concordance with hospital policy of wearing thigh-length stockings after surgery. **Additional non-comparative prophylaxis:** Not reported	**Not applicable** **Additional non-comparative prophylaxis:** Not reported	1 day	**No of patients wearing GCS in accordance with hospital policy**	9/218 (4%)	The 5/14 wearing thigh high GCS incorrectly had them rolled down to below the knee. This leads to graduated compression loss and a constriction band formed by the rolled down band. Staff not routinely offering thigh high stockings.
								No of patients wearing any GCS	99/218 (46%)	
								No of patients wearing thigh GCS	14/99 (14%)	
								No of patients wearing thigh GCS correctly	9/14 (64%)	
								No of patients wearing below knee GCS	85/99 (86%)	
								No of patients wearing below knee GCS correctly	77/85 (91%)	

Patient views on mechanical prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Benko et al., 2001[43]	Patient views of interventions from RCT	3	**Total:** 200 5 randomised groups: 2 brands of thigh-length stockings with 40 patients in each arm 2 brands of knee-length stockings with 40 patients in each arm 1 group of no intervention.	**Type of surgery:** Orthopaedic patients	**Type:** Thigh-length graduated compression stockings (GCS) n = 80 2 brands of thigh-length, 40 in each group **Additional non-comparative prophylaxis:** Not reported	**Type:** Below knee graduated compression stockings n = 80 2 brands of thigh-length, 40 in each group **Additional non-comparative prophylaxis:** Not reported	1 hour	**No. patients with wrinkles in stockings after 1 hour**	**Int:** 14/80 **Cont:** 6/80 **p value:** <0.05	Main aim was to investigate the difference in venous haemodynamics in inpatients prior to surgery. Only results for patient views reported here.
								No. patients reporting discomfort after 1 hour	**Int:** 17/80 **Cont:** 9/80 **p value:** <0.05	
								No. patients unable to manage stockings independently	**Int:** 38/80 **Cont:** 44/80 **p value:** >0.1	

Patient views on mechanical prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Brady et al., 2007[78] **Study design:** Observational **Evidence level:** + **Duration of follow-up:** Short term prophylaxis	**Patient group:** Nursing care patients in teaching hospital with orders for TEDS &/or SCD **Setting:** Teaching hospital, California, from autumn 2003 to winter 2005 **Inclusion criteria:** ▪ Randomly selected patients with orders for thromboembolic deterrent stockings (TEDS) and/or sequential compression device (SCD) admitted to any of these nursing units(neurological, transplantation, vascular, gastrointestinal; ear nose and throat, internal medicine, trauma and orthopaedics) **Exclusion criteria** ▪ Patients who did not have sufficient stamina or mental clarity to complete the 15-minute survey, or restrained patients. ▪ <18 years old **<u>All patients</u>** **N:** 137 out of 150 approached agreed to participate **Drop outs:** 5/137 ("feeling tired") **Male/Female:** 65/72 **Age** , years, range **:** 18 to 92 **% of patients observed to be in bed at time of survey:** 117/137 (85.4%)	TEDS &/or SCD **Types of SCDs used[#]:** ▪ Thigh length: 70/137 (51%) ▪ Knee length: 46/137 (34%) ▪ Unsure: 22/137(16%) **Types of TEDs used:** ▪ Thigh length: 82/137 (60%)[#] ▪ Knee length: 41/137(30%) ▪ Unsure: 14/137 (10%) **Methods:** A survey of patient view on the following ▪ why stockings/SCDs were being used ▪ Comfort ▪ How long they wore per day Observations on the fit of TEDs and/or SCDs. Survey content and observational descriptors determined based on literature review and clinical observations made by nurses. The survey content validity established with clinical nurse experts and piloted with the data collectors for	**Correlation between gender and compliance**	No correlation found. R values not reported	**Funding:** Not stated **Limitations:** ▪ No indication on how timing of checks were determined ▪ Some discrepancies in total number of patients using TEDs and SCDs in the paper. **Additional outcomes:** **Notes:** [#] Discrepancy in total number of patients using/not using SCDs- total 137 for % of patients reported types of SCDs used vs 131 for total of patients using vs not using SCDs [##] Discrepancy in reported in the report – 60% (82/137) reported using thigh length, but number of patients using vs not using totalled up to 74 TEDS= thromboembolic deterrent stockings SCD = sequential
			Correlation between age and compliance	Pearson r =0.247, p<0.01 (older patients more consistent in wearing stockings/SCD)	
			Observation of SCD usage at time of survey	**Wearing[#]:** 40/137 (29.2%) **SCDs in room, but not using:** 65/137 (47%) **No SCDs visible in room**: 26/137 (19%) **<u>Thigh length:</u>** **Wearing:** 21/70 (30%) **Appropriate fit:** 14/70 (20%) **Discomfort reported:** 39/70 (56%) **<u>Knee length:</u>** **Wearing:** 19/46 (41%) **Appropriate fit:** 12/46 (26%) **Discomfort reported:** 15/46 (33%)	
			Observation of TEDs usage at time of survey	**<u>Overall:</u>** **Wearing:** 86/137 (62.8%) **Not wearing:** 51/137 (37%) **Appropriate fit:** 35/86(41%) **<u>Thigh length[##]:</u>** **Wearing:** 58/74 (78%) **Discomfort reported:** 43/74 (58%) **<u>Knee length</u>** **Wearing:** 28/41(68%) **Discomfort reported:** 5/41 (12%)	
			Reasons for not using SCD (N=91) (multiple responses allowed: total of 149 responses)	▪ Had a good reason (just had a bath, ambulated): 46% ▪ SCDs were uncomfortable (hot, itchy): 39% ▪ Registered nurse had never	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
		clarity and revisions were made by consensus of nurse experts. Inter-rater reliability established (93%) between the 6 data-collectors.		initiated them or had not replaced them after transfer from another unit: 13% ▪ Did not know they were off: 2%	compression device. This is also known as intermittent pneumatic compression devices (IPCD)
			Reasons for not using TEDS (N=51) (multiple responses allowed: total of 73 responses)	▪ TEDs were uncomfortable (hot, itchy): 43/51(84%, 59% of responses) ▪ Had a good reason (just had a bath, ambulated): 17/51 (33%, 23% of responses) ▪ Registered nurse had never initiated them or had not replaced them after transfer from another unit: 12/51(23.5%, 16% of responses) ▪ Did not know they were off: 1/51(2% of responses)	
			Easy to put on	**SCDS:** 65% **TEDS:** 46% (30% reported difficult to put on and this was not related to length of stockings)	

Patient views on mechanical prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Chan et al., 2007[103] **Study design:** Observational & cross sectional survey **Evidence level:** + **Duration of follow-up:** Short term prophylaxis	**Patient group:** Lower limb arthroplasty. Trauma patients mostly excluded **Setting:** Department of Orthopaedic and Trauma surgery, Merlin Park Regional Hospital, Galway, Ireland. Patients were from 3 wards, recruited over a 5 months. **Inclusion criteria:** "fully evaluated to the satisfaction of the authors". Complete scheduled observation and questionnaire completion. **<u>All patients</u>** **N:**30 **Type of procedures:** 21 THR, 6 TKR and 3 bipolar hemiarthroplasties **Age,** years, mean ± SD: 72.4±11.2 (range 44-91)	AV Impulse System (Orthofix Vascular Novamedix, Andover UK). Patients required to wear them at all times except during mobilisation on the first operative dat. Patients kept on bed rest 24 hours post arthroplasty and generally commence mobilisation on the first postoperative day. **Methods:** 1. Spot checks randomly performed and recorded at least 1 hour apart, up to 3 checks per day, until patients were found to be non-compliant for 2 consecutive days. Checking times randomised using computer generated random number. Patients and nursing staff unaware that checks were recorded to avoid bias. % of compliance of each patient = number of compliant checks/total number of checks *100% 2. Survey – patients completed questionnaire on day of discharge	**Level of compliance** (%) As shown in graph (exact values not provided)	**Day 1:** 100 **Day 2:** 90-100 **Day 3:** 80-90 **Day 4:** 50-60 **Day 5:** 30 **Day 6:** 20 **Day 7:** 10-20 **P value:** <0.001 using chi-square test from day 3 to 5	**Funding:** Foot pump manufacturer: Novamedix, Andover UK **Limitations:** ▪ Selectiveness of patients included in the analysis – stringent requirement may caused bias and limit external generalisability. ▪ No report of questionnaire validation ▪ Patient's awareness and consent of participation in study may bias compliance rates ▪ Number of patients who were eligible but refused to participate/excluded was not reported **Additional outcomes:** **Notes:** Same foot pump as Pitto2008 and Anand2005
			Correlation of compliance with age	**Spearman rank correlation coefficient, r = -**0.495 **P value** < 0.01 (compliance decrease with increasing age)	
			Comfort level (measured by visual analogue scale of 1-10)	**Mean :** 7.1 (definition of 7.1 not provided)	
			Perceived purpose of device (question: "why are you wearing foot pumps"?) For circulation Don't know To prevent clot Help with mobility/walking To reduce leg swelling To support/splint the leg	 14/30 (46.7%) 8/30(26.7%) 4/30(13.3%) 3/30(10.0%) 2/30(6.7%) 1/30(3.3%)	
			Factors which discourage patients from wearing foot pumps: Sleep patterns disturbed Feet feel too hot Disturb other patients in the ward Too much pressure Noise disturbance/alarm Pump activated too frequently	 17/30 (56.7%) 13/30 (43.3%) 11/30 (36.7%) 9/30 (30.0%) 8/30 (26.7%) 5/30 (16.7%)	

Patient views on mechanical prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Haddad et al., 2001[247] **Study design:** RCT **Evidence level:** + **Duration of follow-up:** Short term	**Patient group:** Elective hip surgery-primary or revision **Setting:** Vancouver , Division of Reconstructive Orthopaedics in a large teaching hospital **Inclusion criteria:** Patients prospectively at random from 1 of 4 orthopaedic surgeons with a major interest in lower limb arthroplasty **<u>All patients</u>** **Before education initiative** **N: 30** **After education initiative** **N: 49**	**IPCD –thigh length, bilateral** Usage followed standard departmental protocol; ▪ All patients should receive pharmacologic and IPCD for DVT and PE prevention. No GCS used ▪ IPCD should be initiated as soon as possible after surgery, ideally within 1 hour post-anaesthetic in recovery room ▪ Interruption allowed when patients were ambulant or undergoing specific treatment such as physiotherapy, change of dressings or investigations. ▪ Any single interruption expected to be , 2 hours and total time should not be >10% in the early postoperative period and not >20% at later periods. Patients should receive ≥21hours/day in the first 2 days and ≥19hours/day subsequently **Method:** ▪ Compliance was measure before and after the nursing education initiative recording using monitoring devices hidden at the bed of study patients for the first 120 hours of use	**Compliance**, % of time using the device, from start to end of study	**Before:** 78±17% **After:** 80.6±14.0%	**Funding:** John Charnley Trust and the BOA/Wishbone Trusts and Norman Capener Travelling Fellowships **Limitations:** Directness of evidence- Canadian study conducted in before mid 1999 **Additional outcomes:** **Notes:** Nursing education was provided: Institutional and manufacturer based on the wards and post-anaesthetic recovery rooms. This comprised supplementary training
			Duration of average interruption, hour, mean±SD, range	**Before:** 3.6±3.0 (0.0 to 15.9) **After:** 2.6±2.7 (0.4 to 12.8)	
			Duration of longest interruption, hour, mean±SD, range	**Before:** 9.3±8.6 (0.0 to 39.6) **After:** 101.+-11.6 (0.7 to 40.0)	

Patient views on mechanical prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
May et al., 2006[430] **Study design:** Qualitative (interview) **Evidence level:** + **Duration of follow-up:** Short term	**Patient group:** Mixed medical and surgical patients **Setting:** East Kent, UK **Inclusion criteria:** Patients who had been hospitalised in the past 2 months, and had worn stockings for ≥ 48 hours **<u>All patients</u>** **N:** 12, identified from a convenience sample of 100 patients 9 wore thigh length, 3 wore knee length stockings.	Graduated compression stockings. **Aim of study:** "to explore patient experiences of GCS, to ascertain their perception about their use and care and to identify any limitations in the information currently provided to inform the design of a patient information leaflet" **Methods:** <u>Recruitment:</u> Researchers gave patients who were interested a brief verbal introduction, consent forms and paid return envelopes. Written project information was sent to potential participants, written and verbal consents obtained. <u>Data collection:</u> Telephone interviews were taped and transcribed. Semi-structured interview schedule with open ended questions which had been piloted in 2 subjects were used. <u>Data analysis:</u> Transcripts were verified by participants. Each researcher (8 of them) individually analysed transcripts for emerging themes and consensus was obtained through discussion. Theme saturation was obtained in a sample of 12 patients <u>List of interview questions:</u> ▪ Have you worn compression stockings before? ▪ Hong long did you have to wear your stockings?	**Amount and type of information received:** Most patients (8 out of 12) could not remember receiving information regarding everyday care of compression stockings. **Amount and type of information desired:** ▪ Some patients perceived that nursed would have supplied necessary information. One participant thought that that in a hospital, "you do as you are told". ▪ Some did not think that information is required ("common sense"), while others thought that it is nice to have a leaflet to read and it would have been helpful to have some information in the hospital. **Other sources of information** Most patients had little alternative source of information other than that acquired in the hospital. The other sources were: ▪ Health information from long haul flights ▪ Previous experience with VTE – self or family. **Reasons for wearing compression stockings:** ▪ Not all patients understood the reason to wear GCS. Some understood that it was meant to prevent DVT, but could not relate to their situation since they did not have DVT. ▪ Some patients who did not understand fully thought that GCS were "given to you for a reason", but it can be taken off if you can't wear them after trying them on. **Experiences with GCS fitting and use** ▪ Poorly fitted stockings – 7 out of 12 were not aware of measured and 2 patients were certain they had not been measured. ▪ There was a lack of information about how to put on and take off the stockings, or how it should fit. Some patients obtained the information from other patients, family and friends or other health care professionals, and this resulted in a variety method which may not be appropriate. ▪ Practical problem of putting on and taking off the		**Funding:** Not stated **Limitations:** ▪ Qualitative study to explore patient experience; not able to tell which concerns were those experienced by most patients **Additional outcomes:**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
		▪ How many pairs were you given and what type? ▪ Were you given a new pair? ▪ What was the reason you had to wear them? ▪ How did nursing staff prepare you for wearing stockings? o Were you measured? o Were you given information sheet? o Where you told about laundering, skin care, when to remove stockings, exercise? ▪ Did you experience any problems with your stockings? o Could you put them on/take them off yourself? o Were they comfortable? o Did they fit? o They you wear them for as long as recommended? ▪ What advice would you give to other patients with compression stockings? ▪ Is there anything else you could like to add?	stockings. Although help from nurses was received initially, this did not always continue. ▪ Latex allergy – blisters form at the top of the stocking. Patient was subsequently given instructions which would have caused wrong fitting (turn the top back slightly). ▪ Confusing or lack of information on duration of putting on the stocking, when to take them off/change them off, particularly whether to stop wearing them or continue wearing them at home. ▪ Most patients did not receive information about how to take stockings off and wash them, resulting them relying on "common sense "and used inappropriate methods. ▪ Lack of information given about prophylactic exercises. ▪ Varied comments about appearance and comforts. Patients found that the stockings were more comfortable that they had imagined.		

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Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Murakami et al., 2003[468] **Study design:** RCT **Evidence level:** + **Duration of follow-up:** Short term	**Patient group:** trauma patients **Setting:** From emergency department until discharge **Inclusion criteria:** ▪ Projected hospitalisation of ≥12 hours ▪ Able to have IPCDs applied to both legs ▪ ≥18 years ▪ No history of venous thromboembolism or requirement of systemic anticoagulation **All patients** **N:** 33 Revised trauma score: 11.7 **Group 1:** SCD-calf length, N=16 **Group 2:** CECT, =17 **Type of injury: SCD/CECT** ▪ Head: 3/3 ▪ Spinal cord:1/1 ▪ Pelvic :4/1 ▪ Lower extremity:1/5 ▪ Chest:1/3 ▪ Abdominal:3/1 ▪ Others:3/3	**Group 1:** SCD-calf length **Group 2:** CECT **For all patients:** ▪ Compression begin immediately after randomisation; study end upon patient discharge ▪ Nursing staff and physicians taught how to use devices ▪ Investigators made no attempt to influence the use of devices once patients enrolled into the study. **Compliance measurement:** counters affixed to the devices to measure the amount of time the device was applied and pumping, and this was checked twice daily to ensure they were working	**Compliance** (total number of minutes device was pumping/ total number of minutes patient was enrolled) * 100%, mean±SD (n)	Emergency department **Group 1:** 57.8±10.5 (12) **Group 2:** 100.0±0.0 (11) **P value:** 0.002* Operating room **Group 1:** 22.1±22.1(4) **Group 2:** 57.1±20.2(7) **P value:** 0.28* ICU **Group 1:** 69.9±12.5(8) **Group 2:** 70.1±10.8(12) **P value:** 0.99* Nursing ward **Group 1:** 46.0±7.2(16) **Group 2:** 72.8±6.1(17) **P value:** 0.008† Total **Group 1:** 58.9±4.6 (16) **Group 2:** 77.7±3.9 (17) **P value:** 0.004† * calculated by authors using Mann Whitney U test † calculated by authors using independent student t-test	**Funding:** Not stated **Limitations:** ▪ Small sample size ▪ Paper stated no attempt was made by investigators to influence pump use after enrolment. However, awareness of RCT participation could have affected the patients and nursing staff **Additional outcomes:** Venous flow velocities of the two devices **Notes:** SCD – sequential compression device, also known as IPCD (intermittent pneumatic compression device) CECT = continuous enhanced circulation therapy group. This is a miniaturised and portable IPCD which is battery powered.

Patient views on mechanical prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Pagella et al., 2007[506] **Study design:** RCT & cross sectional survey **Evidence level:** + **Duration of follow-up:** Short term	**Patient group:** Orthopaedic trauma with surgical procedure of THR/THR patients **Setting:** Transitional trauma and orthopaedic medical –surgical unit, Pennsylvania US, in Feb2002 to July 2002 **Inclusion criteria:** Age> 18 years, physician ordered IPCD **All patients** **N:** 70 (74 patients approached) **Dropouts:** 5 (1 unreliable historian, 2 lost to follow up, 2 with missing data)	IPCD, calf length. Patients randomised to two devices with different sleeve materials 1) Thick stiff plastic 2) Breathable **Methods:** Patients were randomised for either type of device. Nursing staff continued to encourage patients to use the pumps for the maximum number of house possible per day Standardised informational handouts were provided to both groups. On day 3 or at discharge, the patients were given the questionnaire to assess comfort, satisfaction and compliance. Nursing staff complete questionnaire on their impression of the devices at end of study	**Patient questions:** (5=strongly agree, 4=agree, 3=neutral, 2=disagree, 1=strongly disagree) Comfortable Interfered with movement Kept patient awake Loud Hot Made leg sweat Used in bed Used on chair Would not use again	**Thick plastic vs breathable material** 4.3 vs 4.4 2.1 vs 1.3 1.7 vs 2.0 1.5 vs 1.5 2.2 vs 1.5 2.6 vs 2.0 4.7 vs 4.8 2.0 vs 2.3 2.1 vs 2.4	**Funding:** Not stated **Limitations:** Compliance rate generalisability limitation because: ▪ Data obtained from a RCT setting, therefore compliance rate likely to be higher ▪ Patient self reported compliance – potential bias to be higher ▪ Nursing staff rating of their impression of compliance for all patients cared at the end of study ▪ No objective methods of compliance measurement **Additional outcomes:** IPCD = intermittent pneumatic compression device
			Adherence (% time device was used in 24 hours)	**Patient reported:** 81-85%, N=58 **Nursing staff reported**: 66-71%, N=22	

Patient views on mechanical prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Parnaby, 2004[510] **Study design:** Observational **Evidence level:** + **Duration of follow-up:** Cross sectional- one day	**Patient group:** Inpatients **Setting:** 16 mixed surgical specialty wards in Middlesex Hospital, London. January 2003 **Inclusion criteria:** All patients **All patients** **N:** 218	Hospital has an written policy that all patients should be wearing anti-DVT stockings, unless it is contraindicated (peripheral vascular disease or profound limb ulcerations) **Methods:** Each patient was asked and checked to see whether they were wearing GCS-length was noted (thigh vs knee)	**Number of patients wearing observed to be wearing GCS, and wearing it correctly**	**Wearing any GCS:** 99/218 (45%) **Wearing any GCS correctly:** 87/218 (40%) Breakdown by stocking length **Wearing above knee product:** 13 (6%) **Wearing above knee product correctly:** 9/13 (69%) ["Approximately one third wear incorrectly"- rolled or folded down the knee] **Wearing below knee product:** 86 (46%) **Wearing below knee product correctly:** 78/86(91%)	**Funding:** Not stated. **Limitations:** Study conducted **Additional outcomes:** Outcomes (comfort, quality, instruction, and ease of use) from two related trials of UCL developed GCS was also reported. **Notes:** Survey was conducted before the initiation of two trials of GCS products developed by UCL (University College London)

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Study details	Patients	Intervention/Methods	Outcome measures	Effect size	Comments
Pitto & young, 2008[525] and Pitto & young, 2008[524] **Study design:** Observational & cross sectional survey **Evidence level:** + **Duration of follow-up:** Short term prophylaxis	**Patient group:** Total joint replacement (hip or knee), degenerative osteoarthritis **Setting:** Department of Orthopaedic surgery, Auckland **Inclusion criteria:** Consecutive patients admitted from Jan 2003 to Dec2005 **Exclusion criteria:** Patients with diabetes, active malignant tumour, gastrointestinal ulcer, bleeding diathesis and superficial wounds or painful joints **<u>All patients</u>** **N:** 846	**Group 1:** Foot pump + 100mg aspirin (3 orthopaedic surgeons, 1 did not use aspirin) **Group 2:** Foot pump + GCS +100mg aspirin (3 orthopaedic surgeons) GCS used were either thigh or knee length Foot pump used ; AV Impulse System (Orthofix Vascular Novamedix, Andover UK) <u>Foot pump usage:</u> Nurses told to activate foot pump when patients were not weight bearing. Foot pump set at 20/1, with pressure of 130mmHg applied for 1s. <u>Compliance measurement:</u> by internal meter which measured the number of hours the foot pumps of switched on. Patients considered as discontinued foot pump when foot pump not used for 4 continuous hours.	**Discontinued foot pump** (between days 2 and 6, mean 3.2 days.) **Reason for termination:** **Discomfort (around the ankles)** **Sleep disturbances** **Patient opinion about foot pump:** **Painful** **Annoying/difficulty with sleeping** **Uncomfortable** **No discomfort** **Relaxing** **Number of hour used per day (mean, range)**	Total: 46/846 (5.4%) **Group1:**10/416 **Group2:**30/436 **RR:** 0.55 (95% CI:0.31 to 0.99) **P value:**0.049# 14/46(0.3%) 32/46(69.6%) 3/800 (0.4%) 70/800 (8.8%) 10/800 (12.5%) 505/800 (63.1%) 212/800 (26.5%) 15.9 (14-20.5)	**Funding:** Not stated Manufacturer: Novamedix, Andover UK **Limitations:** ▪ Method of eliciting opinion about comfort of foot pump not described ▪ Discrepancy in number of denominator 846 vs 800 [author confirmed 46 dropped out, but did not explain the discrepancy in denominator values] **Additional outcomes:** ▪ Number of DVT events and side effects such as bleeding **Notes:** Same foot pump as Anand2007 and Chan2007A #Calculated by NCC-AC team

Patient views on mechanical prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Robertson et al., 2000[555]	Comparative study	2	**Total:** 224 **Intervention:** n = 120 **Control:** n = 104	**Type of surgery:** Hip replacement	**Type:** Foot pumps (Plexiplus) **Duration:** started on day of surgery and continued until postoperative day 3 Warfarin or heparin was also given to some patients at the discretion of the surgeon **Additional non-comparative prophylaxis:** Not reported	**Type:** Thigh high sequential compression devices (**SCD**) (Kendall) + graduated compression stockings **Duration:** 4 postoperative days Warfarin or heparin was also given to some patients at the discretion of the surgeon **Additional non-comparative prophylaxis:** Not reported	4 days	Average no. of hours per day devices worn	Average number of hours worn per day from the day after surgery: **Int:** 17.4 **Control:** 18.1 **P value:** Not sig Number of hours worn on surgery day: **Int :**8.8 **Control:** 9.8 **P value:** Not sig	
								No. of patients responding as 'comfortable' or no complaints with intervention	**Int:** 85/120 **Control:** 57/104 **p value:** 0.037	
								Reasons for non-compliance with foot pumps	Painful to foot/heal: 5/120 Forceful pulsation: 4/120 Tight: 3/120 Blisters: 1/120	
								Reasons for non-compliance with sequential compression	Hot/sweaty: 14/104 Stockings bothersome: 9/104 Tight: 4/104 Itchy: 4/104 Blisters: 2/104	
								Preference for device in foot pump patients having revision surgery who had previously received SCD.	Foot pump: 24/35 (68.6%) SCD: 7/35 (20%) **p value:** <0.005 No preference: 4/35 (11.4%)	

Patient views on mechanical prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Stewart et a., 2006[626] **Study:** Observational **Evidence level:** + **Duration of follow-up:** Short term	**Patient group:** Surgical patients **Setting:** Santa Barbara, California in a single community teaching hospital **Inclusion criteria:** All patients admitted to the surgical service who had IPCD ordered **<u>All patients</u>** **N:** not reported	**IPCDs** – all patients received **Nurse education** : "Group discussion with nurses", to provide information on benefits and purpose of wearing IPCDs, followed by a question and answer **Patient education:** handing out a one page flier with this statement: "Please notify your nurse if your compression stockings are not on. They are important for preventing blood clots during the hospital stay" **Method:** Residents documented compliance, ie patients had pneumatic stockings attached to both legs and to the pump, and pump was activated. This data was collected twice daily (morning and evening) for a period of two months. Data on morning and afternoon rounds was counted as separate patient entries to evaluate the different nursing shifts taking care of patients None of the nurses or patients were aware of the study	Compliance, observed twice daily based on number of observations.	<u>Before education initiative</u> Surgical ward: 131/213 (61.5%) Non surgical ward: 73/152 (48%) <u>After education initiative</u> Surgical ward: 93/142 (65%) Non-surgical ward: 73/152 (48%)	**Funding:** **Limitations:** Sample size unknown, since outcome reported based on number of observations **Additional outcomes:**

Patient views on mechanical prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Van Blerk et al., 2000[654]	Case series	3	**Total:** 30 **Mean (range) age:** 68 (23-97) **M/F:** 10/20	**Type of surgery:** Elective joint replacement on 2 wards 27 of the patients described as having major orthopaedic surgery **Excluded patient groups:** suspected of having VTE severe peripheral arterial disease severe heart failure any local condition in which garments may interfere such as infections, recent skin grafts or dermatitis	**Type:** IPCD device Flowtron ® Universal DVT Prophylaxis System, Huntleigh Healthcare Ltd Calf garment: n=19 Foot garment: n=10 Calf & foot: n=1 Garment size determined by size of patient, size of limb and surgical procedure **Duration:** mean duration 7 days **Additional non-comparative prophylaxis:** A range of prophylactic procedures being used, around 25% patients used IPCD alone	Not applicable	7 days	No of patients describing the system as comfortable or very comfortable	23/27	Reported no patients received VTE during study period but not stated whether patients were screened **Funding** Not reported
								No. of nurses described as rating the device "highly positively"	20/20	

Patient views on mechanical prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Westrich et al., 2003[687]	Prospective case series	3	**Total:** 100	**Type of surgery:** Knee arthroplasty	**Type:** Pulsatile pneumatic plantar compression PlexiPluse foot wrap Observation started postoperatively and continued until device no longer used. **Additional non-comparative prophylaxis:** Not reported	not applicable	1 hour	**Total 'compliance' recorded by observer** (total time of observed use / total time observed)	Nurses: 5537/6356 hours (87.1%) Researchers: 1314/1970 hours (66.7%) Combined nurses and researchers: 6851/8426 hours (81.3%)	For time used there are two lots of results assessed: nurses assessed use for 24 hours per day, research team assessed use between 9am and 5pm. *Actual compliance excluded times when the device had to be removed such as going to physiotherapy, ambulatory activities, hygiene and for tests conducted in another room.
								Actual 'compliance' recorded by observer (total time of observed use / total time observed that a patient can use the device)*	Nurses: 5537/5957 hours (92.9%) Researchers: 1314/1646 hours (79.8%) Combined nurses and researchers: 6851/7603 hours (90.1%)	

Patient views on mechanical prophylaxis

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Wood et al., 1997[701]	RCT	1+	**Total:** 134 **Intervention:** n = 75 **Control:** n = 59	**Type of surgery:** Anterior lumbar interbody fusion, posterior spine fusion, posterior lumbar interbody fusion, **Intervention:** Mean age: 39.4 (sd 17.2) yrs M/F: 39/36 **Control:** Mean age: 39.6 (sd 18.5) yrs M/F: 39/20	Patients wore thigh-high compression stockings + Foot wraps **Additional non-comparative prophylaxis:** Not reported	Patients wore thigh-high compression stockings + Sequential Pneumatic Compression Wrap	Scanning carried out between post-operative days 5 and 7	**DVT** Confirmed by: Duplex US	**Int:** 1 **Control:** 0 **p value:** N/A	**Comments:** 36 patients (26%) complained of redness, itching, or actual discomfort with the use of the devices. No symptomatic DVTs of PEs **Not reported:** Survival, PTS, bleeding related complications, QoL and LoS
								PE Confirmed by: Duplex US	**Int:** 1 **Control:** 0 **p value:** N/A	
								Visual analogue comfort scale (mean ±SD)	Int: 5.84 ±2.8 **Cont:** 5.56 ±2.9 **p value:** 0.88	

Evidence Table 63: Patient views on heparin

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Chioutan et al., 2003[106] **Study design:** RCT, cross sectional observation and survey **Evidence level:** + **Duration of follow-up:** Short term	**Patient group:** Spinal cord injury **Setting:** Multiple hospitals in Houston, Texas. **Inclusion criteria:** Sequential patients with acute, complete or incomplete spinal cord injury, within 3 months of date of injury. **<u>All patients</u>** **N:** 100 patients were recruited, and 95 met all inclusion criteria. 80 patients completed questionnaires upon study completion. **Age:** 16-65 **Male/female:** 72/23 Most patients were recruited within 4 weeks of injury	**Group 1:** enoxaparin 30 mg, administered subcutaneously 12 hourly **Group 2:** dalteparin, administered once a day During hospitalisation the LMWH was administered by nursing staff. At discharge, the patient or family members received instructions on how to administer injections at home. They received a call every two weeks from research assistant to remind them to fill up log book and determine if there were any problems in getting refills. **<u>Methods:</u>** Log books to collect compliance data Questionnaires at follow up to determine pain, compliance and difficulties related to injections. Scale of 1 to 10.	**Compliance rates** (as recorded in log book of administration time)	<u>Hospital logs</u> **Group 1:** 99.2% **Group2 :** 99.5%	**Funding:** Not stated **Limitations:** ▪ No mention of questionnaire validation ▪ For questions regarding hassles, patients answered that to the hypothetical scenario of taking tablets 3 times per day ▪ Questionnaire format and answer options not provided **Additional outcomes:** The same outcomes – compliance, pain rating and hassles were also obtained from patients who received injections at home.
			Painfulness of injections, mean ± sd, (range) 1=not painful at all, 10=extremely painful	<u>Patients in hospital</u> **Group 1:** 1.45±0.96 (1-4), n=22 **Group2 :** 1.63±0.83 (1-3), n=19 **All:** 1.53±0.61 (1-4)	
			Frequency of missed injections, mean ± sd, (range) 1=never missed, 10=very frequently missed	<u>Patients in hospital</u> **Group 1:** 1.05±0.24(1-2), n=22 **Group2 :** 1.11±0.32(1-2), n=19 **All:** 1.08±0.16, (1-2)	
			Hassle of injections compared to taking pills 3 times a day, mean ± sd, (range) 1= much less of a hassle, 10=very much more of a hassle)	<u>Patients in hospital</u> **Group 1:** 2.82±3(1-10), n=22 **Group2 :** 2.16±1.98(1-7), n=19 **All:** 2.51±2.16, (1-10)	

Patient views on heparin

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Colwell et al., 2005[128]	Case series	3	**Total:** 61 11 excluded Discharged to nursing facility: 5 Surgery cancelled: 2 Using anticoagulant: 1 Retinal hemorrhage before surgery: 1 Withdrew consent: 2	**Type of surgery:** Primary or revision elective total hip and knee surgery. **Age:** 40 to 70 years	**Type:** Self injection of low molecular weight heparin (Enoxaparin) **Dose:** 30mg per day at 9am and 9pm for postoperative days 1 to 7 40mg per day at 9am for postoperative days 8 to 21 Staff nurses gave first injections and explained purpose of heparin, discussed patient's responsibilities following discharge. Patients (or family member) demonstrated their technique. Patients also given a take home self injection kit that included and instructional video developed by the manufacturer and written instructional materials outlining injection technique and potential side effects.	**not applicable**	21 days postoperatively	**Concordance with self injection**	22/40 fully coconcordant:(all doses within one hour of scheduled time) 15/40 partially coconcordant: (at least 6 days of 30mg every 12 hours then at least 13 days of 40mg once per day. All doses within 2 hours of scheduled time) 3/40 non concordant	**Comments:** **Funding:** not reported but manufacturers supplied a video for each participant on injection technique. **Also reported:** No. of patients understanding the importance of self injection No. of patient comfortable giving injection Mild burning and stinging at injection site Mild bruising at injection site **Not reported:**

Patient views on heparin

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Noble et al., 2006[492] **Study design:** Qualitative (interviews) **Evidence level:** + **Duration of follow-up:** Long term	**Patient group:** Metastatic cancer or primary brain tumour with no curative treatment available **Setting:** Specialist palliative care unit within the regional cancer centre (Cardiff), which had established thromboprophylaxis guidelines. **Inclusion criteria:** ▪ Evidence within medical notes that the incurable nature of the disease has been discussed with the patient ▪ The patient had received LMWH prophylaxis for at least 5 consecutive days **All patients** **N (all):** 28 **Patients admitted after spinal cord compression** N=14 **Age** (range): 55-74 **M/F:** 7/7 **Type of cancer:** breast: 5; prostate 3; lung: 2; unknown:2; ovarian: 1; colon: 1 **Treatment:** chemotherapy and	**Aims of study:** "To find out what inpatients with advanced cancer who are receiving palliative care think about the effect of thromboprophylaxis on overall quality of life" **Methods:** Patients identified using screening notes and drug charts. Data collection Semistructured interviews were audio taped and then transcribed. Topics covered: cancer treatments received (such as surgery, chemotherapy, and radiotherapy); insight into prognosis; what was understood about treatment with low molecular weight heparin and thromboprophylaxis; the impact of thromboprophylaxis on overall quality of life; negative aspects of being on heparin treatment.	4 major themes and 3 minor themes identified **Knowledge and understanding** ▪ All patients understood the purpose of heparin and many understood why they were at risk; immobility and surgery were identified as risk factors. ▪ All patients knew death is a consequence, but unaware of DVT symptoms such as painful swollen legs, or of pulmonary embolism, such as dyspnoea. ▪ Most knowledge was based on media coverage: Its association with long haul flights, but there were little understanding of the specific association with cancer. **Acceptability** All patients found thromboprophylaxis with LMWH acceptable, and many could not understand why it would be considered unacceptable. Aspects of acceptability ▪ Recognition that thromboprophylaxis with heparin was part of usual practice: They associate it a reassurance that something is being done for them, and getting the best care. ▪ They considered treatment with heparin was neither pleasant nor unpleasant ▪ Balance of benefits against side effects **Reassurance and optimism** ▪ Patients understood that they had a terminal illness but expressed a desire to optimise quality of life not only by treating symptoms but also by taking measures to prevent other symptoms. ▪ Thromboprophylaxis with heparin reassured most patients that something was being done to prevent other problems and that the medical team had not given up on them.		**Funding:** Velindre small grants scheme **Limitations:** ▪ Qualitative study – range of opinions elicited by % of patients with these views not known ▪ Questions and probes used not reported ▪ Aim stated as effect on overall quality of life but results focused more on acceptability **Additional outcomes:**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	radiotherapy 5; surgery, chemotherapy, and radiotherapy 4; radiotherapy 2; surgery and radiotherapy 2; surgery and chemotherapy 1 **Preadmission ECOG scores** : 0-2 **Previous thromboprophylaxis:** none 8; LWMH: 1; LMWH + GCS: 3; GCS: 3 **Patients admitted primarily for symptom control** **Age (range):** 53-76 **M/F** : 5/9 **Diagnoses:** pancreatic: 3; ovarian: 2; colon: 3; breast: 2; lung: 1; unknown 1; brain: 1, uterine: 1 **Treatment:** none 1; chemotherapy and radiotherapy 1; surgery and radiotherapy 2; surgery and chemotherapy 2; chemotherapy 2; surgery, chemotherapy, and radiotherapy 3; radiotherapy 3 **Preadmission ECOG scores:** 1-3 **Previous thromboprophylaxis:** none 9; LMWH: 2; GCS: 2; LMWH + GCS: 1	Analytical framework and data analysis: Thematic analysis, using an inductive approach. Patients recruited until theoretical saturation (when no further recurring themes emerged from analysis) was achieved.	**Views and concerns about thromboprophylaxis methods and side effects** ▪ Bruising: Bruising was the only negative experiences reported from LMWH but that did not seem to be a big concern/bother, especially when compared with the treatments and side effects experienced for cancer. ▪ Discomfort from GCS: Several patients had worn GCS during previous hospital admissions and all had found them uncomfortable (hot, itchy and tight), and not acceptable for long term wear. LMWH would be preferable **Terminally ill patients wish to be involved in decision making about thromboprophylaxis** ▪ Patients uniformly expressed their need to be involved in decision making, particularly with respect to the withdrawal or non-administration of treatment. Some patients had experienced what they viewed as nihilistic paternalism, and they were angry that major decisions were made about their lives without their involvement.		

Patient views on heparin

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Spahn et al., 2002[614]	Case series	3	**Total:** 207 **Age:** <20 yrs: 26 20-40 yrs: 82 40-60 yrs: 51 >60 yrs: 48 300 patients included in the study, 220 returned the questionnaire, 13 were incomplete.	**Type of surgery:** Knee arthroplasty	**Type:** Injection of low molecular weight heparin (Fraxiparin) Injection by: Self: n = 160 Family member or friends: n = 31 Nursing service: 16 **Dose:** Depended on body weight and further risk factors. Instructions were given by a physician or qualified nurse. Patients carried out first and last injection in the presence of the instructor and got a pack containing 10 syringes, disinfection swabs and an information brochure. Assessment of patient use by anonymous questionnaire.	**not applicable**	10 days post-operatively	**Problems with self /family member injection**	None: 107/191 (56%) Initially: 72/191 (37.7%) All the time: 12/191 (6.3%)	**Comments:** Not reported **Funding:** Not reported **Also reported:** **Not reported:** Not reported
								Perception of injection 'very unpleasant'	Injection by: Self: 18/160 (11%) Family: 9/31 (29%) Nurses: 5/16 (31%)	
								No. self/family member infection patients with unsure prophylaxis	54/191 (28.3%)	
								No. self/family member infection patients who forgot prophylaxis	34/191 (17.8%)	
								No. self/family member infection patients discontinued injections early	25/191 (13.1%)	

Evidence Table 64: Patient views on mechanical vs pharmacological

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Anand & Asumu, 2007[16] **Study design:** Cross sectional survey **Evidence level:** + **Duration of follow-up:** Short term prophylaxis	**Patient group:** Hip and knee replacement, **Setting:** Royal Oldham Hospital, Oldham, UK **Inclusion criteria:** Consecutive elective THR or TKR patients who were able to give informed consent **Exclusion criteria:** Gastrointestinal ulceration or painful foot conditions **<u>All patients</u>** **N:** 43 **Male/Female:** 14/29 **Age, mean:** 69.9 (range 36 t o 85) **Type of surgery:** ▪ **TKR:** 27/43 (one with bilateral knee replacements) ▪ **THR**: 16/43 **Length of hospital stay:** mean of 6.58 days (mode of 7 days)	**All patient received:** 1. LMWH (dalteparin): once daily, subcutaneously through abdominal wall using 26 gauge needle, starting 12 hours before surgery and 24 hours thereafter 2. Foot pumps (A-V Impulse System, Novamedix, Andover UK): applied to both feet, in the recovery room after operation, and used whenever patient not weight bearing. Pump activated every 20s to a pressure of 130mmHg for a period of 1s. **Methods:** Patients asked to inform nurses if they find any of the methods uncomfortable and wished to discontinue Patients surveyed on day of discharge with questionnaires which consistent of a visual analogue scale (VAS) to mark level of comfort associated with thromboprophylaxis method and agreement to statements (choice of "strongly disagree", "disagree", "neutral", "agree", "strongly agree")	**Comfort** VAS scale score, 0= most uncomfortable, 10= most comfortable	**LMWH:** 6.3 **Foot pumps:**7.3 **P value (t-test):** 0.07	**Funding:** Not reported. Foot pump manufactured by Novamedix, Andover UK **Limitations:** ▪ Validation of questionnaire not reported ▪ Errors in some of the percentages reported; inclusion of neutral answers to the % of patients who would rather not have injections or foot pumps **Additional outcomes:** <u>For foot pumps only</u> : comfort, restriction of mobility, soothing effect, interference with sleep, preferred time of use, willingness to us again if have another operation **Notes:** Same foot pump as Pitto2008 and Chan2007A
			Painful: "agree" or "agree strongly"	**LMWH:** 5/43 (11.6%) **Foot pumps:** 6/43 (14.0%)	
			"rather not have these", "agree" or "agree strongly"	**LMWH:** 6/43 (14.0%) **Foot pumps:** 16/43 (37.2%)	
			" willing to continue these ... at home for 4 weeks after my discharge from the hospital" : "agree" or "agree strongly"	**LMWH:** 33/43 (76.7%) **Foot pumps:** 22/43 (51.2%)	
			Discontinuation of foot pump in hospital due to pain (one in day 2, the other in day 3)	2/43 (4.7%)	
			The foot pumps: ▪ comfortable ▪ restrict mobility ▪ soothing effect ▪ interfere with sleep Preference for usage: ▪ only during day time ▪ only at night ▪ during the day and the night ▪ If I have another hip or knee operation, I would like to use the foot pumps	22/43 (51.2%) 28/43 (65.1%) 23/43 (53.5%) 12/43 (27.9%) 19/43 (44.2%) 16/43 (37.2%) 12/43 (27.9%) 31/43 (72.1%)	

Patient views on mechanical vs pharmacological

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Maxwell et al., 2001[429]	Questionnaire of views and concordance carried on participants of RCT	3	**Total:** 228 **Intervention:** n = 104 **Control:** n = 103 Not all patients in trial were lost to follow up or incapable of participating in postoperative survey.	**Type of surgery:** "Major" procedure for gynaecological malignancy **Intervention:** Median age: 62 (35-85) yrs Gender not reported Mean duration of surgery: not reported **Control:** Median age: 60 (41-87) years Gender not reported Mean duration of surgery: not reported	**Type:** External pneumatic compression sleeves **Timing:** Started with induction of anaesthesia and continued for first 5 days postoperatively. Device stopped when patient was walking and restarted when back in bed. **Additional non-comparative prophylaxis:** Not reported	**Type:** Low molecular weight heparin (Dalteparin) **Dose:** 2500 units subcutaneously 1-2 hours before surgery and 2500 units 12 hours after first dose. Then from postoperative day 1 5000 units per day up to post operative day 5. If the patient was confined to bed after day 5, continued prophylaxis until day of discharge or ambulatory. **Additional non-comparative prophylaxis:** Not reported	**Control:** 5 days **Int:** 5 days (patients also telephoned 30 days postoperatively and questioned for signs and symptoms of delayed VTE)	**Overall comfort/pain**	**Int:** 26% **Cont:** 4%	**Comments:** Screened everyone for DVTs, only reported proximal. Trial designed to detect differences in complications. **Funding:**not reported **Also reported:** No significant difference in proximal DVTs, median external bleeding loss, thrombocytopenia. **Not reported:** All DVTs, PE, postthrombotic leg, QoL, survival, length of hospital stay
								Suboptimal performance or administration of prophylaxis	**Int:** 10/104 **Cont:** 6/103 **p value:** not significant	
								Postoperative preference for the intervention used	**Int:** 74% **Cont:** 78%	
								Postoperative preference for other intervention	**Int:** 3 **Cont:** 4%	

Anaesthesia

Evidence Table 65: Regional vs general anaesthesia

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Mitchell et al., 1991[454]	RCT	1+	**Total:** 72 Intervention : n = 34 Control: n = 38	**Type of surgery:** total knee arthroplasty **Duration of surgery:** Intervention : mean 122 min Control: mean 121 min **Both study groups:** Mean age: 64 (range38-84) yrs M/F:45/27 No between-group differences for age or sex	**Type:** Epidural anaesthesia **Dose:** **Timing:** Operative period **Additional non-comparative prophylaxis:** Males received 650mg aspirin beginning eve pre-surgery, females received adjusted dose warfarin PTT 15-16 secs. All patients CPM machine daily and physical therapy	**Type:** General anaesthesia **Dose:** sodium theopental **Timing:** Operative period **Additional non-comparative prophylaxis:** Males received 650mg aspirin beginning eve pre-surgery, females received adjusted dose warfarin PTT 15-16 secs. All patients CPM machine daily and physical therapy	Scan performed up to day 8 after surgery	**DVT** Confirmed by: bilateral venography 6,7 and 8th post-op days	**Int:** 12/34 **Control:** 10/38 **p value:** Not significant All asymtomatic	**Comments:** Male patients received aspirin, female warfarin. No differences in sex between study groups, and incidence and distribution of DVT not affected by pharmacological prophylaxis. **Not reported:** PTS, bleeding, QoL, survival, funding
								Proximal DVT Confirmed by:	Incidence of Proximal DVT reported to be 46% in epidural and 63% in general anaesthesia groups. (actual numbers can't be reliably calculated from these figures)	
								PE Confirmed by: V/Q scan on 6,7 and 8th post-op days	10% of patients reported as having positive V/Q scan, all asymptomatic. No information on group.	
								Length of Hospital Stay	**Int:** Mean 10.4 days **Control:** Mean 11.0 days **p value:** not reported	

Regional vs general anaesthesia

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Modig et al., 1981[456]	RCT	1+	**Total:** 30 Intervention: n = 15 Control: n = 15	**Type of surgery:** Total hip replacement (for severe osteoarthritis) **Duration of surgery:** Intervention: 147±27.9min Control: 161.3±34.5 min **Intervention:** Mean age: 66.5±5.5 yrs M/F:7/8 **Control:** Mean age: 65.4±6.3 M/F:8/7	**Type:** Continuous lumbar epidural block **Dose:** 0.5% bupivacaine with epinephrine (5µg/ml) **Post op:** 4-6 ml of 0.5% bupivacaine with epinephrine ever 4 hours for 16 hours **Timing:** Prolonged into post-op period for pain relief **Additional non-comparative prophylaxis:** Physiotherapy program with early ambulation	**Type:** General anaesthesia **Dose:** thiopentone **Post-op:** Parenteral analgesics on demand **Timing:** Intraoperatively. **Additional non-comparative prophylaxis:** Physiotherapy program with early ambulation	Scanning was performed 14 days before surgery and 14 days postoperatively	**DVT** Confirmed by: Bilateral venography on 14th post-op day	**Int:** 5/15 **Control:** 11/15 **p value:** 0.0281	**Not reported:** PTS, QoL, survival, LoS, funding
								Proximal DVT Confirmed by:	**Int:** 3/15 **Control:** 11/15 **p value:** <0.05	
								PE Confirmed by: all patients had V/Q scan on 14th post-op day	**Int:** 2/15 **Control:** 7/15 **p value:** Not significant Only 3 PEs (all in control group) were symptomatic	
								Bleeding related complications **Intraoperative blood loss:** (no measurement criteria) **Post-operative blood loss:** (no measurement criteria)	**Intraoperative blood loss:** **Int:** 1100±316 ml **Control:** 1757±426ml **p value:** <0.001 (Significant) **Postoperative blood loss:** **Int:** 1200±350 ml **Control:** 1800±400 ml **p value:** <0.001 (Significant)	

Regional vs general anaesthesia

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Nielsen et al., 1990[488]	RCT	1+	**Nos randomised:** Total: 36 Intervention: n = 18 Control: n = 18 7 patients withdrawn – 5 epidural, 2 general	**Type of surgery:** primary or revision knee arthroscopy **Duration of surgery:** Intervention: median 80 (55-100) min Control: min **Intervention:** Median age: 70 (range 46-87) yrs M/F:5/13 **Control:** Median age: 65 (range38-85) M/F:6/12 **Pre-existing risk factors:** Cardiac disease, varicose veins. Higher BMI in control group	**Type:** lumbar epidural anaesthesia **Dose:** 2% mepivacain **Additional non-comparative prophylaxis:** Thigh-length stocking on contralateral leg pre-op until full ambulation. Calf-length stocking on operated leg immediately post-op until ambulation. Quad exercises on 1st post-op day, active knee mobilisation with full weight bearing from 2nd day.	**Type:** general anaesthesia **Dose:** **Additional non-comparative prophylaxis:** Thigh-length stocking on contralateral leg pre-op until full ambulation. Calf-length stocking on operated leg immediately post-op until ambulation. Quad exercises on 1st post-op day, active knee mobilisation with full weight bearing from 2nd day.	**Both groups:** 9-11 days post-op	**DVT** Confirmed by: bilateral ascending venography on 9-11th day post-op	**Int:** 2/13 **Control:** 10/16 **p value:** <0.05	**Not reported:** PTS, PE,QoL, survival, LoS, funding
								Proximal DVT Confirmed by: bilateral ascending venography on 9-11th day post-op	**Int:** 1/13 **Control:** 3/16 **p value:** Not reported	
								Bleeding related complications Suction drain volume	**Median suction drain volume:** **Int:** 1060 (340-1940) ml **Control:** 990 (195-3275) **p value:** >0.4 Not significant	

Regional vs general anaesthesia

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Poikolainen and Hendolin 1983[529]	RCT	1+	**Total:** 38 Intervention: n = 17 Control: n = 21	**Type of surgery:** Prostatectomy **Duration of surgery:** Intervention: 71±3 min Control: 74±3 min **Intervention:** All male Mean age: NR. No differences between groups for age **Control:** All male Mean age: NR. No differences between groups for age **Pre-existing risk factors:** NR. No differences between groups	**Type:** lumbar epidural anaesthesia **Dose:** Butanilicaine 2% **Additional non-comparative prophylaxis:** Not reported	**Type:** General anaesthesia **Dose:** Thiopentone	**NR**	**DVT** Confirmed by: ^{125}I FUT test (timing NR). Positive result confirmed by venography	**Int:** 2/17 **Control:** 11/21 **p value:** <0.02 (Significant)	**Comments:** Study measured changes in flow velocity in femoral vein. Induction of epidural anaesthesia led to significant increase in velocity of blood flow in femoral vein ($p<0.001$), whereas flow velocity fell significantly with general anaesthesia.

Regional vs general anaesthesia

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Roderick et al., 2005 11 RCT studies[81,146,147,197,275,276,315,438,455,558,696] All of these studies were included in the guideline review.	Systematic Review	1+	**Total:** 939 Int:367 Cont: 384 Misc: 188 (not reported number in each arm)	**Type of surgery:** General (1 study) Urological (1 study) Orthopaedic (9 studies)	**Regional Anaesthesia** **Timing:** Ranged from 73 mins to 3 days Not addressed in 4 studies **Additional non-comparative prophylaxis:** LMWH + GCS (one study); GCS (two studies); Dextran 70 (one study); Dextran 40 + 7500 IU H (one study); ASA, GCS on no-op limb (one study).	**General Anaesthesia** **Timing:** Ranged from 79 – 150 mins. Not addressed in 6 studies. **Additional non-comparative prophylaxis:** LMWH + GCS (one study); GCS (two studies); Dextran 70 (one study); Dextran 40 + 7500 IU H (one study); ASA, GCS on no-op limb (one study).	Between 4 to 14 days postoperatively	**DVT** confirmed by venograph or fibrinogen uptake	**Int :** 130/417 **Cont:** 198/416 **p value:** 0.0000	**Not reported:** LoS, QoL and PTS.
								PE confirmed by scan	**Int :** 21/281 **Cont:** 32/264 (reported in 6 studies) **p value:** 0.0672	
								Major bleeds	**Int :** 0/317 **Cont:** 5/315 (reported in 7 studies) **p value:** 0.0243	
								Proximal DVTs	**Int :** 14/268 **Cont:** 47/253 (reported in 6 studies) **p value:** 0.0000	

Evidence Table 66: Regional + general vs general anaesthesia

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Dauphin et al., 1997[145]	RCT	1+	**Total:** 37 Intervention : n = 20 Control: n = 17 (40 randomised – 3 drop-outs)	**Type of surgery:** Total hip arthroplasty **Duration of surgery:** Intervention 2.28±0.27 hr. Control: 2.5±5.3 **Intervention:** Mean age: 70.9±6.7 yrs M/F:7/13 **Control:** Mean age: 66.2±14.3 M/F:7/10	**Type:** General anaesthesia plus lumbar epidural anaesthesia **Dose:** General: Thiopental sodium. Specific drug and dose chosen by anaesthesiologist Epidural: 10 ml 0.5% bupivacaine **Timing:** For the operative period **Additional non-comparative prophylaxis:** Coumadin daily from 1st post-op day until discharge.	**Type:** General anaesthesia **Dose:** Thiopental sodium. Specific drug and dose chosen by anaesthesiologist **Timing:** For the operative period **Additional non-comparative prophylaxis:** Coumadin daily from 1st post-op day until discharge.	Daily ^{125}I scan for 3 days, impedence plethysmography on days 5,7 and 9 and venography on the planned day of discharge	**DVT** Confirmed by: ^{125}I FUT test daily for 3 days post-op. Venography on day of discharge	**Int:** 4/20 **Control:** 4/17 **p value:** 0.79	**Comments:** Possible error in standard deviation of surgery duration in control group (5.3hrs!). Paper reports no significant difference between the two groups in operation length. **Not reported:** Proximal DVT, PE, PTS, QoL, LoS, survival
								Bleeding related complications Intraoperative blood loss: sponge weights and suction bottle contents Post-operative blood loss: measured from wound drainage (using the Dalvol Reliavac 400 system)	**Intraoperative blood loss:** **Int:** 663.8±299.0 **Control:** 1259.2±366.0 **p value:** <0.001 **Post-operative blood loss:** **Int:** 444.0±300.8 **Control:** 600.8±390.8 **p value:** 0.18 **Total blood loss:** **Int:** 1107.8±378.6 **Control:** 1860.0±616.6 **p value:** <0.001	

Nursing care

Evidence Table 67: Foot elevation

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Rosengarten and Laird 1971(ROSENGARTEN1971A}	RCT	1+	**Total**: 25 Intervention: n = Control: n =	**Type of surgery:** Elective surgery (operations on leg below groin excluded) (& Duration of surgery) **Intervention:** Mean age: 58.6±11.1 yrs M/F:6/6 **Control:** Mean age: 58.0±12.4 yrs M/F:6/7	**Type:** Leg elevation **Dose:** Both legs elevated at 15 degrees **Timing:** From premedication (including during surgery) until 1 week post-op. Ambulation allowed but patients discouraged from sitting. **Additional non-comparative prophylaxis:** Not reported	Noprophylaxis	**NR**	**DVT** Confirmed by: Bilateral ^{125}I FUT daily (for 3 weeks?)	**Int:** 4/12 **Control:** 4/12 **p value:** 0.9 3/8 DVTs were symptomatic	**Comments:** Mean duration of increased activity in legs denoting presence of thrombosis was 5.0±2.5 days in intervention and 10.8±4.1 in the control group **Not reported:** PE, PTS, QoL, LoS, survival, bleeding
								Proximal DVT Confirmed by:	**Int:** 1/12 **Control:** 1/12 **p value:** N/A	

Evidence Table 68: Hydration

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Janvrin et al., 1980[308]	RCT	1+	**Total:** 60 **Interventio n:** 30 **Control:** 30 **Dropouts:** 3	**Type of surgery:** Routine abdominal surgery (any patient requiring blood transfusions perioperatively was withdrawn from the trial). **Intervention:** Mean age: 57±10 yrs M/F:15/15 **Control:** Mean age: 58.0±12 yrs M/F: 12/18.;	**Type:** Intravenous Hartmann's solution/ Dextose-saline **Dose and timing:** 1 litre of per hour of operation. 2-3 litres of dextrose saline 24hs for 2 days. **Additional non-comparative prophylaxis:** Not reported	**Type:** No IV fluids during or postoperatively. Water by mouth. **Dose:** "Small, increasing amounts of water were taken by mouth from the first day onwards". **Timing:** Not reported **Additional non-comparative prophylaxis:** Not reported	7 days	**DVT** measured by FUT. Bilateral daily then alternate days.	**Int:** 9/30 **Cont:** 2/30 **p value:** <0.03	**Comments:** Three dropouts, but analysis by denominators of 30, i.e. presumably analysed by intention to treat. Also measured risk factors (varicose veins, smoker, etc), impendance clotting time and packed cell volume. **Not reported:** PE, PTS, QoL, LoS, survival, bleeding, proximal DVT.

Central venous catheters

Evidence Table 69: Central venous catheters

UFH vs no prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Abdelkefi et al., 2004[4] **Country of study:** Tunisia **Study design:** RCT **List who was masked to interventions:** Unclear – placebo used but no mention of blinding participants or healthcare professionals. Outcome assessors were blinded to treatment group. **Evidence level:** 1+ **Duration of follow-up:** * weeks after catheter removal	**Patient group:** Haemato-oncological disease requiring a central venous line. **Setting:** Unclear **Inclusion criteria:** Between 4 and 60 years with haemato-oncological disease and requiring a central venous line. **Exclusion criteria:** Presence of a central venous line at admission, a catheterisation for less than 7 days, a contraindication to the use of subclavian catheterisation due to major blood coagulation disorders (i.e., platelet count <50x10^9 /L, disseminated intravascular coagulation), a history of previous thrombosis or prior allergic reactions to heparin. **<u>All patients</u>** **N:** 111 patients randomised **Dropouts:** 3 patients – catheter insertion failure. (128 catheter procedures – counted as separate events) **Age (median):** Gp1: 27 (range: 4-58) Gp2: 28 (range 7-58) **M/F:** 65:43 **Additional risk factors:** Body mass Index >30: Gp1 4, Gp2 3 Prior mediastinal irradiation: Gp1 3, Gp2 3 Number of catheters per patient 1: Gp1 48, Gp2 46	**Group 1** Unfractionated Heparin Start time: Unclear End time: Until day of discharge Dose and frequency: Continuous infusion of 100U/kg/daily with a maximum mdose of 10,000U daily **Group 2** Placebo - Normal saline solution Start time: Unclear End time: Until day of discharge Dose and frequency: 50ml/daily as a continuous infusion **Additional non-comparative prophylaxis:** No additional prophylaxis mentioned	**Catheter related thrombosis** (screened for by: ultrasonography of brachial, axillary, subclavian and jugular vein just before or <24 hours after catheter removal or in case of clinical signs of thrombosis. For veins inaccessible to direct insonation the criteria of monophasic flow to detect occlusive thrombosis was used.)	**Group1:** 1/65 **Group 2:** 8/63 **P value:** 0.016*	**Funding:** No information provided. **Limitations:** Study included children but unclear how many. Randomisation method not provided, no information about allocation concealment. **Outcomes not reported:** All cause mortality, pulmonary embolism, lower leg DVT, pulmonary hypertension, post thrombotic syndrome, quality of life, length of stay, minor bleeding **Additional outcomes reported:** Catheter dysfunction **Notes:** * Calculated by NCC team using Fisher Exact Test
			Fatal bleeding (description:)	**Group1:** 0/65 **Group 2:** 1/63 **P value:** 0.429*	
			Major bleeding (description: 'severe' bleeding)	**Group1:** 2/65 **Group 2:** 3/63 **P value:** NS	
			Heparin induced thrombocytopaenia	**Group1:** 0/65 **Group 2:** 0/63 **P value:** NS	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	2 4 4 3 3 3 Underlying disease Gp1 Gp2 Malignant disease 38 36 Acute myeloid leukaemia 10 7 Acute lymphoblastic leukaemia 4 5 Chronic myeloid leukaemia 0 1 Multiple myeloma 12 13 Lymphoma 12 10 Non Malignant Disease 17 17 Aplastic anemia 16 15 Hemoglobinopathy 1 2 **Group 1** **No. randomised:** 55 **No of catheter periods:** 65 **No. of dropouts:** Unclear **Group 2** **No. randomised:** 53 **No of catheter periods:** 63 **No. of dropouts:** Unclear				

Warfarin vs no prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Bern et al., 1990{BERN1990 **Country of study:** US **Study design:** RCT (pilot study) **List who was masked to interventions:** Investigators reading venograms. **Evidence level:** 1+ **Duration of follow-up:** 90 days	**Patient group:** Patients receiving infusion chemotherapy via chronic indwelling central venous catheter (CVC) with a projected survival of > 3 months. **Setting:** NR **Exclusion criteria:** • Baseline platelet counts under 125 x 10^9/L • Acquired or congenital coagulopathies • Previous subclavian vein catheters • Obstructing mediastinal tumors • Previous history of deep vein thrombophlebitis • Anatomic lesions that bleed • Taking drugs that suppress platelet function • Serum creatinine level >1.6mg/dL **All patients** **N:** 121 **Group 1** **No. randomised:** 60 **No. completing study:** 42 **Mean ±SD age:** 56 ±13.5 **M/F:** 27/33 **Group 2** **No. randomised:** 61 **No. of dropouts:** 45 **Mean ±SD age:** 60.6 ±10.7 **M/F:** 32/29	**Group 1** Fixed low-dose warfarin: 1mg 1x/day orally started 3 days before catheter insertion & continued for 90 days or until venographic evidence of thrombosis **Group 2** No warfarin **Additional non-comparative prophylaxis:** None reported	**All Cause Mortality** (Note: all deaths due to cancer)	**Group1:** 12/60 **Group 2:** 14/61 **P value:** 0.69	**Funding:** Pharmacia-NaTech and E.I. DuPont Company **Outcomes not reported:** Lower limb DVT, pulmonary embolism, major & minor bleeding, post-thrombotic syndrome, pulmonary hypertension, quality of life **Additional outcomes reported:** Time to catheter associated thrombosis, premature catheter removals **Notes:** * unclear what type of thrombosis this refers
			Asymptomatic or symptomatic thrombosis* (confirmed by venogram).	**Group1:** 4/42 **Group 2:** 15/40 **P value:** <0.001	
			Symptomatic thrombosis (confirmed by venogram)	**Group1:** 4/54 **Group 2:** 13/54 **P value:** 0.03	

UFH vs no prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Brismar et al., 1982[83] **Country of study:** Sweden **Study design:** RCT **List who was masked to interventions:** No one **Evidence level:** 1+ **Duration of follow-up:** Duration of catheterisation – not well recorded. Catheter Period days: Silicon – 38 Polyvinylchloride - 15	**Patient group:** Consecutive central venous catheterisations. (53 catheterisations in 50 patients –i.e. some received >1 catheterisation) Gastrointestinal malignancy: 16/53 Crohn's Disease: 16/53 Gastric or duodenal ulcer: 5/53 Ulcerative colitis: 4/53 Diverticulitis: 2/53 Sigmoid polypus: 2/53 Intestinal Obstruction: 2/53 Other: 6/53 **Setting:** Not stated **Inclusion criteria:** Patients requiring catheterisation for parenteral nutrition. **Exclusion criteria:** Patients with a negative blood culture and 'abnormal' phlebographic findings at the time of catheter insertion **<u>All patients</u>** **N:** 50 **Age (mean):** 55 (range 21-84) **M/F:** 26/24 **Additional risk factors:** Gp1 Gp2 Operations: 13 19 **<u>Group 1</u>** **No. randomised:** 24 patients (26 catheter periods) **No. of dropouts:** 3 catheter periods (due to haemorrhagic complications) **<u>Group 2</u>** **No. randomised:** 26 patients (27 catheter periods)	**Group 1** Unfractionated Sodium Heparin Start time: from time of insertion of catheter End time: at catheter removal Duration: Dose and frequency: 5000IU / 6 hours. (NB. No heparin was given during the 36 hours immediately after surgery) **Group 2** No heparin prophylaxis **Additional non-comparative prophylaxis:** None reported.	**Thrombus formation** (confirmed by: phlebography)	**Total thrombus** **Group1:** 5/23 **Group 2:** 14/26 **P value:** 0.039* **Sleeve thrombus** **Group1:** 5/23 **Group 2:** 10/26 **P value:** 0.057* **Catheter tip thrombus** **Group1:** 0/23 **Group 2:** 3/26 **P value:** 0.093* **Occlusion of Vessel** **Group1:** 0/23 **Group 2:** 1/26 **P value:** NS* **Surgical patients** **Group1:** 4/13 **Group 2:** 11/19 **P value:** 0.166* **Non surgical patients** **Group1:** 1/10 **Group 2:** 3/7 **P value:** 0.250*	**Funding:** **Limitations:** 64% patients underwent surgery. Paper states that there were no differences between patients operated on and those who were not in the respects mentioned. Paper does not provide information on randomisation method or allocation concealment. Intention to treat analysis not completed Duration of follow up not well defined. **Outcomes not reported:** Pulmonary Embolism, Lower limb DVT, bleeding, heparin induced thrombocytopaenia, post thrombotic syndrome, pulmonary hypertension, quality of life, length of stay. **Additional outcomes reported:** Haemoglobin level, serum albumin level, Prothrombin time, blood cultures **Notes:** * Calculated by NCC team using Fishers exact

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No. of dropouts: 1 catheter periods (patient given heparin due to catheter related thrombophlebitis)				test. Two different types of catheter were used in the study and results are presented by catheter.

Warfarin vs no prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Couban et al., 2005[136] **Country of study:** Canada **Study design:** Multicentre RCT **List who was masked to interventions:** Investigators to CVC thrombosis, death and bleeding events. Patients to treatment (placebo trial). **Evidence level:** 1+ **Duration of follow-up:** Until CVC removed. Median follow up 25 weeks for those without CVC associated thrombosis	**Patient group:** Mixed cancer patients ≥16 years requiring indwelling central venous catheter (CVC) for at least 7 days recruited between March 1999 and July 2002. **Setting:** 3 tertiary care centres **Exclusion criteria:** • Central venous catheter had already been in place >72 hours • Known allergy to warfarin • Thrombosis in the vein in which the catheter was to be placed • Patient had experienced major bleeding within 6 weeks that would contraindicate anticoagulation • INR >1.5 at screening and did not correct with vitamin K • Medical condition requiring long-term anticoagulation • Pregnancy • Patient had previously participated in this study **All patients** **N:** 255 **Group 1** **No. randomised:** 130 **No. of dropouts:** 20 **Median (range) age:** 52 (14-82) **M/F:** 81/49 **Group 2** **No. randomised:** 125 **No. of dropouts:** 19 **Median (range) age:** 51 (17-84) **M/F:** 71/54	**Group 1** Fixed low-dose warfarin: 1mg 1x/day orally **Group 2** Placebo 1x/day **Start time:** within 72 hours of catheter insertion **End time:** continued until the catheter was removed, the patient died or the patient developed catheter associated thrombosis **Duration of treatment in wks:** **Median (range)** **Group1:** 8 (0-48) (n=130) **Group 2:** 9 (0-70) (n=125) **Additional non-comparative prophylaxis:** None reported Permitted the use of other antiplatelet medication, low dose (≤100 U/kg/d) standard heparin or low molecular weight heparin as veno-occlusive disease prophylaxis in patients undergoing bone marrow or peripheral blood transfusion.	**All Cause Mortality**	**Group1:** 22/130 **Group 2:** 21/125 **P value:** 0.98	**Funding:** Not reported **Outcomes not reported:** Asymptomatic lower limb DVT or pulmonary embolism, post-thrombotic syndrome, pulmonary hypertension, quality of life **Additional outcomes reported:** Time to catheter associated thrombosis, premature catheter removals **Notes:** * catheter associated thrombosis defined as thrombosis of either the vein or veins in which the CVC was placed or a contiguous vein. # objective tests not defined Study reports the low incidence of CVC associated thrombosis meant the study was underpowered
			Symptomatic catheter associated thrombosis* at 90 days (confirmed by ultrasonography or venography).	**Group1:** 6/130 **Group 2:** 5/125 **P value:** 0.81	
			Symptomatic non-CVC associated DVT or pulmonary embolism (confirmed by "objective tests"#)	**Group1:** 3/130 **Group 2:** 3/125 **P value:** 0.96	
			Major bleeding (associated with fall in haemoglobin concentration of ≥20g/L or need for ≥2 units of blood transfusion in any 24-hour period; central nervous system bleeding, bleeding with hypotension,)	**Group1:** 0/130 **Group 2:** 3/125 **P value:** 0.07	
			Any bleeding	**Group1:** 5/130 **Group 2:** 6/125 **P value:** 0.74	

Warfarin vs no prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Heaton et al., 2002[265] **Country of study:** New Zealand **Study design:** RCT **List who was masked to interventions:** NR **Evidence level:** 1+ **Duration of follow-up:** 90 days	**Patient group:** Adult patients with central venous catheter (CVC) and haematological malignancies. **Setting:** Haematology ward **Exclusion criteria:** • None reported **<u>All patients</u>** **N:** 88 patients & 102 catheters **No. patients 1 catheter:** 77 **No. patients 2 catheter:** 8 **No. patients 3 catheter:** 3 **<u>Group 1</u>** **No. randomised:** 45 patients & 51 catheters **No. of dropouts:** 0 **Mean age:** 55 **<u>Group 2</u>** **No. randomised:** 43 patients & 51 catheters **No. of dropouts:** 0 **Mean age:** 41	**Group 1** Fixed low-dose warfarin: 1mg 1x/day orally started on day of insertion & continued for 90 days; a clot developed; catheter was removed or INR exceeded 1.5 **Group 2** No warfarin **Additional non-comparative prophylaxis:** None reported	**All Cause Mortality**	**Group1:** 0/45 **Group 2:** 0/43 **P value:** NA	**Funding:** None reported **Outcomes not reported:** Lower limb DVT, pulmonary embolism, post-thrombotic syndrome, pulmonary hypertension, quality of life. **Additional outcomes reported:** No. reaching 90 days without thrombosis, catheter removals before 90 days, INR >1.5, line infection requiring line removal, line infection not requiring line removal, **Notes:** Poorly reported study States "patients were NOT excluded if they had been in the trial with a previous catheter"
			Symptomatic catheter thrombosis (confirmed by venography).	**Group1:** 6/45 **Group 2:** 4/43 **P value:** 0.55	
			Symptomatic catheter associated venous thrombosis (confirmed by venography).	**Group1:** 2/45 **Group 2:** 1/43 **P value:** 0.59	

LMWH vs no prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Karthaus et al., 2006KARTHAUS2006} **Country of study:** 48 centres from 12 countries **Study design:** RCT **List who was masked to interventions:** Patient, clinician and outcome assessor **Evidence level:** 1+ **Duration of follow-up:** 16 weeks	**Patient group:** Patients with documented cancer with central venous catheter. **Setting:** Unclear **Inclusion criteria:** Patients with histologically confirmed malignancy; placement of a CVC for chemotherapy within 5-7 days prior to randomisation and treatment; expected length of catheter use of at least 12 weeks; age ≥ 18 years; weight ≥ 40kg; Eastern Cooperative Oncology Group performance status of 0,1 or 2; life expectancy of at least 16 weeks; adequate pre-treatment organ function as demonstrated by a platelet count of at least 100,000/mm^3; absolute neutrophil count of at least 1500/mm^3; total bilirubin and serum creatinine of up to 2 x the upper limit of normal; AST up to 3 x (patients without liver metastasis) or 5 x (patients with liver metastasis) the upper limit of normal; a PT/aPTT up to 1.5 x the upper limit of normal. **Exclusion criteria:** known hypersensitivity to dalteparin; other LMWH or unfractionated heparin; active gastrointestinal or genitourinary tract bleeding; known coagulopathy; requirement for aspirin, dipyridamole, UFH, other LMWHs, warfarin or other anticoagulation therapy; active uncontrolled infection, including suspected catheter related infection,; known HIV positivity or AIDS related illness; eye, ear or NS surgery or a CNS trauma within the last 3 months; intracranial or intraocular haemorrhage (within1 year) or retinal detachment (within 6 months); mental incapacitation or psychiatric illness that would prevent the provision of informed consent; uncontrolled cardiac arrhythmia; severe concurrent disease; leukaemia requiring induction/consolidation chemotherapy during the 16 study week period; requirement of high dose chemotherapy and	**Group 1** Low Molecular Weight Heparin (Dalteparin) Start time: unclear End time: unclear Duration: 16 weeks Dose and frequency: 5000IU injected subcutaneously once daily **Group 2** Placebo Start time: Unclear End time: Unclear Duration: 16 weeks Dose and frequency: 0.2ml saline solution **Additional non-comparative prophylaxis:** Catheter flushing with unfractionated heparin (500IU)/saline boluses were allowed during catheter use.	**All Cause Mortality**	**Group1:** 4/285 **Group 2:** 1/140 **P value:** NS	**Funding:** Pfizer **Limitations:** • 2:1 randomisation of dalteparin: placebo. • Significantly more patients had solid tumours in the Dalteparin group. **Outcomes not reported:** Deep vein thrombosis, Heparin induced thrombocytopaenia, pulmonary hypertension, post thrombotic syndrome, Quality of life, length of stay **Additional outcomes reported:** Catheter related infection, non-catheter related arterial or venous thromboembolic events **Notes:** * Calculated by the NCC team using Fisher exact test. Catheter related thrombosis 1. Clinically relevant catheter related thrombosis = thrombosis that was symptomatic or that required anticoagulant
			Catheter related clinically relevant pulmonary embolism (confirmed by: ventilation perfusion scan or spiral CT scan)	**Group1:** 1/294 **Group 2:** 0/145 **P value:** NS	
			Clinically relevant catheter related thrombosis[1] (screened for by: upper extremity evaluation by venography, ultrasound or computed tomography CT scan)	**Group1:** 10/294 **Group 2:** 5/145 **P value:** 0.980*	
			Asymptomatic catheter related thrombosis[2] (confirmed by: upper extremity evaluation by venography, ultrasound or computed tomography CT scan)	**Group1:** 10/294 **Group 2:** 6/145 **P value:** 0.788*	
			Major bleeding (description: as described by adjudication committee)	**Group1:** 1/294 **Group 2:** 1/145 **P value:** 0.522*	
			All bleeding (Table of all recorded bleeding (including location of bleed) is provided as table 5 in the paper)	**Group1:** 50/285 **Group 2:** 21/140 **P value:** 0.581*	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	stem cell transplantation during the 16 week study period; use of investigational or unapproved catheter devices; and pregnancy, breastfeeding or likelihood of pregnancy. **<u>All patients</u>** **N:** 439 **Age (mean):** Gp 1 Gp2 Mean ± SD 55.2±12.91 57.4 ±12.72 **M/F (% female):** 59.2 57.2 **Additional risk factors**: Gp1 Gp2 Weight mean (kg) ± SD 71.41±15.41 70.73±14.28 % Caucasian 94.6 93.8 Solid: Haematological tumours 271:23 125:20 Haematologica **<u>Group 1</u>** **No. randomised:** 294 **No. of dropouts:** 9 patients did not receive 1 dose 94 patients withdrew early from the study (reasons provided) **<u>Group 2</u>** **No. randomised:** 145 **No. of dropouts:** 9 patients did not receive 1 dose 94 patients withdrew early from the study (reasons provided)				therapy or therapeutic infusion of a fibrinolytic agent with or without catheter removal 2. Asymptomatic catheter thrombosis = not requiring any intervention.

Warfarin vs LMWH

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Mismetti et al., 2003[452] **Country of study:** France **Study design:** Multicentre RCT (pilot study) **List who was masked to interventions:** Venograms were reviewed by an independent reading team **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** Consecutive patients ≥18 years with non-hematologic cancer scheduled to undergo placement of long-term subclavian venous catheter having an expected survival of >3 months. **Setting:** Hospital **Exclusion criteria:** • Central venous catheters implanted previously • Need for long-term anticoagulant treatment for a chronic comorbid condition • Stroke within previous 2 months • Active bleeding • Bacterial endocarditis • Platelet count <100x10⁹/L • Prothrombin time >15 s • Activated partial thromboplastin time >10 s • Prior history of allergy to heparin or heparin-induced thrombocytopenia • Hypersensitivity to iodinated contrast medium • Impaired renal or liver function **All patients** **N:** 60 **Group 1** **No. randomised:** 30 **No. of dropouts:** 0 **Mean ±SD age:** 60.3 ±9.5 **Previous history of thrombotic events:** 6 **Group 2** **No. randomised:** 30 **No. of dropouts:** 1 **Mean ±SD age:** 57.1 ±9.0 **Previous history of thrombotic events:** 8	**Group 1** Fixed low-dose warfarin: 1mg 1x/day orally starting 3 days before catheter insertion & continued for 90 days **Group 2** LMWH 2850 IU subcutaneous Nadroparin 1x/day starting 2 hours before catheter insertion and continued for 90 days **Additional non-comparative prophylaxis:** None reported Prohibited use of other anticoagulants, high dose aspirin (>500mg/day) ticlopidine, pyrazolone and miconazole. Discouraged use of aspirin (<500mg), other non-steroidal anti-inflammatory drus and corticosteriods.	**All Cause Mortality**	**At 90 days** **Group1:** 4/30 **Group 2:** 6/29 **P value:** 0.46 **At 6 months** **Group1:** 5/30 **Group 2:** 10/29 **P value:** 0.12	**Funding:** Sanofi-Synthelabo **Outcomes not reported:** Asymptomatic lower limb DVT or pulmonary embolism, post-thrombotic syndrome, pulmonary hypertension, quality of life **Additional outcomes reported:** Severe thrombocytopenia at 90 days (<50x10⁹/L) **Group1:** 1/24 **Group 2:** 2/21 **P value:** 0.49 Severe thrombocytopenia at 6 months (<50x10⁹/L) **Group1:** 3/24 **Group 2:** 2/21 **P value:** 0.75 **Notes:** After 90 days, patients not receiving antithrombotic agent according to protocol
			Asymptomatic or symptomatic upper extremity thrombosis at 90 days (confirmed by bilateral venography).	**Group1:** 4/24 **Group 2:** 6/21 **P value:** 0.48	
			Symptomatic DVT of lower limb at 90 days (confirmed by Doppler ultra sonography &/or venography)	**Group1:** 0/24 **Group 2:** 1/22 **P value:** 0.46	
			Symptomatic pulmonary embolism at 90 days (confirmed by ventilation perfusion lung scan, pulmonary angiography or helical computed tomography)	**Group1:** 0/24 **Group 2:** 0/22 **P value:** NA	
			Any thromboembolic event at 6 months	**Group1:** 4/30 **Group 2:** 8/29 **P value:** 0.13	
			Major bleeding (need for ≥2 units of blood transfusion; fatal, retroperitoneal or intracranial bleeding, bleeding involving another critical organ)	**At 90 days** **Group1:** 0/24 **Group 2:** 1/21 **P value:** 0.45 **At 6 months** **Group1:** 2/24 **Group 2:** 1/21 **P value:** 0.64	
			Heparin-induced thrombocytopenia at 90 days (laboratory confirmed)	**Group1:** 0/24 **Group 2:** 0/21 **P value:** NA	

LMWH vs no prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Monreal et al., 1996[457] **Country of study:** Spain **Study design:** RCT **List who was masked to interventions:** Venogram interpreters. **Evidence level:** 1+ **Duration of follow-up:** 90 days	**Patient group:** Cancer patients with central venous catheters **Setting:** Unclear **Inclusion criteria:** all cancer patients who underwent placement of a long term Port-a-Cath subclavian venous catheter and had projected survivals of over 3 months. **Exclusion criteria:** Patients who had baseline platelet counts under $100x10^9/l$, previous subclavian vein catheters, obstructing mediastinal tumours, previous history of DVT, or anatomic lesions that bleed. **<u>All patients</u>** **N:** 32 **Age (mean):** 54 (range 27 – 77) **M/F:** 17:15 **Additional risk factors:** Cancer location Gp1 Gp2 Colon 8 7 Breast 4 2 Sarcoma 2 1 Mesothelioma 1 2 Stomach 1 1 Metastases Gp1 Gp2 Liver 6 7 Lung 5 4 Bone 2 1 Brain 1 1 Others 2 1 Gp1 Gp2 Infection 0 1 **<u>Group 1</u>** **No. randomised:** 17 **No. of dropouts:** 1 died	**Group 1** LMWH (Fragmin) Start time: 2 hours before insertion of the catheter Duration: 90 days or until there was venographic evidence of thrombosis. Dose, and frequency: 2500IU subcutaneously once daily. **Group 2** No prophylaxis **Additional non-comparative prophylaxis:** None mentioned	**All Cause Mortality** Mortality from cancer progression **Asymptomatic subclavian DVT** (confirmed by: Venography) Paper reports that 8/9 events were symptomatic but does not provide details of which group they occurred in. **Major bleeding** (description: haematoma requiring surgical intervention)	**Group1:** 1/17 **Group 2:** 2/15 **P value:** 0.589* **Group1:** 1/16 **Group 2:** 8/13 **P value:** 0.003* **Group1:** 1/16 **Group 2:** 0/12 **P value:** NS	**Funding:** No information is provided regarding funding. **Limitations:** No information about randomisation method, allocation concealment in the paper. The paper does not state whether patients or clinicians were blind to treatment allocation. **Outcomes not reported:** Pulmonary embolism, lower extremity DVT, Fatal, neurological or minor bleeding, post thrombotic syndrome, pulmonary hypertension, heparin induced thrombocytopaenia, quality of life, length of stay. **Additional outcomes reported:** Infection **Notes:** * Calculated by NCC using Fisher exact tests.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 2 **No. randomised:** 15 **No. of dropouts:** 2 died				

LMWH vs no prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Niers et al., 2007[489] **Country of study:** The Netherlands **Study design:** RCT **List who was masked to interventions:** Patient, healthcare professionals and investigators assessing outcome **Evidence level:** 1+ **Duration of follow-up:** 3 weeks	**Patient group:** Patients with haematologic malignancies requiring central venous catheters, **Setting:** Unclear **Inclusion criteria:** Consecutive patients with haematologic malignancies who were going to receive a CVC for high-dose chemotherapy including autologous stem cell transplantation. **Exclusion criteria:** • Patients aged less than 17 years • allergy to i.v. contrast medium, • previous catheter related CVT, • current use or indication for anticoagulant treatment • acute promyelocytic leukaemia • Previous CVC • Evident haemorrhagic diathesis • Renal failure (creatinine >200 µmol/L) **<u>All patients</u>** **N:** 202 eligible, 113 randomised Reasons for non-randomisation given **Age :** Gp1 Gp2 mean ± SD 58±10 53±13 **M/F:** 62:51 **Additional risk factors:** Haematologic tumours Gp1 Gp2 Acute myeloid leukaemia 23 17 Multiple lymphoblastic leukaemia 2 10 Multiple myeloma 14 16 (Non)-Hodgkin lymphoma – relapsed 17 14 **<u>Group 1</u>** **No. randomised:** 56	**Group 1** Low Molecular Weight Heparin Nandoparin (Fraxiparin) Start time: 2hr before CVC insertion End time: 3 weeks or until day of catheter removal whichever came first Dose, and frequency: 2850 antifactor Xa (antiFXa) units subcutaneously once daily **Group 2** Placebo (no details provided) Dose and frequency: subcutaneous injections once daily **Additional non-comparative prophylaxis:** None indicated in the paper.	**Symptomatic catheter related central venous thrombosis** (confirmed by: venography)	**Group1:** 0/41 **Group 2:** 1/46 **P value:** NS	**Funding:** Paper states that the study drug was obtained commercially and there was 'financial support' for the study. No further details were provided. **Limitations:** No information about method of randomisation and allocation concealment. 24% of randomised patients did not complete the study **Outcomes not reported:** Pulmonary Embolism, Lower limb DVT, pulmonary hypertension, post thrombotic syndrome, quality of life, length of stay, all cause mortality. **Additional outcomes reported:** Catheter related infection **Notes:** CVT – central venous thrombosis CVC – central venous catheter *Calculated by the NCC using Fisher Exact Test
			Catheter related central venous thrombosis (confirmed by: ultrasound confirmed by venography)	**Group1:** 7/41 **Group 2:** 4/46 **P value:** 0.336*	
			Major bleeding (description: overt bleeding with a fall in haemoglobin of 2g/dL or more, or leading to a transfusion of 2 or more units of packed red blood cells or bleeding in a critical organ such as intracranial, retroperitoneal or pericardial bleeding, or contributing to death.)	**Group1:** 0/56 **Group 2:**0/57 **P value:** NS	
			Clinically relevant non-major bleeding (description: overt bleeding not meeting the criteria for major bleeding, and included skin haematoma if the size was larger than 100cm^2, epistaxis lasting for more than 5 min or repetitive or leading to an intervention, macroscopic haematuria if spontaneous or lasting for more than 24 hr after instrumentation or any other bleeding type that was considered to have clinical consequences for the patient.)	**Group1:** 2/56 **Group 2:** 2/57 **P value:** NS	
			Minor bleeding (description: all other bleeding episodes not meeting the criteria for clinically relevant non-major bleeding)	**Group1:**5/56 **Group 2:** 2/57 **P value:** 0.271*	
			Heparin induced thrombocytopaenia	**Group1:** 0/56 **Group 2:** 0/57	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	No. of dropouts: 15 (27%) **<u>Group 2</u>** **No. randomised:** *57* **No. of dropouts:** 11 (19%)		(description: clinical suspicion and positive antibodies against the heparin-platelet FIV complex)	**P value:** NS	

LMWH vs no prophylaxis

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Verso et al., 2005[663] **Country of study:** Italy **Study design:** RCT **List who was masked to interventions:** Patients, healthcare professionals and investigators assessing VTE end points **Evidence level:** 1+ **Duration of follow-up:** 3 months	**Patient group:** Cancer patients with a central venous catheter **Setting:** Unclear **Inclusion criteria:** Consecutive patients aged 18 years or older who were scheduled for CVC insertion for chemotherapy if they had a life expectance of at least 3 months and adequate venous access to perform venography of the upper limb and if the CVC was to be left in site for longer than 6 weeks. **Exclusion criteria:** • Renal failure (serum creatinine >2.0 mg/dL) • Known hypersensitivity to x-ray contrast medium • Previous CVC insertion on the ipsilateral side • Cerebral thrombosis or bleeding in the previous 6 months or known cerebral metastasis • Bleeding disorders (APTT and/or prothrombin time 30% longer than control values) or platelet count less than 80 x 10^9/L • Active gastric peptic ulcer or severe hepatic disease • Uncontrolled arterial hypertension • Known hypersensitivity to unfractionated heparin or LMWHs • Objectively confirmed DVT within the previous 3 months • Treatment with heparin, LMWH, oral anticoagulants or antiplatelet agents within 5 days before CVC insertion • Pregnancy • Anticipated inability to participate in	**Group 1** Low Molecular Weight Heparin - Enoxaparin (Clexane) Start time: 2 hours prior to CVC insertion Duration: 42 days ±2 days Dose, and frequency: 40mg injection subcutaneously once per day. **Group 2** Placebo Start time: 2 hours prior to CVC insertion Duration: 42 days ±2 days **Additional non-comparative prophylaxis:** Paper states treatment with aspirin, antiplatelet agents or nonsteroidal anti inflammatory agents were not allowed during the trial.	**All cause mortality**	**After treatment** **Group1:** 5/191 **Group 2:** 2/194 **P value:** 0.281* **After follow up (3 months)** **Group1:** 13/191 **Group 2:** 20/194 **P value:** 0.2875*	**Funding:** Supported by a grant from Aventis Pharmaceuticals. **Limitations:** The paper states that randomisation was completed using 'random numbers' but no indication of how these were generated. No information about allocation concealment. **Outcomes not reported:** Lower limb DVT, Pulmonary Embolism, Neurological bleeding, Upper GI bleeding, Heparin induced thrombocytopaenia, post thrombotic syndrome, pulmonary hypertension, quality of life, length of stay **Additional outcomes reported:** Thrombocytopaenia **Notes:** * calculated by NCC team using Fisher Exact Test
			Fatal pulmonary embolism (confirmed by: autopsy)	**Group1:** 0/191 **Group 2:** 0/194 **P value:** NS	
			Symptomatic upper limb DVT (confirmed by: venography)	**Group1:** 2/155 **Group 2:** 6/155 **P value:** 0.283*	
			asymptomatic or symptomatic upper limb DVT (confirmed by: venography)	**Group1:** 22/155 **Group 2:** 28/155 **P value:** 0.44*	
			Major bleeding (description: decrease in haemoglobin level of at least 2g/dL or requiring a transfusion of two or more units of packed red cells. Intracranial, retroperitoneal, and intraocular bleeding and bleeding requiring surgical intervention)	**Group1:** 0/191 **Group 2:** 0/194 **P value:** NS	
			Minor bleeding (description: All other bleeding)	**Group1:** 12/191 **Group 2:** 7/194 **P value:** 0.248*	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	the study for 3 months • Patients with CVC for parenteral nutrition only **<u>All patients</u>** **N:** 385 **Age:** Gp 1 Gp2 Mean±SD 59.1±11.9 59.5±12.4 **M/F:** 176:209 **Additional risk factors:** Cancer Localisation Gp1 Gp2 Gastrointestinal 100 108 Hepatic or biliary tract 0 7 Pancreatic 3 6 Genitourinary 14 10 Lung 4 3 Head and neck 13 6 Breast 34 34 Haematological 16 17 Skin 1 2 Other 7 3 Unknown 2 2 Cancer Histology Gp1 Gp2 Adenocarcinoma 157 162 Lymphoma and leukaemia 13 14 Sarcoma 4 2 Other 15 11 Unknown 1 4 Cancer stage Gp1 Gp2 Metastatic 145 139 Non metastatic 41 45 Unknown 4 4 Surgery, No of patients Gp1 Gp2 Previous ≤3 months 83 79 Recent <3 months 72 68 Planned 3 4 Unknown 32 41 Chemotherapy Gp1 Gp2 Before CVC insertion 88 75 After CVC insertion 102 118 One agent 45 34 ≥2 agents 145 159				

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Other risk factors **Gp1** **Gp2** Axillary node dissection 27 28 Previous CVC of upper limb 16 23 Previous chest surgery 17 11 History of radiation to chest wall 15 12 History of previous VTE (<3months) 1 0 Axillary node involvement 11 6 Compression of superior vena cava 3 5 Family history of VTE 2 4 Oestrogen containing medications 1 1 Upper limb immobilisation 0 1 **Group 1** **No. randomised:** 191 **No. of dropouts:** 36 (18.8%) **Group 2** **No. randomised:** 194 **No. of dropouts:** 39 (20.1)				

Warfarin vs. No Prophylaxis and - Fixed vs. Adjusted Dose Warfarin

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Young et al., 2008[707] **Country of study:** UK **Study design:** RCT **List who was masked to interventions:** Investigators assessing radiographs were blinded to treatment allocation. **Evidence level:** 1+ **Duration of follow-up:** Median follow-up was 45 months (range 26 to 88 months)	**Patient group:** Cancer patients with central venous catheters (CVCs). **Setting:** 68 Clinical centres with nursing teams. **Inclusion criteria:** Histologically confirmed diagnosis of cancer; requirement for CVC insertion for administration of chemotherapy; aged at least 16 years with adequate hepatic, renal and haematological function. **Exclusion criteria:** Patients with contraindication to warfarin and pregnant or lactating women **All patients** **N:** 1590 **No. of dropouts:** 24 (1.5%) All patients were included in the analysis **Group 1 warfarin** **No. randomised:** 408 This includes patients on 1 mg fixed dose of warfarin n= 324 (82 of these patients were also included in group 3) and DAW patients n=84 (these 84 patients were also included in group 4) **Gender**- Male N (%): 252 (62%) **Age** (yrs) Median (IQR): 60 (53-68) **Group 2 No warfarin** **No. randomised:** 404 **Gender-** Male N(%): 247 (61%) **Age** (yrs) Median (IQR): 61 (53-68) **Group 3 FDW** **No. randomised:** 471 82 patients in this group were also included in group 1	**Control comparison** Clinicians who were' uncertain' of the benefits of warfarin randomised patients to: **Group 1: Warfarin** This includes patients on 1 mg fixed dose of warfarin (FDW) and patients with daily dose adjusted warfarin (DAW) to maintain the international normalised ratio (INR) between 1.5 and 2.0. **Group 2: No warfarin** **'Dose evaluation' comparison** Clinicians who were 'certain' of the indication of warfarin randomised patients to: **Group 3: FDW** 1 mg fixed dose warfarin **Group 4: DAW** Daily dose adjusted warfarin to maintain the international	**All cause mortality**	There were 1058 deaths: n=921 (87%) due to cancer n= 53 (5%) due to other causes n=84 (8%) unknown Warfarin vs. control: HR=0.98 95%CI: 0.77-1.25 P=0.26 FDW vs. DAW: HR=0.91 95%CI: 0.73-1.14 P=0.53	**Funding:** Clinical research fellowship funding from the Medical Research Council and data management funding from Cancer Research UK **Limitations:** The planned length of the study is not clear. Patients and healthcare professionals were not blinded. **Outcomes not reported:** Fatal Pulmonary Embolism Heparin induced thrombocytopaenia Post thrombotic syndrome Pulmonary hypertension Length of stay Quality of life **Additional outcomes reported:** Median time to CRT Combined toxicity (major bleeding and thrombosis) The study also aimed to report health service related costs (not reported in this paper). **Notes:** 166 patients (10.4%)
			Symptomatic pulmonary embolism (confirmed by: ventilation-perfusion (VQ)/ Spiral CT by two investigators, blinded to treatment allocation, using a central protocol.)	Data from text: 2 out of 85 CRT were pulmonary emboli 9 out of 36 non-CRT events were pulmonary emboli and 1 out of these 36 non-CRT was located in pulmonary vein (results not provided by group)	
			Catheter Related Thrombosis Events (confirmed by: venogram, ultrasound or ventilation-perfusion (VQ)/ Spiral CT by two investigators, blinded to treatment allocation, using a central protocol. Patients were not screened and so events are assumed to be symptomatic.)	Total no. of events: n=85 Group 1 Warfarin: 24/408 (5.9%) Group 2 No warfarin: 24/404 (5.9%) RR (95% CI): 1.00 (0.74,1.34) **P value:** 0.98 Group 3 FDW: 34/471 (7.2%) Group 4 DAW : 13/473 (2.8%) RR (95% CI): 0.67 (0.56, 0.81) **P value:** 0.002 Note: 166 (10.2%) patients are counted in both comparisons (control vs warfarin and FDW vs DAW); 10 of these patients had a thrombotic event	
			All Thrombotic Events (Catheter related plus non catheter related thromboses) (confirmed by: venogram, ultrasound or ventilation-perfusion (VQ)/ Spiral CT by	Total no of events: n = 36 Group 1 Warfarin: 30/408 (7.4%) Group 2 No warfarin: 38/404 (9.4%) RR (95% CI): 0.88 (0.70, 1.10) **P value:** 0.30	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Gender- Male N(%): 253 (54%) **Age** (yrs) Median (IQR): 59 (51-66) **Group 4 DAW** **No. randomised:** 473 84 patients in this group were also included in group 1. **Gender-** Male N(%): 265 (56%) **Age** (yrs) Median (IQR): 60 (53-67) **Stage of disease:** No residual/early: Group 1 warfarin: 134/408 (33%) Group 2 No warfarin: 130/404 (32%) Group 3 FDW: 171/471 (36%) Group 4 DAW : 138/473 (29%) Advanced: Group 1 warfarin: 269/408 (66%) Group 2 No warfarin: 273/404 (68%) Group 3 FDW: 294/471 (62%) Group 4 DAW : 330/473 (70%) Not known: Group 1 warfarin: 5/408 (1%) Group 2 No warfarin: 1/404 (0.3%) Group 3 FDW: 6/471 (1%) Group 4 DAW : 5/473 (1%) **Disease site:** Colorectal: Group 1 warfarin: 217/408 (53%) Group 2 No warfarin: 201/404 (50%) Group 3 FDW: 226/471 (48%) Group 4 DAW : 243/473 (51%) Upper GI: Group 1 warfarin: 92/408 (23%) Group 2 No warfarin: 109/404 (27%) Group 3 FDW: 95/471 (20%) Group 4 DAW : 98/473 (21%) Breast: Group 1 warfarin: 32/408 (8%) Group 2 No warfarin: 32/404 (8%) Group 3 FDW: 82/471 (17%)	normalised ratio (INR) between 1.5 and 2.0. **Duration (all warfarin groups)** Start of warfarin, if allocated, was permitted from 3 days prior to CVC insertion. Warfarin was taken daily until thrombosis or catheter removal for any reason could be temporarily discontinued in the face of significant chemotherapy induced thrombocytopenia (platelets<=50x10^9/L) **Additional non-comparative prophylaxis:** None recorded	two investigators, blinded to treatment allocation, using a central protocol. Patients were not screened and so events are assumed to be symptomatic.) **Major bleeding** (description: Major bleeding episodes were defined as intracranial, retroperitoneal, requiring transfusion or hospitalisation or directly leading to death. Increased INR was classified by the investigators as mild: (2<INR<5), moderate (5<=INR<8) or severe (INR>=8).	Group 3 FDW: 37/471 (7.9%) Group 4 DAW : 26/473 (5.5%) RR (95% CI): 0.84 (0.67, 1.04) **P value:** 0.15 Note: 166 (10.2%) patients are counted in both comparisons (control vs warfarin and FDW vs DAW); 10 of these patients had a thrombotic event. **Total major bleeding:** Group 1 Warfarin: 7/408 (1.7%) Group 2 No warfarin: 1/404 (0.3%) RR (95% CI): 4.01 (0.64, 25.11) **P value:** 0.07 Group 3 FDW: 7/471 (1.5%) Group 4 DAW : 16/473 (3.4%) RR (95% CI): 1.66 (0.90, 3.08) **P value:** 0.09	were included in two groups. Of 1590, n=4 were found to be ineligible (3 on clinical parameters and 1 declining chemotherapy immediately post randomisation), n=4 did not have CVCs inserted post randomisation. n=12 did not receive any allocated warfarin treatment (8 on warfarin 1 mg and 4 on DAW) mostly due to patient choice. All were included in the analysis. 26 (2.3%) of patients who started on warfarin did not conform to warfarin dose. 106 (9%) of patients who started warfarin, stopped 'early' (more) than 7 days before the catheter was removed) largely due to their chemotherapy being completed and the CVC was still in situ but also because of patient choice or thrombocytopenia.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 4 DAW : 67/473 (14%) **Catheter placement:** <u>Central:</u> Group 1 warfarin: 150/408 (37%) Group 2 No warfarin: 146/404 (36%) Group 3 FDW: 266/471 (48%) Group 4 DAW : 228/473 (48%) <u>Peripheral:</u> Group 1 warfarin: 258/408 (63%) Group 2 No warfarin: 258/404 (64%) Group 3 FDW: 245/471 (52%) Group 4 DAW : 245/473 (52%) **Treatment length:** <u><24 hours:</u> Group 1 warfarin: 68/408 (17%) Group 2 No warfarin: 64/404 (16%) Group 3 FDW: 87/471 (18%) Group 4 DAW : 86/473 (18%) <u>>=24 hours:</u> Group 1 warfarin: 340/408 (83%) Group 2 No warfarin: 340/404 (84%) Group 3 FDW: 384/471 (82%) Group 4 DAW : 387/473 (82%)				

Venal Cava Filters

Evidence Table 70: Venal cava filters vs no filters

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
Decousus et al 1998[154] Long term follow up at 8 years published by The PREPIC Study Group [636] (see next entry)	RCT	1+	**Total**: 400 Intervention : n = 200 Control: n = 200	**Hospitalised patients:** with proximal DVT considered to be at high risk for PE **Intervention:** Mean age: 73±11 yrs M/F:92/108 **Control:** Mean age: 72±11.5 M/F:98/102 **Pre-existing risk factors:** History of VTE, Chronic cardiac or respiratory insufficiency, Surgery in past 60 days, cancer, symptomatic initial PE	**Type:** Permanent vena Caval filter **4 types:** Vena Tech LGM, titanium Greenfield, Cardial and Bird's nest **Timing:** Inserted through femoral or jugular vein immediately after randomisation **Additional non-comparative prophylaxis:** All patients received OAC from 4th day and for at least 3 months. Patients randomised to receive either UFH or LMWH for 8-12 days	No filter **Additional non-comparative prophylaxis:** All patients received OAC from 4th day and for at least 3 months. Patients randomised to receive either UFH or LMWH for 8-12 days	**Both groups:** visits at 4 months and 1 year. Telephone follow up at 2 yrs Additional follow-up at 8 years	**Symptomatic & asymptomatic PE** on 8-12th day	**Int:** 2/200 **Control:** 9/200 **p value:** 0.05	**Comments:** 2x2 factorial design. Patients also randomised to receive either UFH or LMWH. Denominators used for analysis of primary outcomes unclear. Thrombosis at filter site was found in 16 patients. **At 2 years** there were no significant differences between groups in all principal end-points - symptomatic PE, recurrent DVT, major bleeding, death. * **Major bleeding** described as Overt haemorrhage that
								Symptomatic PE at 2 yrs Confirmed by: V/Q scan	**Int:** 6/200 **Control:** 12/200 **p value:** 0.16	
								Fatal PE Based on clinical diagnosis	**Int:** 1/200 **Control:** 5/200 **p value:** 0.14	
								Recurrent DVT at 2 years: Clinical suspicion investigated with venography	**Int:** 37/200 **Control:** 21/200 **p value:** 0.03	
								Major bleeding at 12 days: *	**Int:** 9/200 **Control:** 6/200 **p value:** 0.17	
								Major bleeding at 2 years: *	**Int:** 17/200 **Control:** 22/200 **p value:** 0.40	
								All cause mortality: At 12 days	**Int:** 5/200 **Cont:** 5/200 **P value** 1.00	

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
								All cause mortality: At 2 years	**Int:** 43/200 **Cont:** 40/200 **P value** 0.71	was fatal or required transfusion of at least 2 units of red cells, surgical intervention, or cessation of treatment **Not reported:** QoL, PTS, funding

Vena caval filters vs no filters

Bibliographic reference	Study Type	Evidence level	No. of patients	Patients characteristics	Intervention	Comparison	Length of follow up	Outcome measures	Effect size	Comments
The PREPIC Study Group[636] This study is the long term follow up at 8 years of the RCT published by Decousus et al., 1998 [154]	RCT	1+	**Total**: 400 Intervention : n = 200 Control: n = 200	**Hospitalised patients:** with proximal DVT considered to be at high risk for PE **Intervention:** Mean age: 73±11 yrs M/F:92/108 **Control:** Mean age: 72±11.5 M/F:98/102 **Pre-existing risk factors:** History of VTE, Chronic cardiac or respiratory insufficiency, Surgery in past 60 days, cancer, symptomatic initial PE	**Type:** Permanent vena Caval filter **4 types:** Vena Tech LGM, titanium Greenfield, Cardial and Bird's nest **Timing:** Inserted through femoral or jugular vein immediately after randomisation **Additional non-comparative prophylaxis**: All patients received OAC from 4th day and for at least 3 months. Patients randomised to receive either UFH or LMWH for 8-12 days	No filter **Additional non-comparative prophylaxis**: All patients received OAC from 4th day and for at least 3 months. Patients randomised to receive either UFH or LMWH for 8-12 days	8 years	**Symptomatic PE at 8 yrs** Confirmed by: V/Q scan	**Int:** 9/200 **Control:** 24/200 **p value:** 0.009	* **Major bleeding** described as Overt haemorrhage that was fatal or required transfusion of at least 2 units of red cells, surgical intervention, or cessation of treatment **Not reported:** QoL, funding
								Fatal PE at 8 yrs Based on clinical diagnosis	**Int:** 2/200 **Control:** 5/200 **p value:** 0.27	
								Symptomatic venous thrombo-embolism at 8 yrs	**Int:** 57/200 **Control:** 41/200 **p value:** 0.74	
								Post-thrombotic syndrome at 8 years:	**Int:** 109/200 **Control:** 107/200 **p value:** 0.84	
								Major bleeding at 8 years: *	**Int:** 26/200 **Control:** 31/200 **p value:** 0.48	
								Mortality at 8 years	**Int:** 26/200 **Cont:** 31/200 **P value** 0.62	

Economic evidence

Evidence Table 71: Economic evidence tables

Bibliographic reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Comments
Bhatia et al., 1998[60] Canada	**Economic analysis:** Cost analysis **Study design:** Retrospective, before and after **Time horizon:** NA **Discount rates:** NA	**Patient group:** Patients who had a vena cava filter **Intervention:** N:15 Mean age: 63 M/F:9/6 **Control:** N:15 Mean age: 55 M/F:8/7 **Pre-existing risk-factors:** NR	**Int:** Radiologic percutaneous placement of vena tech LGM filter **Control:** Surgical cutdown of 24 Fr Greenfield filter **Additional non-comparative prophylaxis:** NR	**PE**	**Int:** 0 **Control:** 0	**Funding:** NR **Outcomes not included:** DVT FPE, PTS, Bleeding, HRQL, Survival, LOS, LE, **Other limitations:** (1) Small patient numbers (2) Bias associated with before and after studies **Other comments:** Most of the difference in cost was due to the cost of supplies and the cost of the product itself.
				Mean Cost (Canadian $, year not specified, product and administration costs) Converted to £ using PPPs	**Int:$**1580 (£1193) **Control:** $2282 (£1723)	
				Sensitivity analysis:	NR	

Bibliographic reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Comments
Brasel et al., 1997[80] US	**Economic analysis:** CEA **Study design:** Decision analysis **Time horizon:** 30 days **Discount rates:** NR	**Patient group:** High risk trauma patients **Patients:** Model assumes all patients are high risk, age > 45 years, pelvic fracture, lower extremity fracture or venous repair, Injury severity score ≥ 15, or spinal cord injury, LOS ≥ 3 days **Pre-existing risk-factors:** High risk	1. Duplex ultrasound, twice weekly screening 2. Inferior vena cava filters, inserted in operating room 3. Subcutaneous unfractionated heparin (5 days) and warfarin sodium (6 months) and/or sequential compression devices **Additional non-comparative prophylaxis:** All patients were receiving subcutaneous unfractionated heparin and/or sequential compression devices	**PE** (Incidence of PE)	**1.** 0.02 **2.** 0.01 **3.** 0.04	**Funding:** NR **Outcomes not included:** DVT FPE, PTS, Bleeding, HRQL, Survival, LOS, LE. **Other limitations:** Short-term time horizon **Other comments:** Since this is a model, p-values, etc are NA
				Mean Cost (US $, year not specified, product and administration costs) Converted to £ using PPPs	**1.** $971 (£606) **2.** $2856 (£1782) **3.** $45 (£28)	
				Cost-effectiveness: (cost per PE prevented)	**1 vs. 3:** $46,300 (£28,891) **2 vs. 3:** $93,700 (£58,469)	
				Sensitivity analysis:	Location of placement of vena cava filters was identified as a sensitive variable. When vena cava filters are placed in the operating room then (1) is always more cost-effective. When they are placed in radiology then (1) and (2) have equivalent cost-effectiveness until LOS > 2 weeks, when radiology placement of (2) becomes more cost-effective than (1).	

Bibliographic reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Comments
Chau et al., 2003[105] USA	**Economic analysis:** CUA **Study design:** Markov model, probabilities obtained from 24 patients in s cancer center. **Time horizon:** Lifetime **Discount rates:** Costs=3%	**Patient group:** Patients with malignant brain tumours and DVT of the lower extremities **All patients:** N: 24 Mean age: 50 M/F:NR **Pre-existing risk-factors:** DVT	**Int:** Bird's nest filter and anticoagulation (heparin). **Control:** Anticoagulation only (heparin) **Additional non-comparative prophylaxis:** NR	**PE** (PE free months)	**Int:** 11.6 months **Control:** 9.4 months (p=0.24)	**Funding:** NR **Outcomes not included:** DVT PTS, Bleeding, HRQL, LOS, LE. **Other limitations:** 1. Probability data based on a small sample size of nonrandomised, non-controlled patients, in which there was a survival difference between the two groups. 2. Survival time was short – filters may be more cost-effective for groups of patients with longer survival times. Since this is a model, p-values for costs, etc are NA
				PE (rate of PE – per 100 person-months at risk)	**Int:** 0.57 **Control:** 1.05 (no p value)	
				Survival (mean)	**Int:** 12.1 months **Control:** 9.5 months (p=0.13)	
				Mean Cost (US $, 1999, costs included all hospital costs associated with a PE) Converted to £ using PPPs	**Int:** $7,502 (£4,821) **Control:** $4,730 (£3,046)	
				Quality-adjusted life-years (utility value of 0.7 was assigned to a PE from Tengs et.al. 2000)	**Int:** 2.34 **Control:** 2.33	
				Cost-effectiveness: (cost per QALY)	**ICER =** $198,852 (£128,061)	
				Sensitivity analysis: Rate of PE, cost of PE and 5-yr mortality rate were all varied.	Rate of PE of control would have to exceed 1.51 for ICER < $50,000 Cost of PE would have to exceed $35,000 for the filter to be a cost-effective strategy. The 5-yr mortality rate was varied using survival data from patients with lung cancer and breast cancer. In patients with a longer LE filters could be cost-effective.	

Bibliographic reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Comments
Hye et al., 1990[303] USA	**Economic analysis:** CA **Study design:** Retrospective **Time horizon:** 25 months mean time to follow-up **Discount rates:** NR	**Patient group:** All patients who had undergone placement of Greenfield vena cava filters at one hospital. **Intervention:** N:121 Mean age: 51 M/F:87/34 **Control:** N:48 Mean age: 49 M/F:28/20 **Pre-existing risk-factors:** Patients had trauma (20%), Malignancy (7%), neurologic disease (4%), pulmonary hypertension (59%), other disease (10%).	**Int:** Percutaneous placement of Greenfield vena cava filter. **Control:** Surgical placement of Greenfield vena cava filter. **Additional non-comparative prophylaxis:**	**Successful placements**	**Int:** 99% **Control:** 94%	**Funding:** NR **Outcomes not included:** DVT FPE, PTS, Bleeding, HRQL, Survival, LOS, LE. **Other limitations:** 1. Non-controlled, non-randomised, therefore inherent bias. 2. Short period of follow-up for complications to appear. 3. Costs data limited, source of cost data not given.
				Bleeding related complications (post-procedural hematoma, bleeding)	**Int:** 6% **Control:** 2%	
				Femoral vein thrombosis/leg edema	**Int:** 4 patients **Control:** 0	
				PE	**Int:** 1 patient **Control:** 0	
				Mean Cost (US $, year not specified, cost includes cost of product and cost of administration) Converted to £ using PPPs	**Int:** $2744 (£1679) **Control:** $4699 (£2876)	
				Sensitivity analysis:	NR	

Bibliographic reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Comments
Sarasin & Eckman,1993[583] USA	**Economic analysis:** cost utility **Study design:** decision analysis **Time horizon:** NR **Discount rates:** Costs=5% Effects (specify)=5 %	**Patient group:** Patients with advanced malignancies prone to develop thromboembolic events, patients with acute proximal DVT, and patients who have survived a first episode of PE.	**Int:** vena cava filter **Control:** observation **Control 2:** long-term anticoagulant therapy (heparin followed by warfarin) starting immediately **Additional non-comparative prophylaxis:** low-intensity anticoagulant therapy or aspirin	**Gain in Quality of Life (Quality-Adjusted Life Months)** Patients with acute DVT (breast, gastrointestinal, lung, pancreas cancer)	**Contr1 vs Contr2:** 1.5 - 1.1 – 1 - 0.8 **Int vs Contr1:** 2.5 - 1.5 - 1.2 - 0.9 **Int vs Contr2:** 1 - 0.3 - 0.2 - 0.1	**Funding:** NR **Outcomes not included:** DVT PE, FPE, PTL, Bleeding, HRQL, Survival, LOS, LE, **Other limitations:** - specific population - time horizon and patient group are not clearly stated **Other comments:** - Costs relative to complications (PE, venous thrombosis, death) are reported.
				Gain in Quality of Life (Quality-Adjusted Life Months) Survivors of PE (breast, gastrointestinal, lung, pancreas cancer) Quality-of-life adjustment Factors used are systemic haemorrhage, chronic anticoagulation therapy, chronic lower extremity oedema, PE, venous thrombosis. QALY values were derived by expert opinions from clinicians at the institution.	**Contr1 vs Contr2:** 3.3, 2.1, 1.8, 1.3 **Int vs Contr1:** 4.3, 2.4, 2, 1.5 **Int vs Contr2:** 1, 0.3, 0.2, 0.1	
				Costs US$ 1993 in the setting of lung cancer for acute PE patient	**Int: $**3,338 (£2,080) **Control 1: $**5,215 (£3,249) **Control 2:** $3,768 (£2,348) **p value:** NR	
				Costs US$1993 in the setting of lung cancer for acute DVT patient	**Int: $**2,771 (£1,727) **Control1 : $**3,563 (£2,220) **Control2**: $3,032 (£1,889) **p value:** NR	
				QALMs in the setting of lung cancer for acute PE patient	**Int:** 11.1 **Control 1:** 9.1 **Control 2:** 10.9 **p value:** NR	
				QALMs in the setting of lung cancer for acute DVT patient	**Int:** 11.2 **Control 1:** 10 **Control 2:** 11 **p value:** NR	
				Cost-effectiveness	The vena cava filter placement is the dominant intervention	
				Sensitivity analysis: Lung cancer patients	Threshold analysis: Control 2 is preferred if the monthly rate of acute DVT exceeds 3.5%. VCF is preferred only if the monthly rate of acute DVT exceeds 1.6% per month and if the efficacy is more than 75%.	

Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital

Appendices E – I

APPENDICES

Produced by the National Collaborating Centre for Acute Care

Contents

Appendix E

Meta-Analyses Forest Plots

List of abbreviations

CVC	Central Venous Catheters
GCS	Graduated Compression Stockings
FID	Foot Impulse Devices
IPCD	Intermittent Pneumatic Compression Devices
LMWH	Low Molecular Weight Heparin
UFH	Unfractionated Heparin
VKA	Vitamin K Antagonists

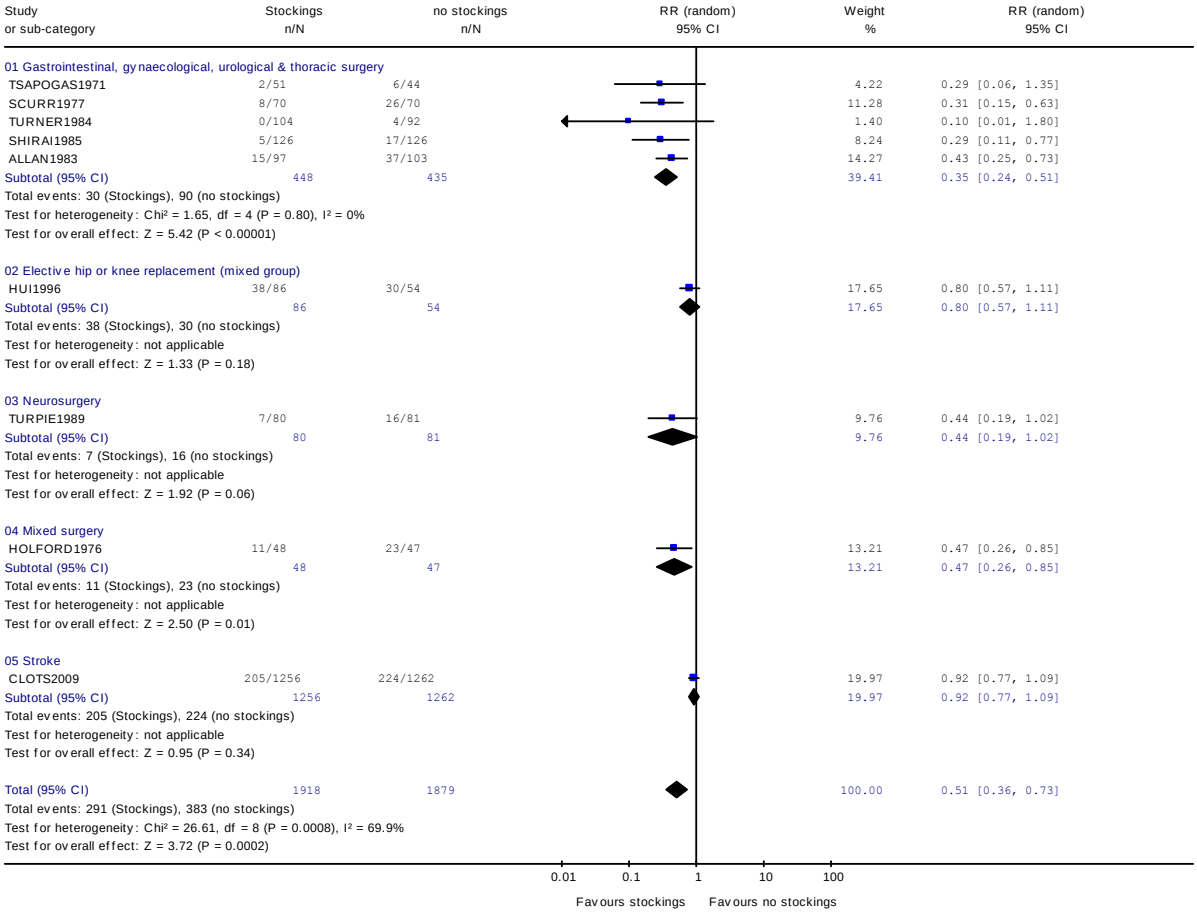
List of Forest Plots

Prophylaxis vs No Prophylaxis

GCS vs No Prophylaxis

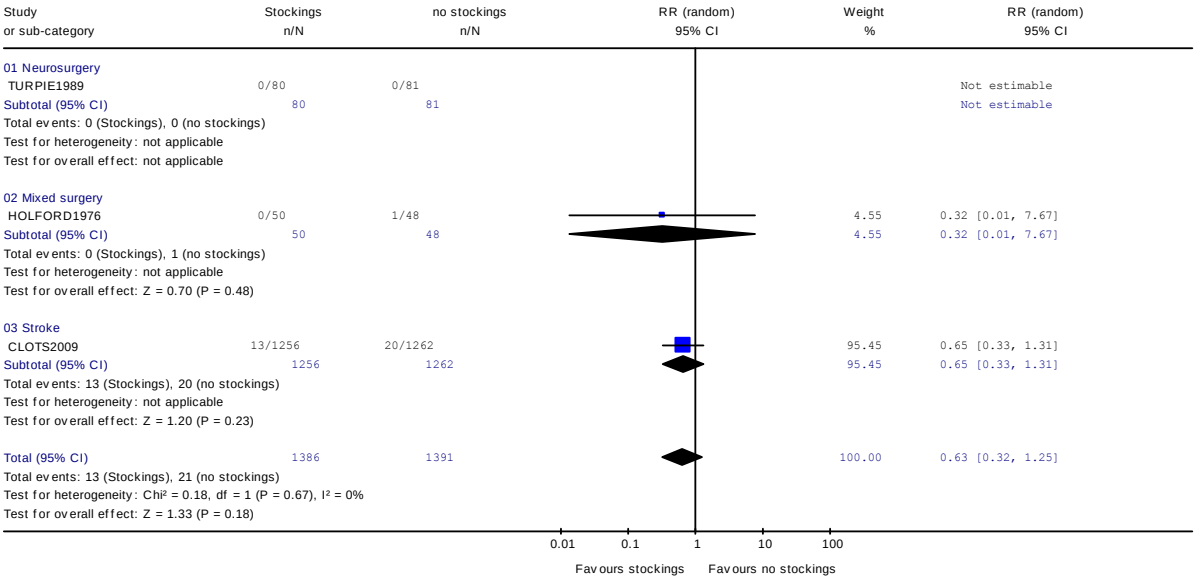
Forest Plot 1. GCS vs No Prophylaxis - DVT

Review: VTE Mechanical - V2
Comparison: 03 Stockings vs no prophylaxis - all
Outcome: 01 DVT - subgrouped by population



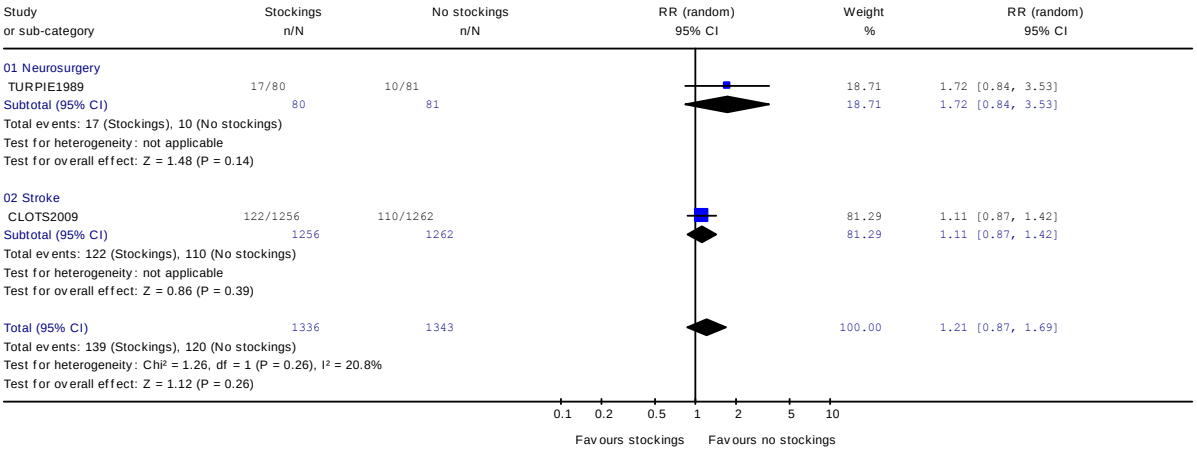
Forest Plot 2. GCS vs No Prophylaxis - Pulmonary Embolism

Review: VTE Mechanical - V2
Comparison: 03 Stockings vs no prophylaxis - all
Outcome: 11 Pulmonary embolism - subgrouped by population



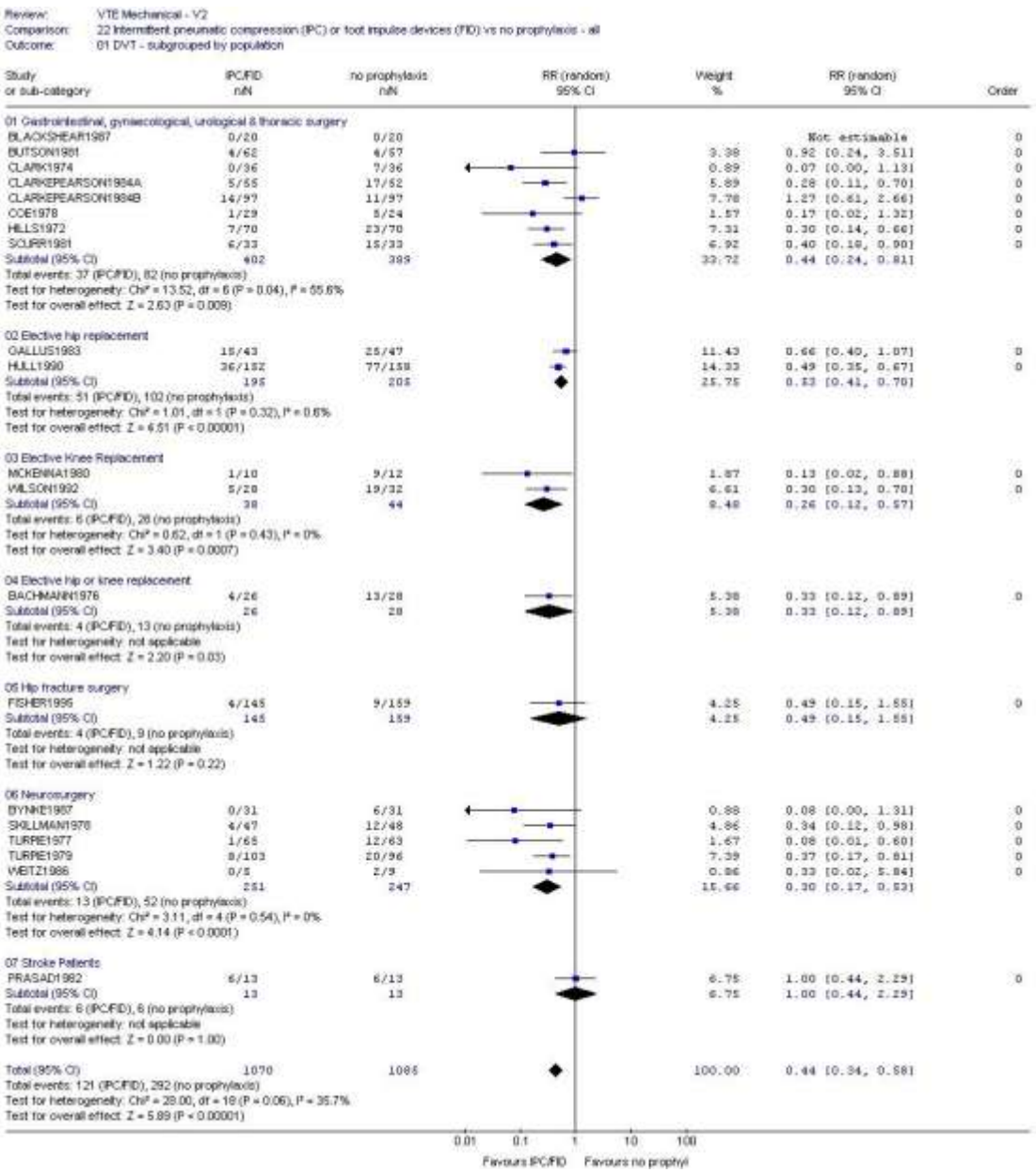
Forest Plot 3. GCS vs No Prophylaxis - Mortality

Review: VTE Mechanical - V2
Comparison: 03 Stockings vs no prophylaxis - all
Outcome: 21 Mortality - subgrouped by population

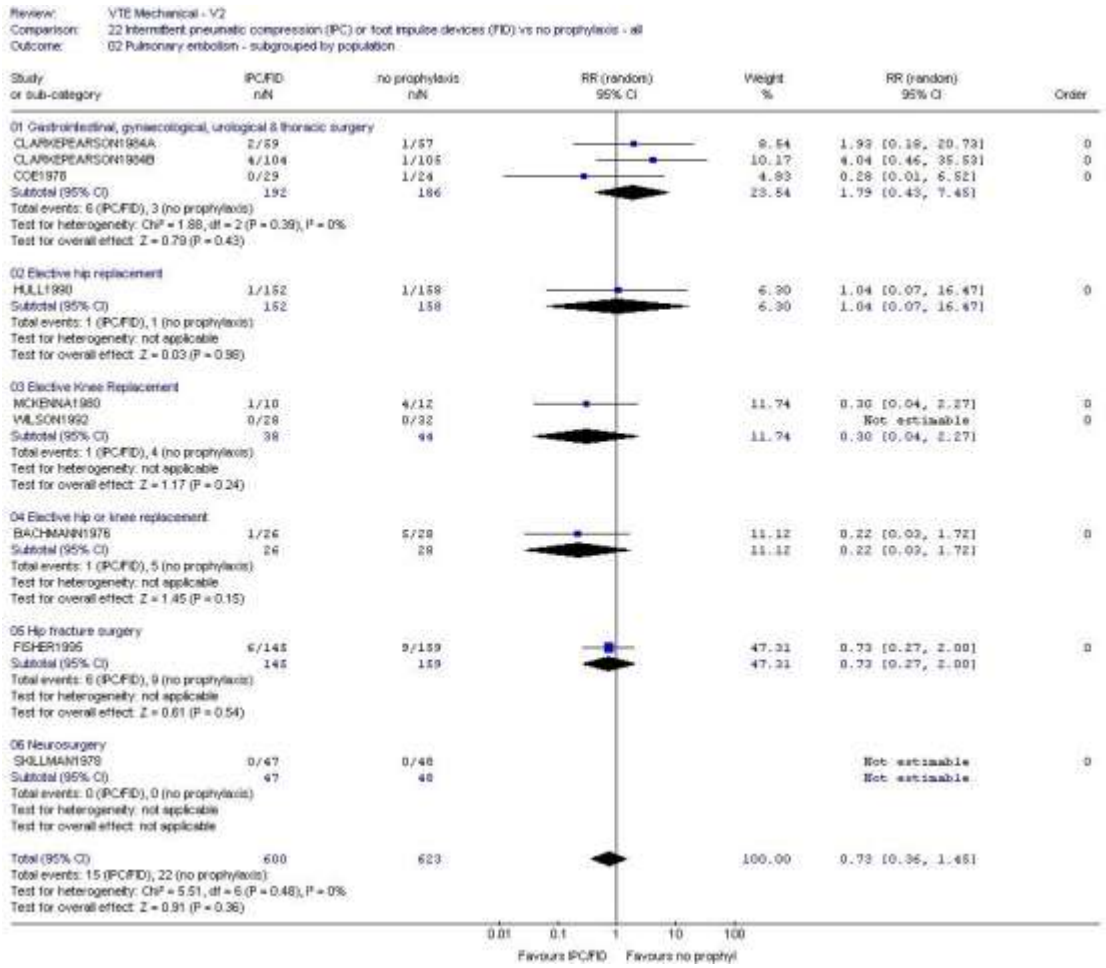


IPCD or FID vs No Prophylaxis

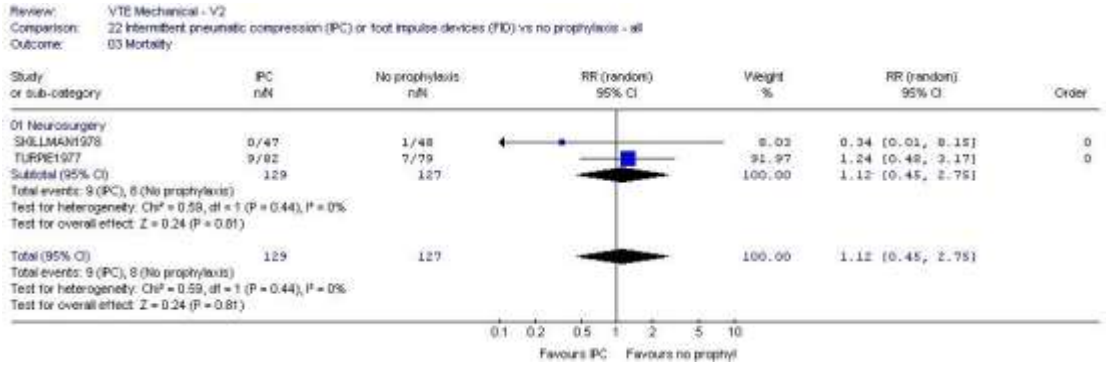
Forest Plot 4. IPCD/FID vs No Prophylaxis - DVT



Forest Plot 5. IPCD/FID vs No Prophylaxis - Pulmonary Embolism

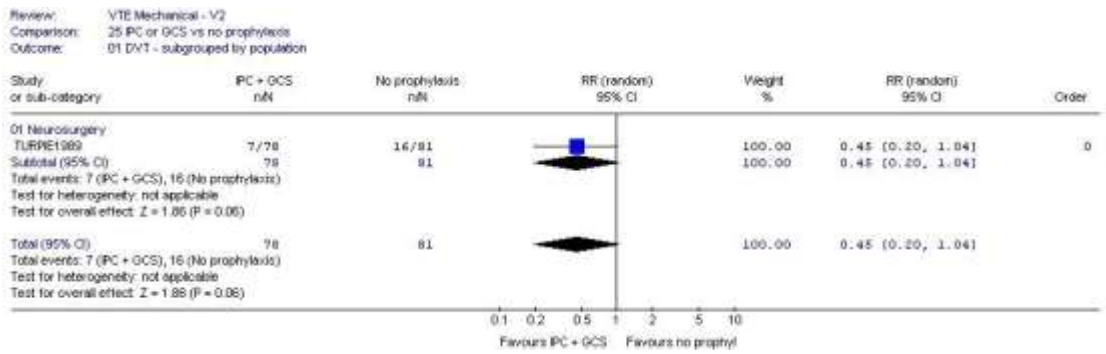


Forest Plot 6. IPCD/FID vs No Prophylaxis - Mortality

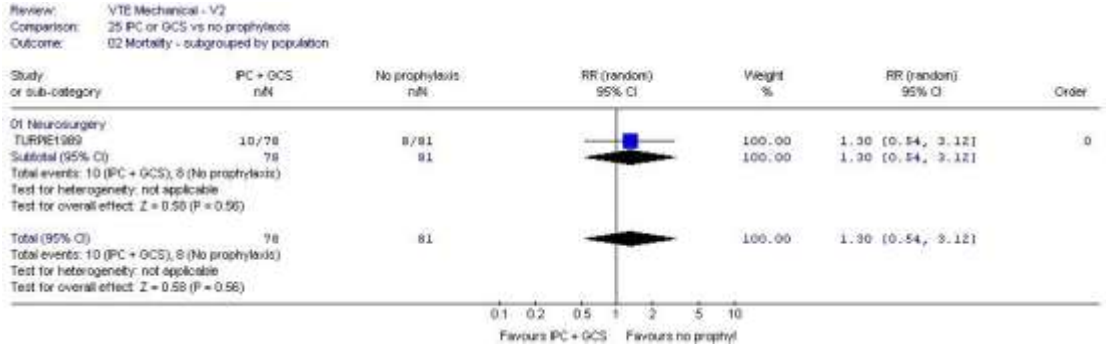


IPCD or GCS (Mixed Studies) vs No Prophylaxis

Forest Plot 7. IPCD or GCS (Mixed Studies) vs No Prophylaxis - DVT

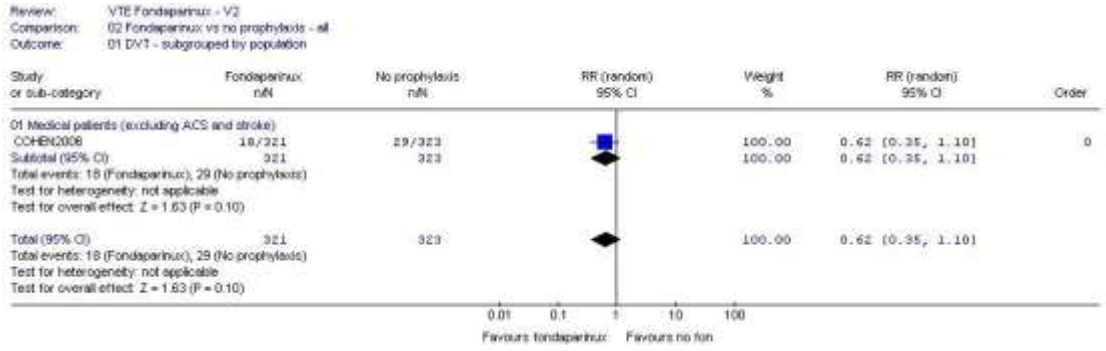


Forest Plot 8. IPCD or GCS (Mixed Studies) vs No Prophylaxis - Mortality

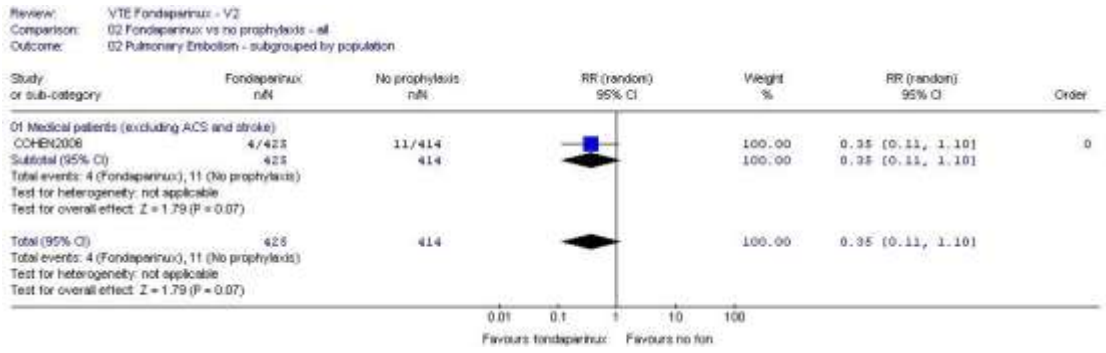


Fondaparinux vs No Prophylaxis

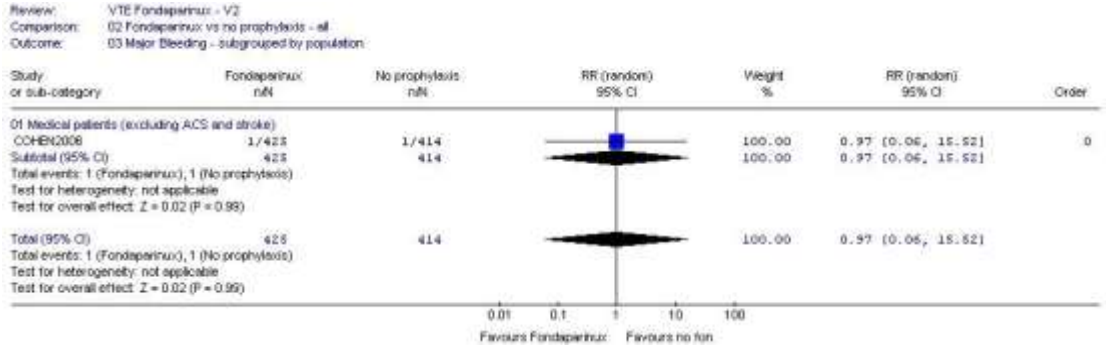
Forest Plot 9. Fondaparinux vs No Prophylaxis – DVT



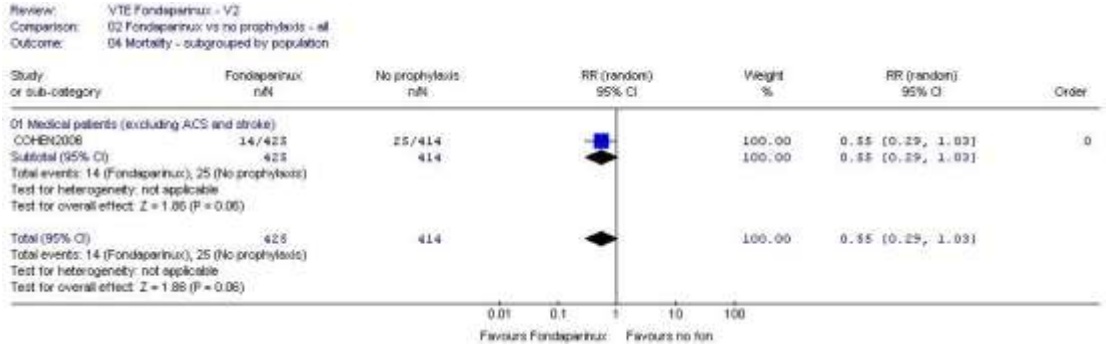
Forest Plot 10. Fondaparinux vs No Prophylaxis – Pulmonary Embolism



Forest Plot 11. Fondaparinux vs No Prophylaxis – Major Bleeding

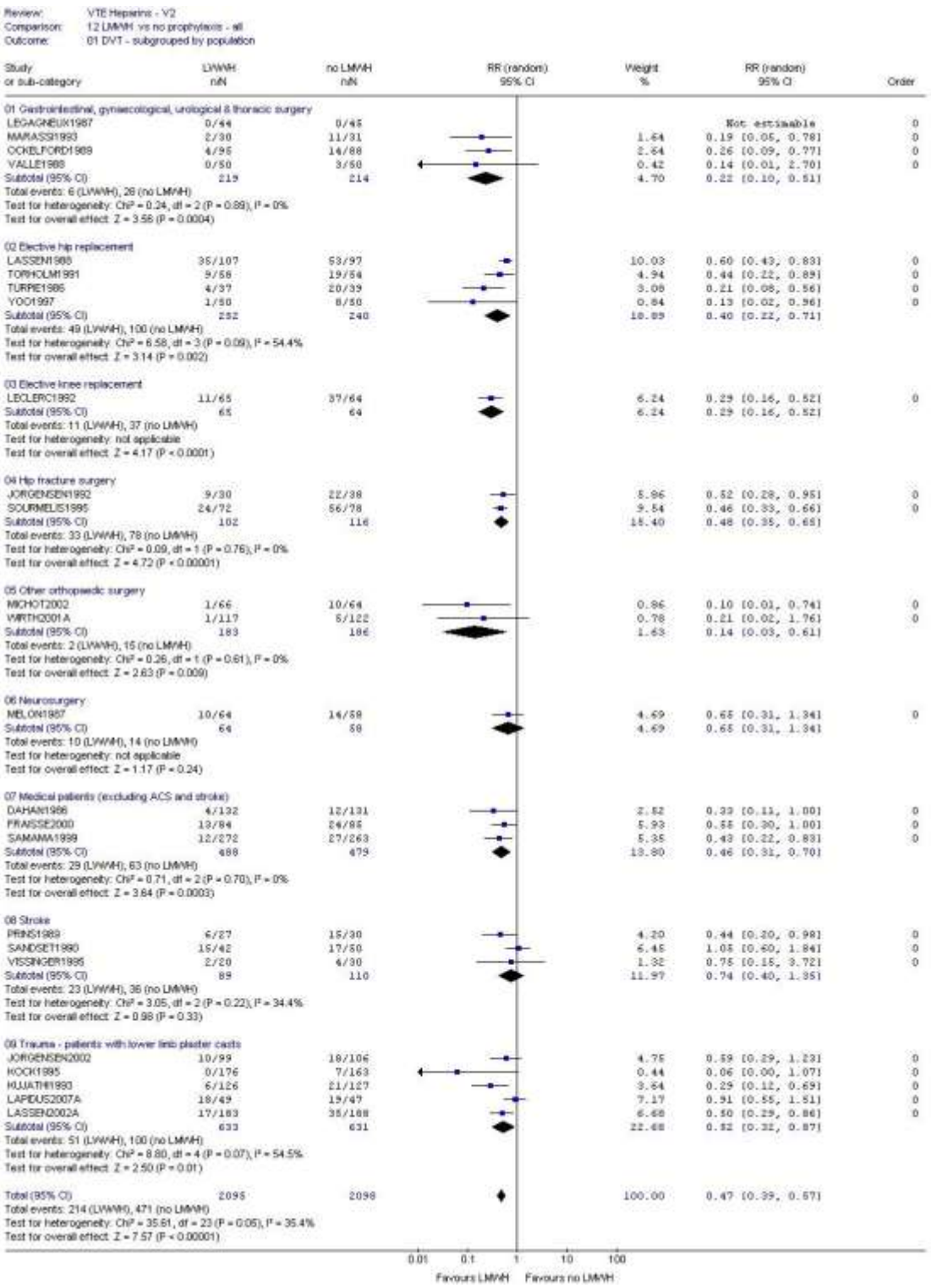


Forest Plot 12. Fondaparinux vs No Prophylaxis – Mortality

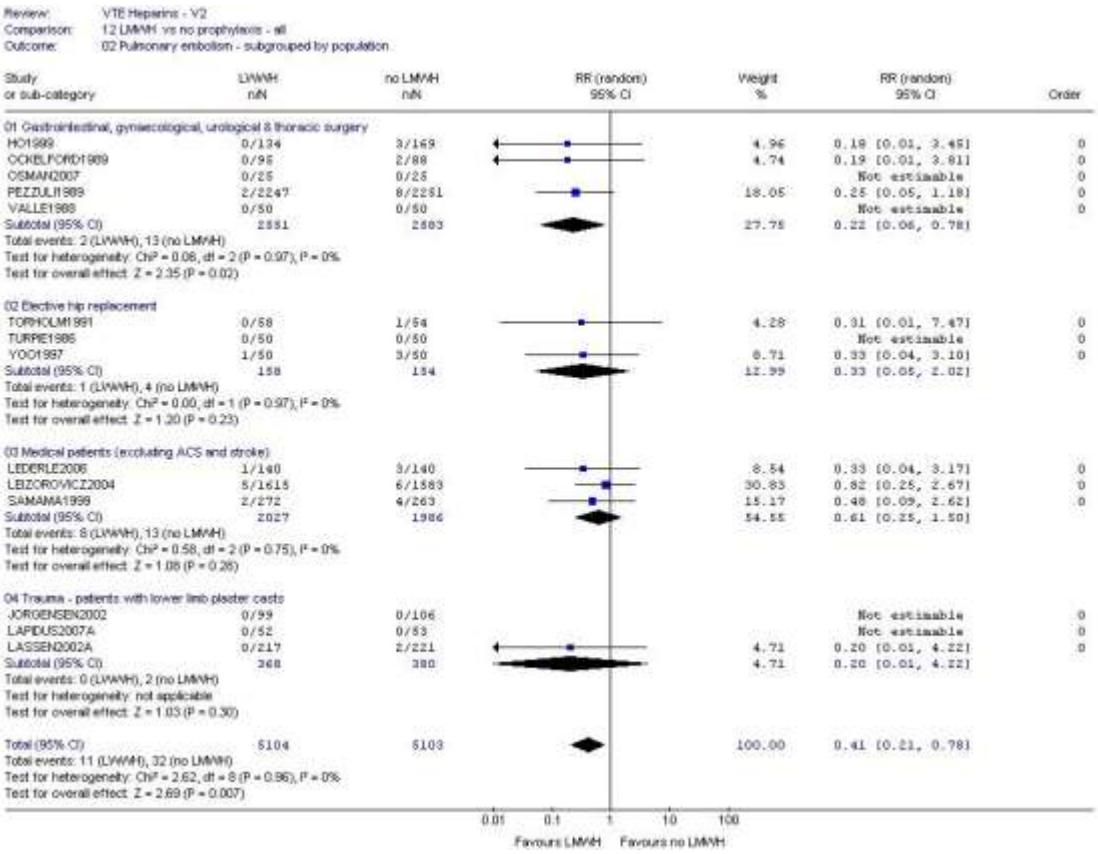


LMWH vs No Prophylaxis

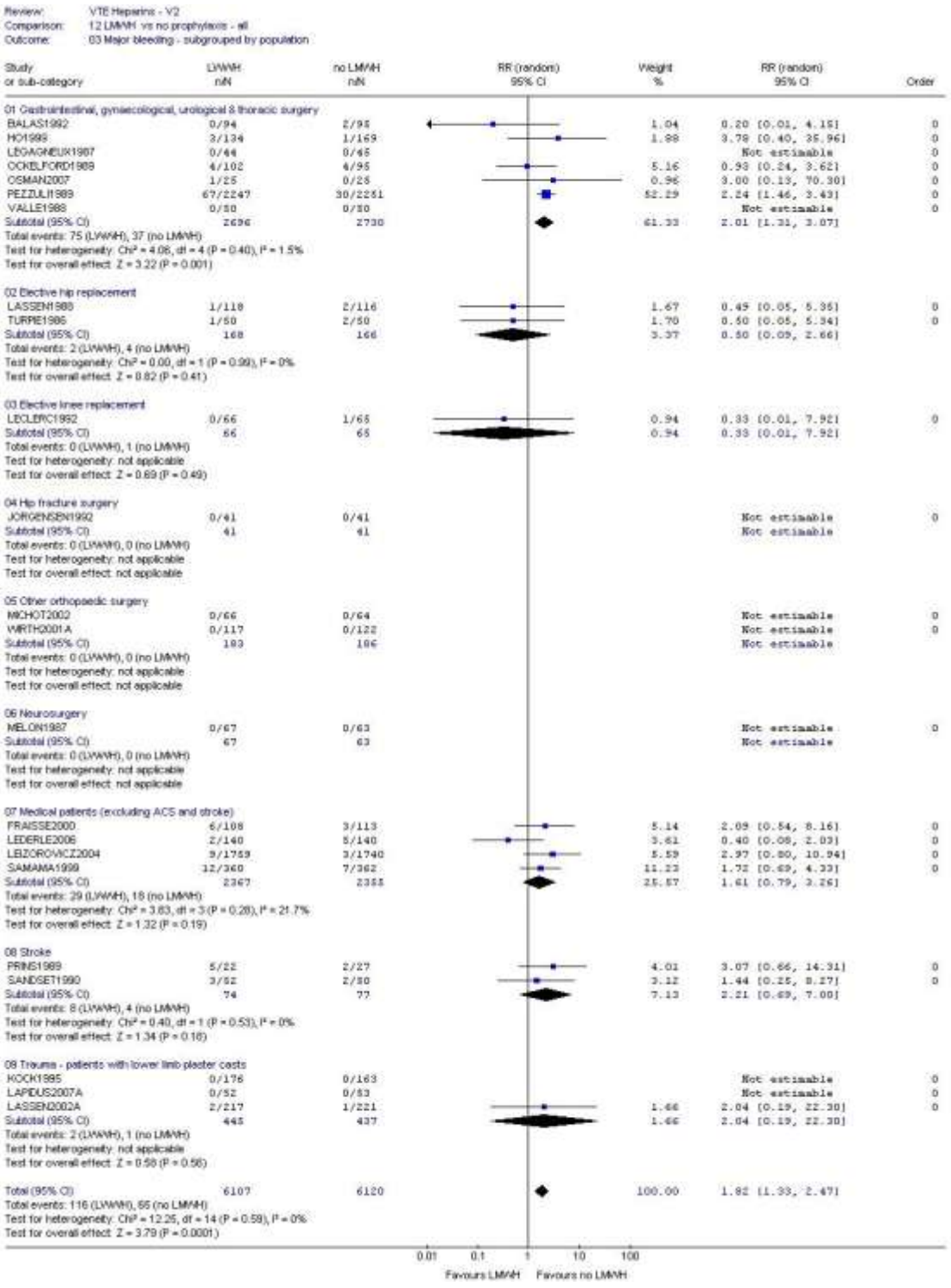
Forest Plot 13. LMWH vs No Prophylaxis – DVT



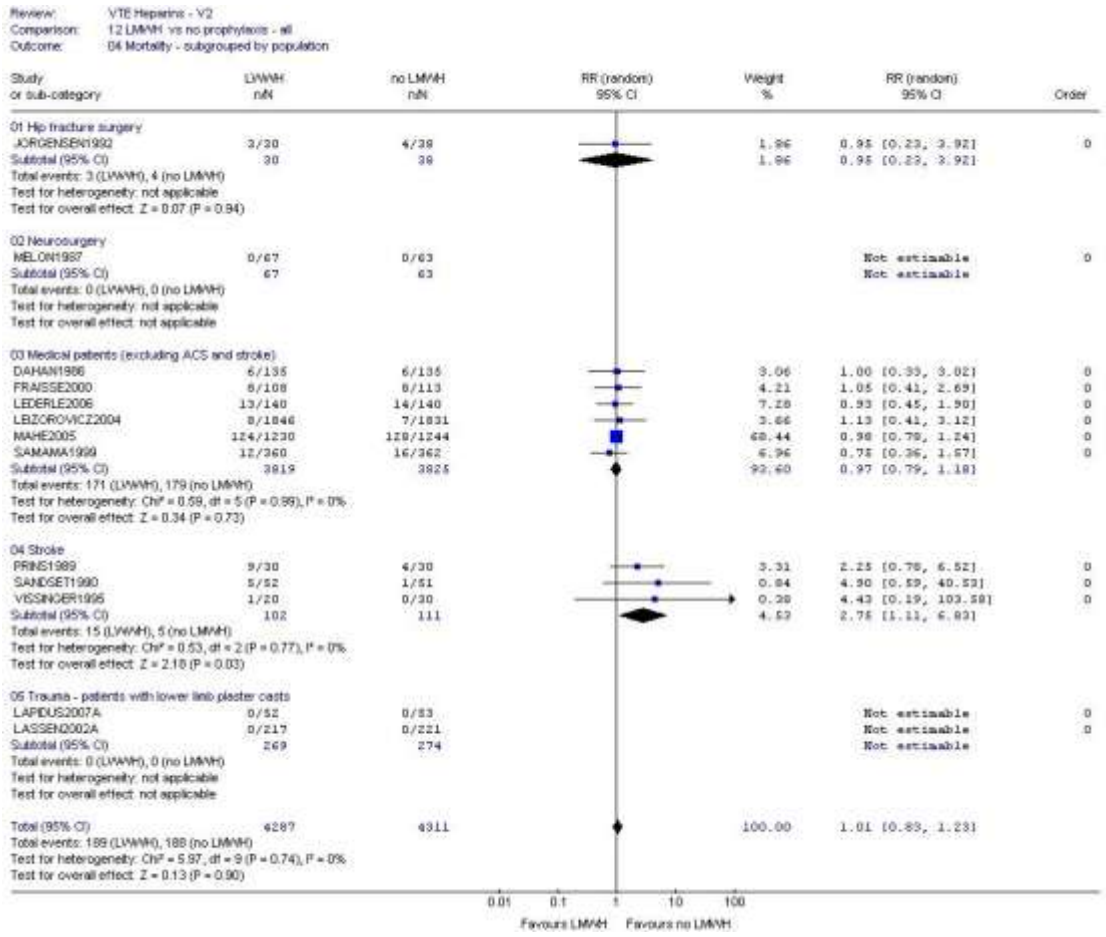
Forest Plot 14. LMWH vs No Prophylaxis – Pulmonary Embolism



Forest Plot 15. LMWH vs No Prophylaxis – Major Bleeding

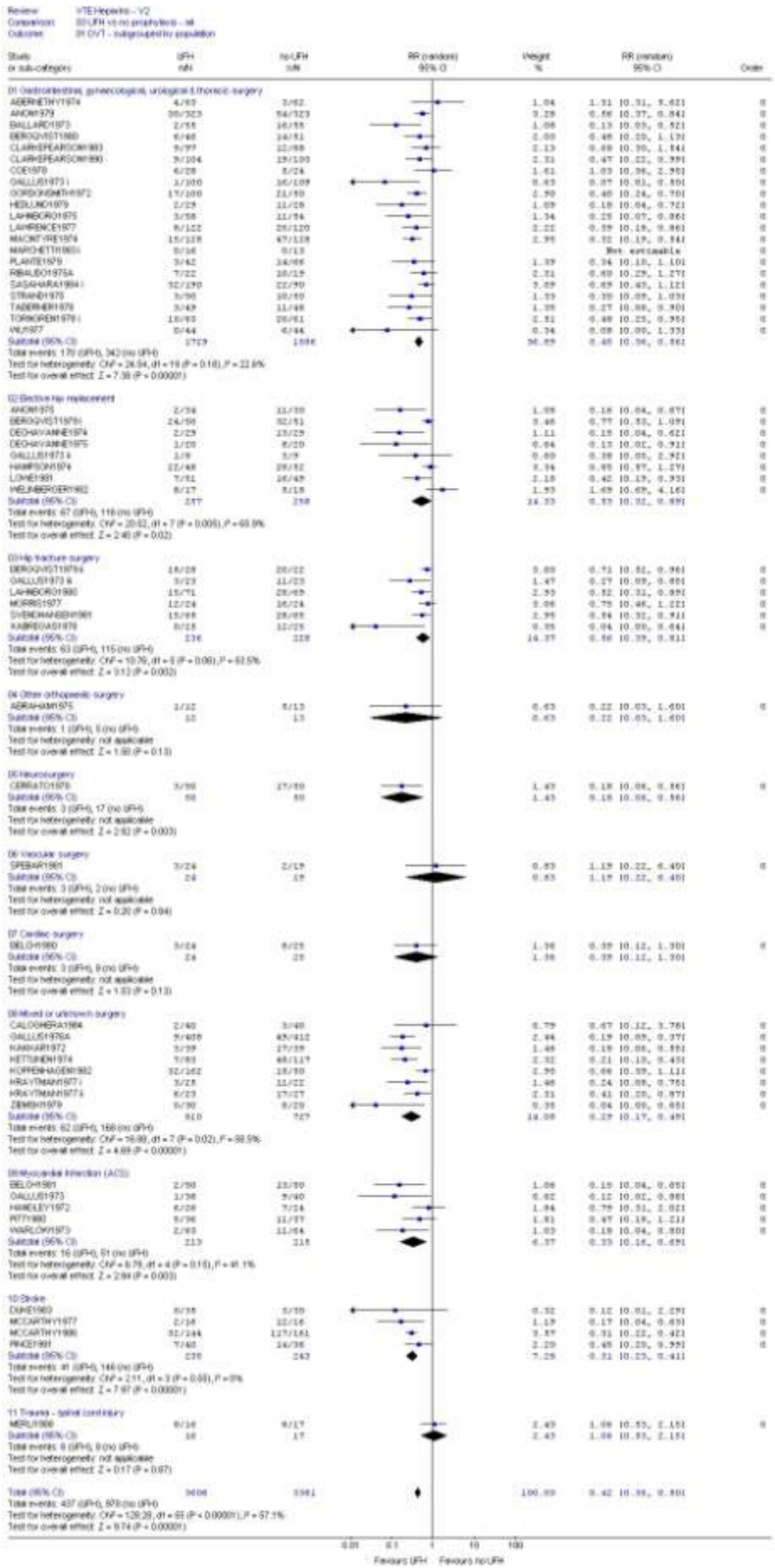


Forest Plot 16. LMWH vs No Prophylaxis – Mortality

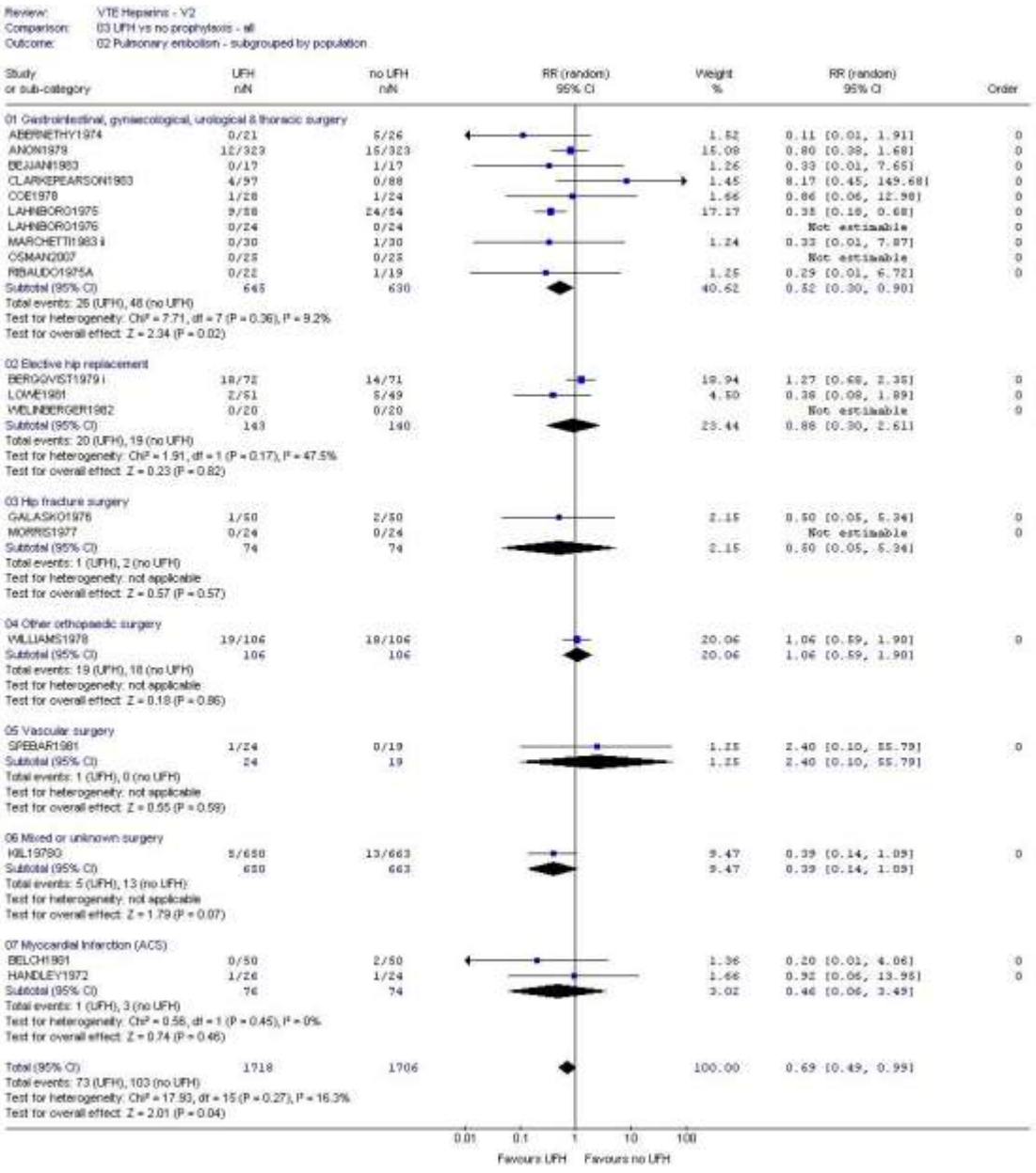


UFH vs No Prophylaxis

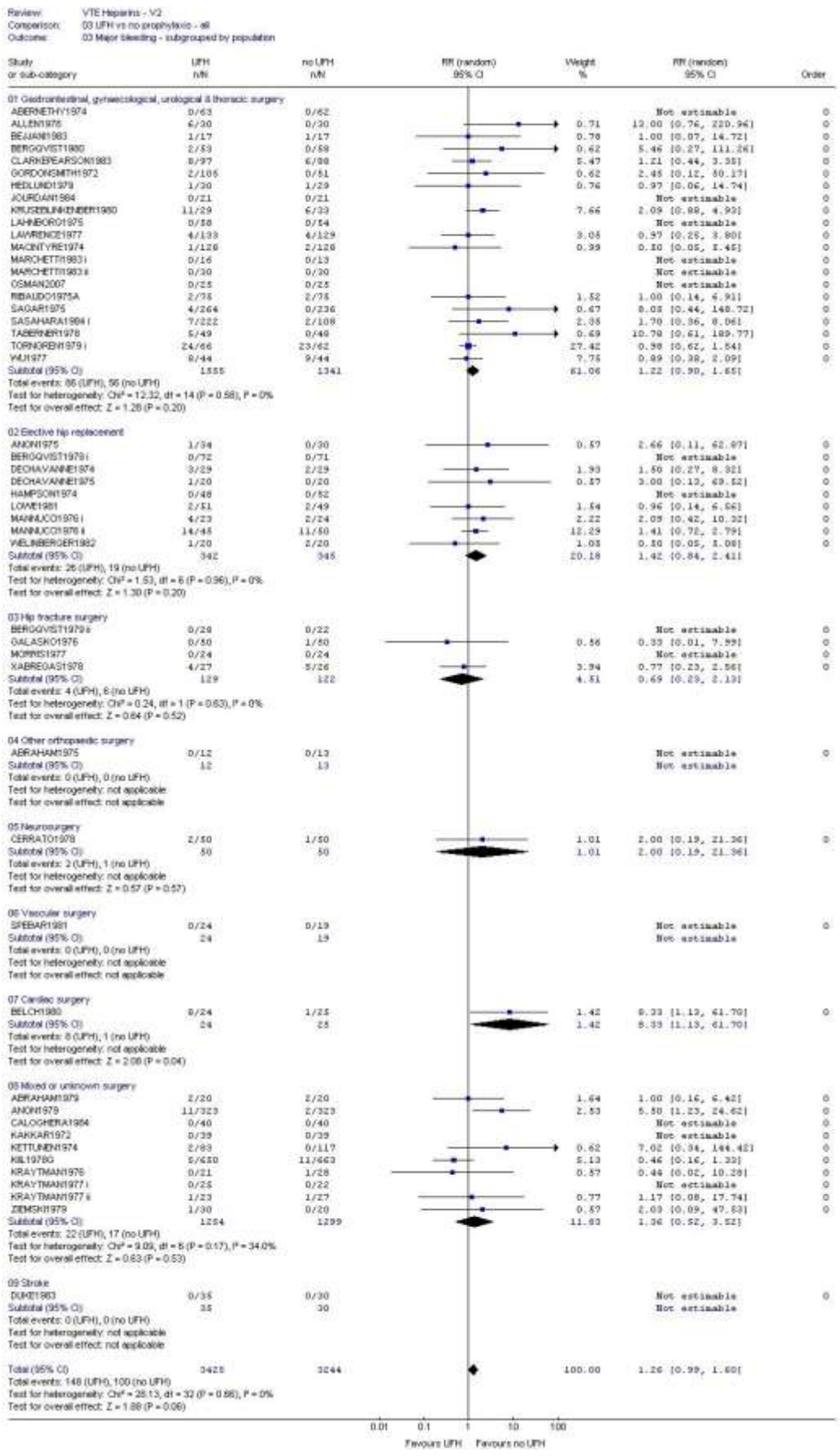
Forest Plot 17. UFH vs No Prophylaxis – DVT


Review: VTE Hepatitis - V2
Comparison: 03 UFH vs no prophylaxis - all
Outcome: 01 DVT - subgrouped by population
Study or sub-category
UFH n/N
no UFH n/N
RR (random) 95% CI
Weight %
RR (random) 95% CI
Order
01 Gastrointestinal, gynaecological, urological & thoracic surgery
ABERNETHY1974 4/60 3/62 1.04 1.31 [0.31, 5.62] 0
ANON1979 35/323 54/323 3.28 0.56 [0.37, 0.84] 0
BALLARD1973 2/55 16/55 1.06 0.13 [0.03, 0.52] 0
BERGQVIST1980 6/46 14/51 2.00 0.48 [0.19, 1.19] 0
CLARKEPEARSON1983 5/97 12/98 2.13 0.49 [0.18, 1.34] 0
CLARKEPEARSON1990 5/104 15/103 2.31 0.47 [0.22, 0.99] 0
COE1978 6/28 5/24 1.61 1.03 [0.36, 2.95] 0
GALLUS1973 1 1/100 16/109 0.63 0.07 [0.01, 0.50] 0
GORDONSMITH1972 17/100 21/50 2.90 0.40 [0.24, 0.70] 0
HEDLUND1979 2/29 11/26 1.09 0.18 [0.04, 0.72] 0
LAHNBORG1975 3/56 11/54 1.34 0.26 [0.07, 0.86] 0
LAWRENCE1977 9/122 25/120 2.22 0.35 [0.18, 0.86] 0
MACINTYRE1974 15/118 47/118 2.99 0.32 [0.19, 0.54] 0
MARCHETTI1985 0/16 0/13 Not estimable 0
PLANTE1979 3/62 14/66 1.39 0.34 [0.10, 1.10] 0
RIBAUD1975A 7/22 20/19 2.51 0.49 [0.25, 1.27] 0
SASAHARA1994 I 52/170 22/90 3.09 0.69 [0.45, 1.12] 0
STRAND1975 3/50 10/50 1.39 0.30 [0.09, 1.03] 0
TADEHER1978 3/49 11/48 1.35 0.27 [0.08, 0.90] 0
TORKGREN1978 I 15/93 25/91 2.51 0.49 [0.25, 0.95] 0
WU1977 0/44 4/44 0.34 0.09 [0.00, 1.73] 0
Subtotal (95% CI) 1729 1686 36.89 0.40 [0.30, 0.56]
Total events: 170 (UFH), 342 (no UFH)
Test for heterogeneity: Chi² = 26.54, df = 16 (P = 0.16), I² = 22.6%
Test for overall effect: Z = 7.38 (P = 0.00001)
02 Elective hip replacement
ANON1975 2/34 11/30 1.09 0.16 [0.04, 0.67] 0
BERGQVIST1978 I 24/50 32/51 3.46 0.77 [0.53, 1.09] 0
DEOHAYANNE1974 2/23 13/23 1.11 0.15 [0.04, 0.62] 0
DEOHAYANNE1975 1/20 8/20 0.64 0.13 [0.02, 0.92] 0
GALLUS1973 4 1/8 3/8 0.69 0.33 [0.05, 2.32] 0
HAMPSON1974 22/48 28/52 3.34 0.85 [0.57, 1.27] 0
LOWE1981 7/51 16/49 2.18 0.42 [0.19, 0.93] 0
WELJNBERGER1982 8/17 5/18 1.53 1.69 [0.65, 4.41] 0
Subtotal (95% CI) 257 258 14.33 0.53 [0.32, 0.89]
Total events: 67 (UFH), 116 (no UFH)
Test for heterogeneity: Chi² = 20.62, df = 7 (P = 0.005), I² = 66.0%
Test for overall effect: Z = 2.40 (P = 0.02)
03 Hip fracture surgery
BERGQVIST1978 II 18/28 20/22 3.89 0.71 [0.52, 0.96] 0
GALLUS1973 5 3/23 11/23 1.47 0.27 [0.09, 0.80] 0
LAHNBORG1980 15/71 28/69 2.93 0.52 [0.31, 0.89] 0
MORRIS1977 12/24 16/24 3.06 0.75 [0.48, 1.22] 0
SVENDHANSEN1981 13/69 28/69 2.99 0.54 [0.32, 0.91] 0
KABREOAS1979 0/18 12/25 0.35 0.04 [0.00, 0.64] 0
Subtotal (95% CI) 230 229 14.37 0.58 [0.39, 0.83]
Total events: 63 (UFH), 115 (no UFH)
Test for heterogeneity: Chi² = 10.76, df = 5 (P = 0.06), I² = 53.5%
Test for overall effect: Z = 3.13 (P = 0.002)
04 Other orthopaedic surgery
ABRAHAM1975 1/22 5/13 0.63 0.22 [0.03, 1.60] 0
Subtotal (95% CI) 22 13 0.63 0.22 [0.03, 1.60]
Total events: 1 (UFH), 5 (no UFH)
Test for heterogeneity: not applicable
Test for overall effect: Z = 1.60 (P = 0.13)
05 Neurosurgery
CERRATO1979 3/50 17/50 1.43 0.18 [0.06, 0.56] 0
Subtotal (95% CI) 50 50 1.43 0.18 [0.06, 0.56]
Total events: 3 (UFH), 17 (no UFH)
Test for heterogeneity: not applicable
Test for overall effect: Z = 2.92 (P = 0.003)
06 Vascular surgery
SPEAR1981 3/24 2/19 0.83 1.19 [0.22, 6.40] 0
Subtotal (95% CI) 24 19 0.83 1.19 [0.22, 6.40]
Total events: 3 (UFH), 2 (no UFH)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.20 (P = 0.84)
07 Cardiac surgery
BELOH1980 3/24 8/25 1.36 0.39 [0.12, 1.30] 0
Subtotal (95% CI) 24 25 1.36 0.39 [0.12, 1.30]
Total events: 3 (UFH), 8 (no UFH)
Test for heterogeneity: not applicable
Test for overall effect: Z = 1.53 (P = 0.13)
08 Mixed or unknown surgery
CALOGHERA1984 2/40 3/40 0.79 0.67 [0.12, 3.76] 0
GALLUS1976A 5/408 45/412 2.44 0.19 [0.05, 0.37] 0
KAHKAR1972 3/39 17/39 1.46 0.18 [0.06, 0.55] 0
KETTUNEN1974 7/83 48/117 2.32 0.21 [0.10, 0.45] 0
KOPPENHAGEN1982 52/162 18/80 2.95 0.69 [0.39, 1.11] 0
KRAYTMAN1977 I 3/28 11/22 1.46 0.24 [0.08, 0.76] 0
KRAYTMAN1977 II 6/23 17/17 2.31 0.41 [0.20, 0.87] 0
ZEMSH1979 0/30 8/29 0.35 0.04 [0.00, 0.65] 0
Subtotal (95% CI) 810 727 14.08 0.29 [0.17, 0.49]
Total events: 82 (UFH), 168 (no UFH)
Test for heterogeneity: Chi² = 16.88, df = 7 (P = 0.02), I² = 58.5%
Test for overall effect: Z = 4.69 (P = 0.00001)
09 Myocardial infarction (ACS)
BELOH1981 2/50 23/50 1.06 0.15 [0.04, 0.65] 0
GALLUS1973 1/38 9/40 0.62 0.12 [0.02, 0.88] 0
HAMDLEY1972 6/28 7/14 1.94 0.79 [0.31, 2.02] 0
PITT1980 5/36 11/37 1.81 0.47 [0.19, 1.21] 0
WARLOW1973 2/63 11/64 1.03 0.18 [0.04, 0.80] 0
Subtotal (95% CI) 215 215 6.37 0.33 [0.16, 0.69]
Total events: 16 (UFH), 61 (no UFH)
Test for heterogeneity: Chi² = 5.79, df = 4 (P = 0.15), I² = 30.9%
Test for overall effect: Z = 2.94 (P = 0.003)
10 Stroke
DUHE1960 0/35 0/30 0.32 0.12 [0.01, 2.29] 0
MCCARTHY1977 2/18 12/16 1.19 0.17 [0.04, 0.65] 0
MCCARTHY1986 52/144 117/161 3.87 0.31 [0.22, 0.42] 0
PRICE1991 7/40 14/36 2.29 0.45 [0.20, 0.99] 0
Subtotal (95% CI) 236 243 7.26 0.31 [0.23, 0.41]
Total events: 61 (UFH), 146 (no UFH)
Test for heterogeneity: Chi² = 2.11, df = 3 (P = 0.55), I² = 0%
Test for overall effect: Z = 7.97 (P = 0.00001)
11 Trauma - spinal contrtuary
MERLI1989 0/16 0/17 2.43 1.09 [0.53, 2.25] 0
Subtotal (95% CI) 16 17 2.43 1.09 [0.53, 2.25]
Total events: 0 (UFH), 0 (no UFH)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.17 (P = 0.87)
Total (95% CI) 3404 3361 100.00 0.42 [0.36, 0.50]
Total events: 437 (UFH), 870 (no UFH)
Test for heterogeneity: Chi² = 128.28, df = 55 (P < 0.00001), I² = 57.1%
Test for overall effect: Z = 9.74 (P = 0.00001)
0.01 0.1 1 10 100
Favours UFH Favours no UFH

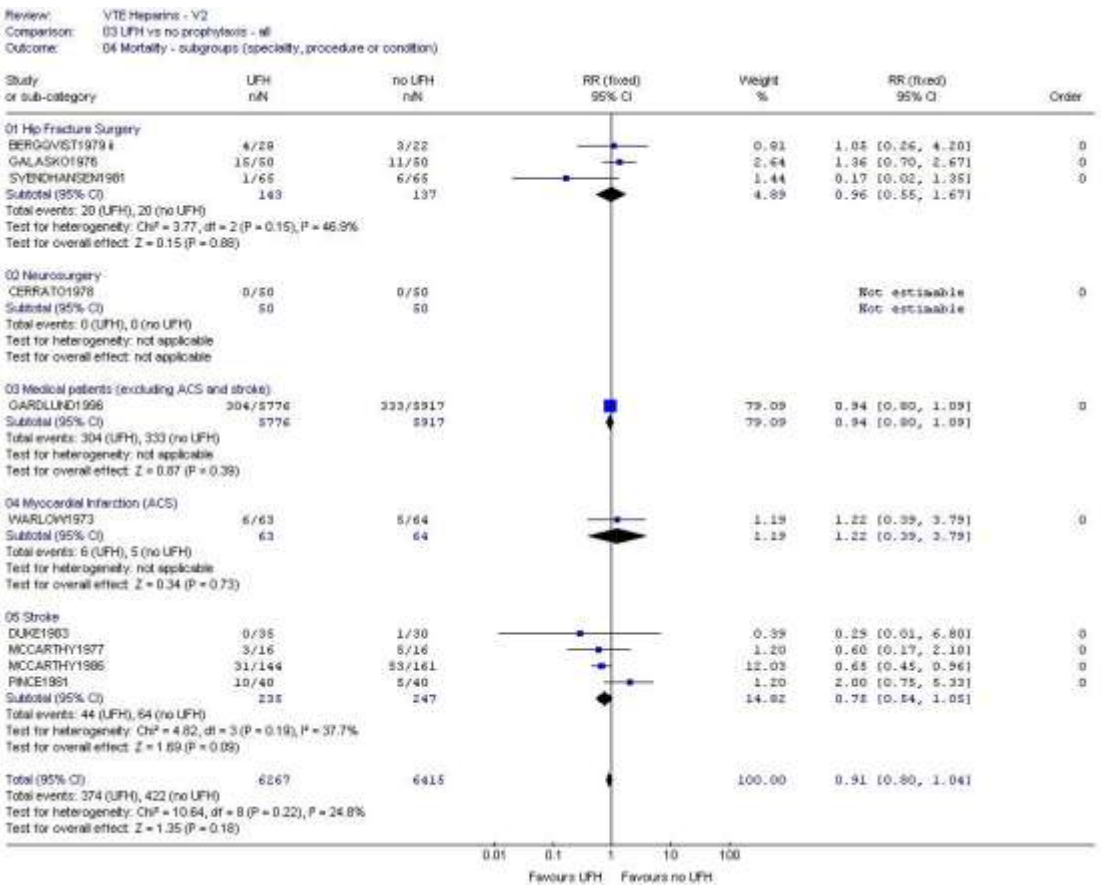
Forest Plot 18. UFH vs No Prophylaxis – Pulmonary Embolism



Forest Plot 19. UFH vs No Prophylaxis – Major Bleeding

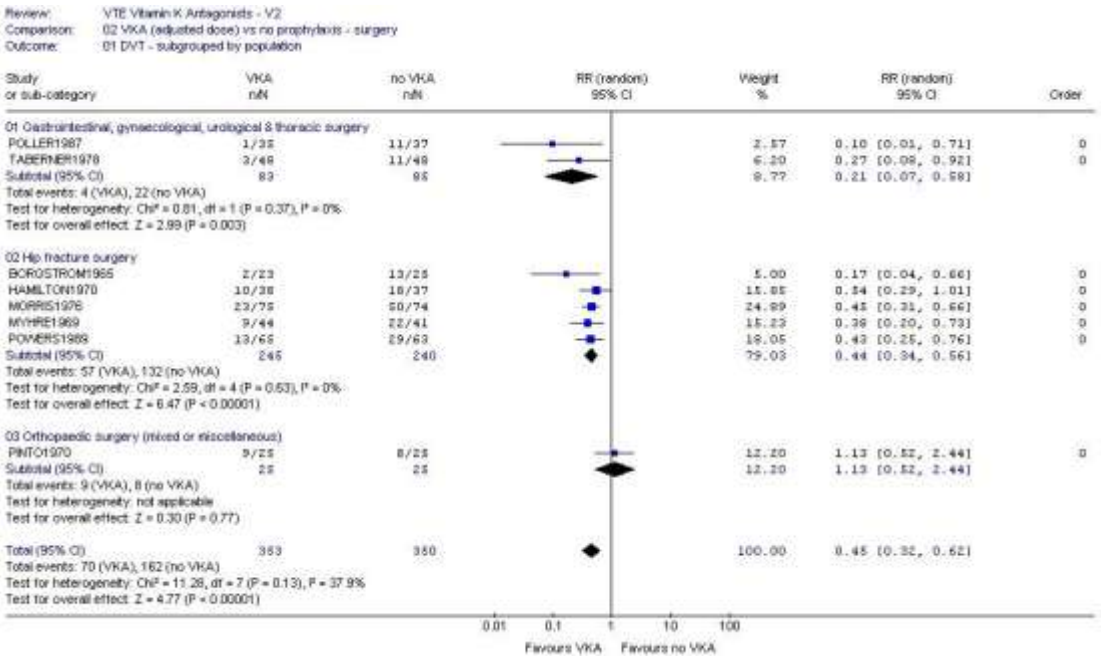


Forest Plot 20. UFH vs No Prophylaxis – Mortality

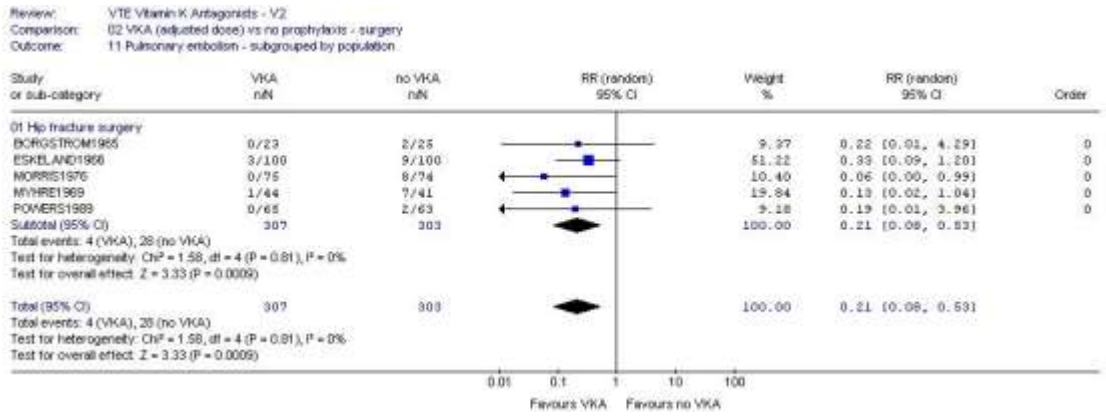


VKA (Adjusted Dose) vs No Prophylaxis – Surgical Patients

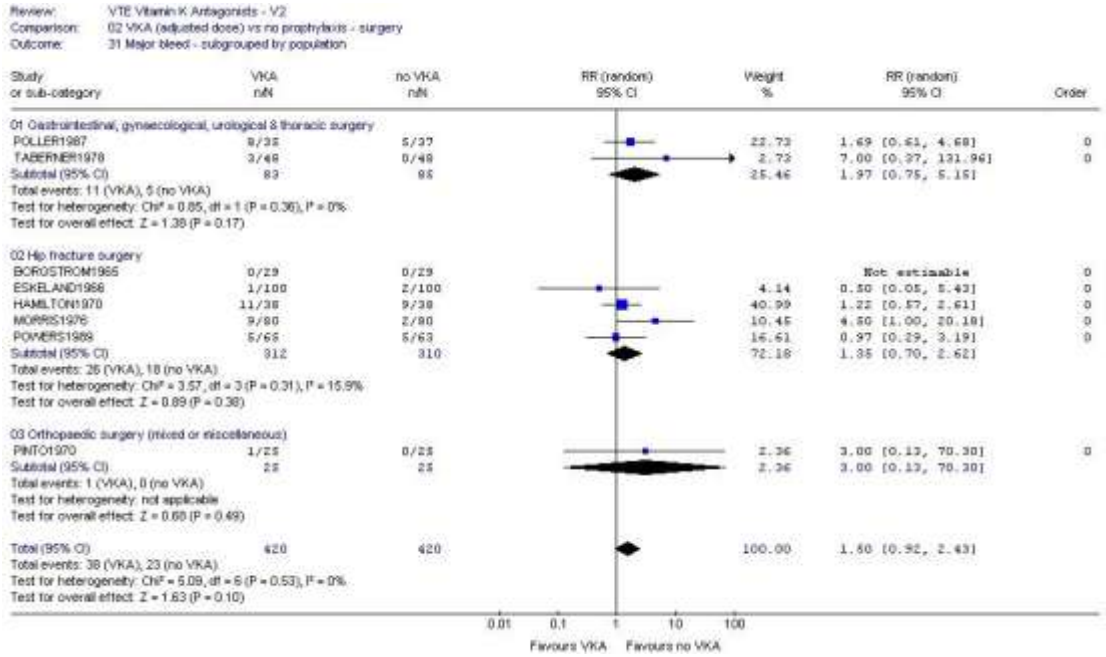
Forest Plot 21. VKA (Adjusted Dose) vs No Prophylaxis – DVT (Surgical Patients)



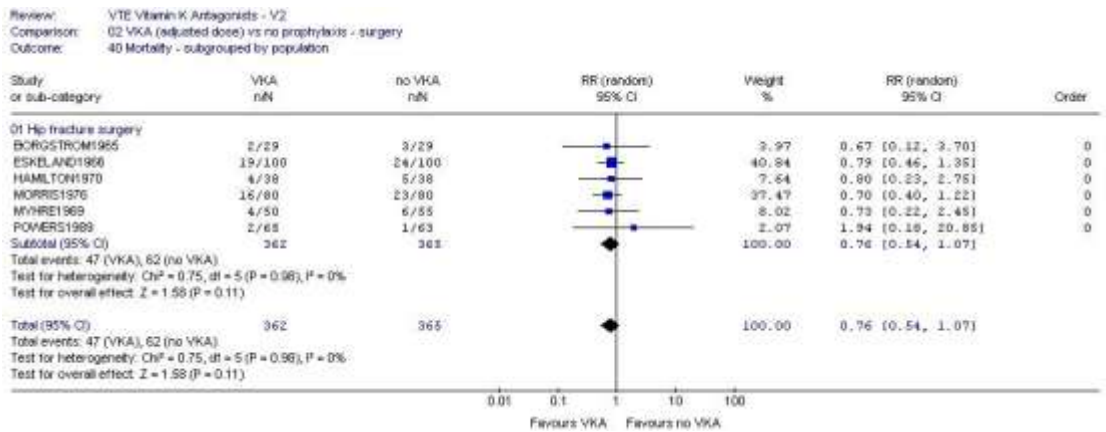
Forest Plot 22. VKA (Adjusted Dose) vs No Prophylaxis – Pulmonary Embolism (Surgical Patients)



Forest Plot 23. VKA (Adjusted Dose) vs No Prophylaxis – Major Bleeding (Surgical Patients)

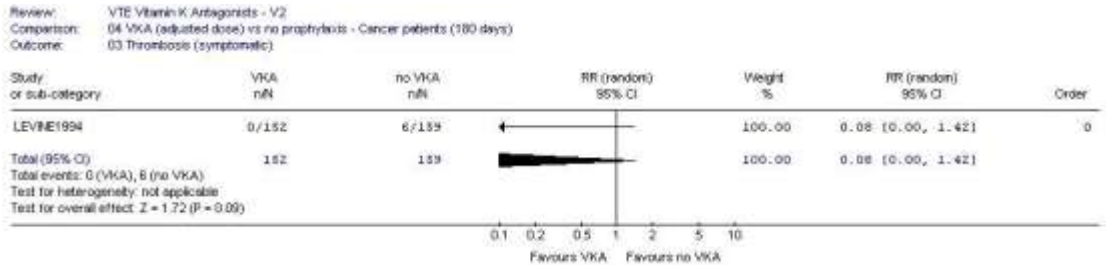


Forest Plot 24. VKA (Adjusted Dose) vs No Prophylaxis – Mortality (Surgical Patients)

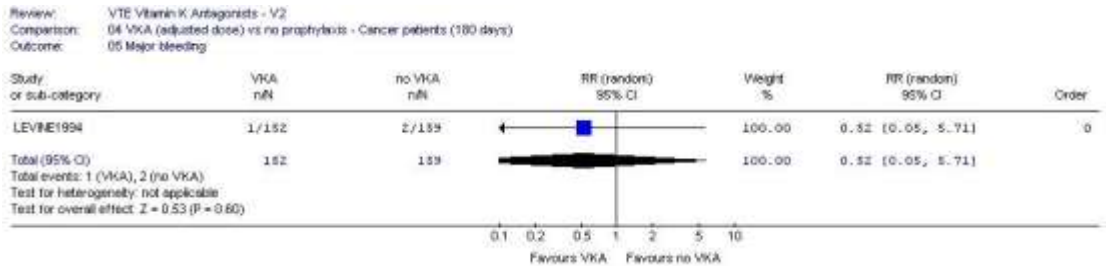


VKA (Adjusted Dose) vs No Prophylaxis – Cancer Patients

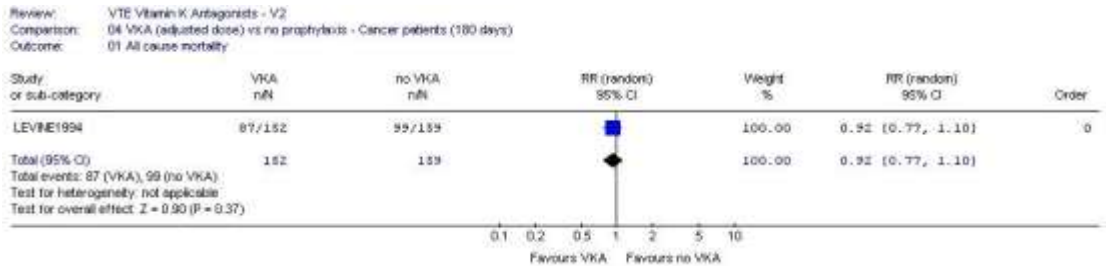
Forest Plot 25. VKA (Adjusted Dose) vs No Prophylaxis – Symptomatic Thrombosis (Cancer Patients)



Forest Plot 26. VKA (Adjusted Dose) vs No Prophylaxis – Major Bleeding (Cancer Patients)

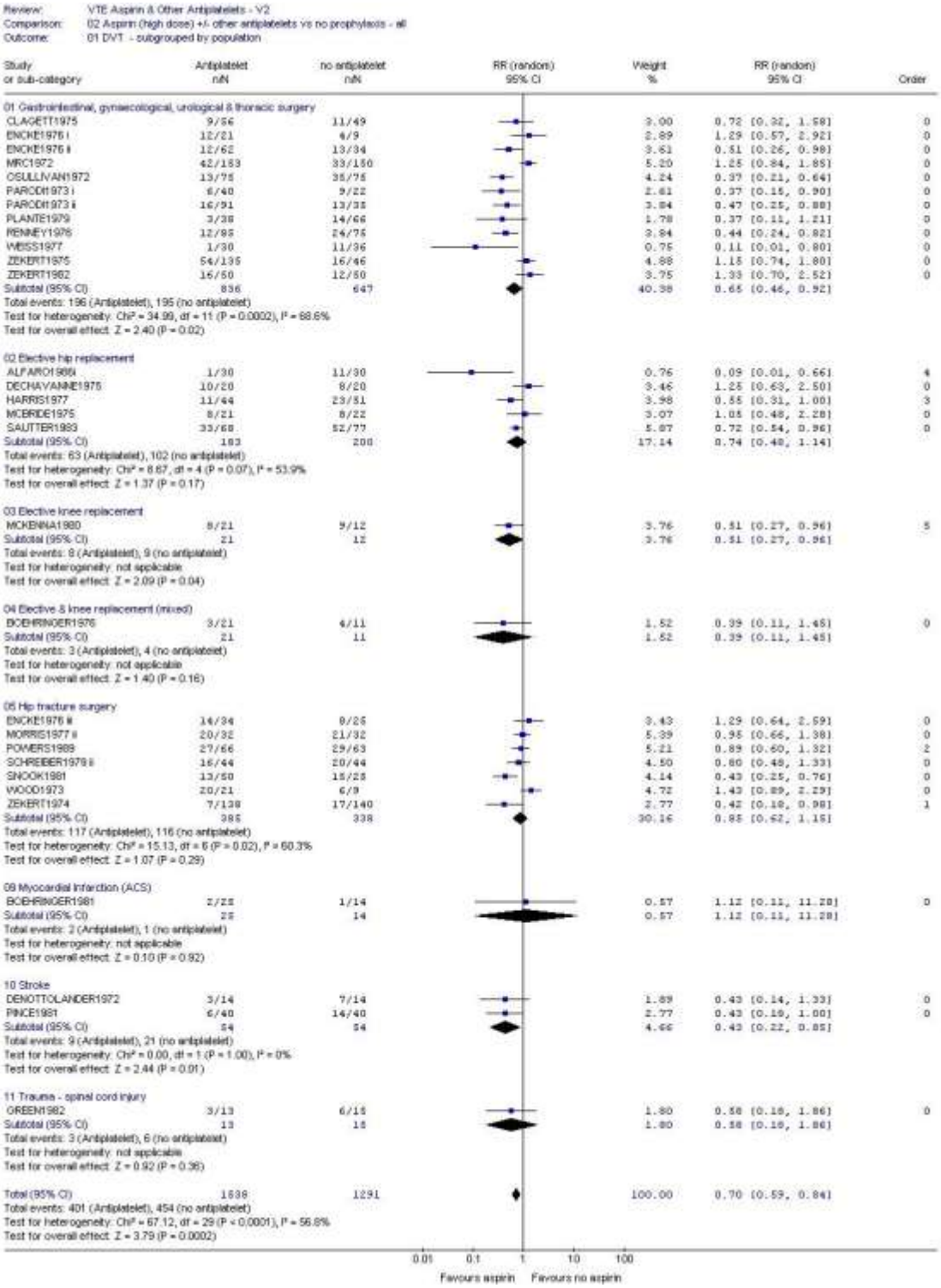


Forest Plot 27. VKA (Adjusted Dose) vs No Prophylaxis – Mortality (Cancer Patients)

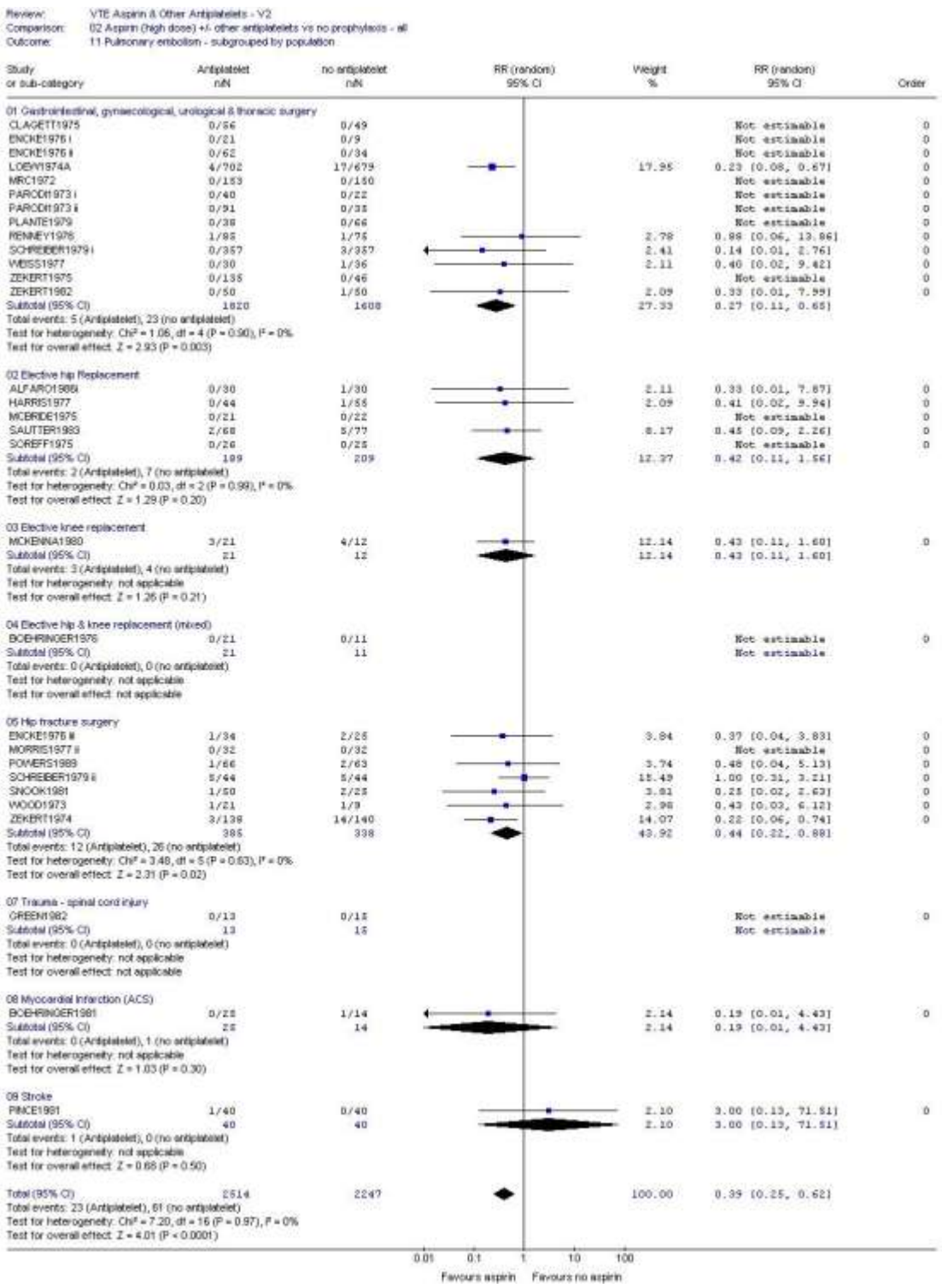


Aspirin +/- Antiplatelet Therapy vs No Prophylaxis

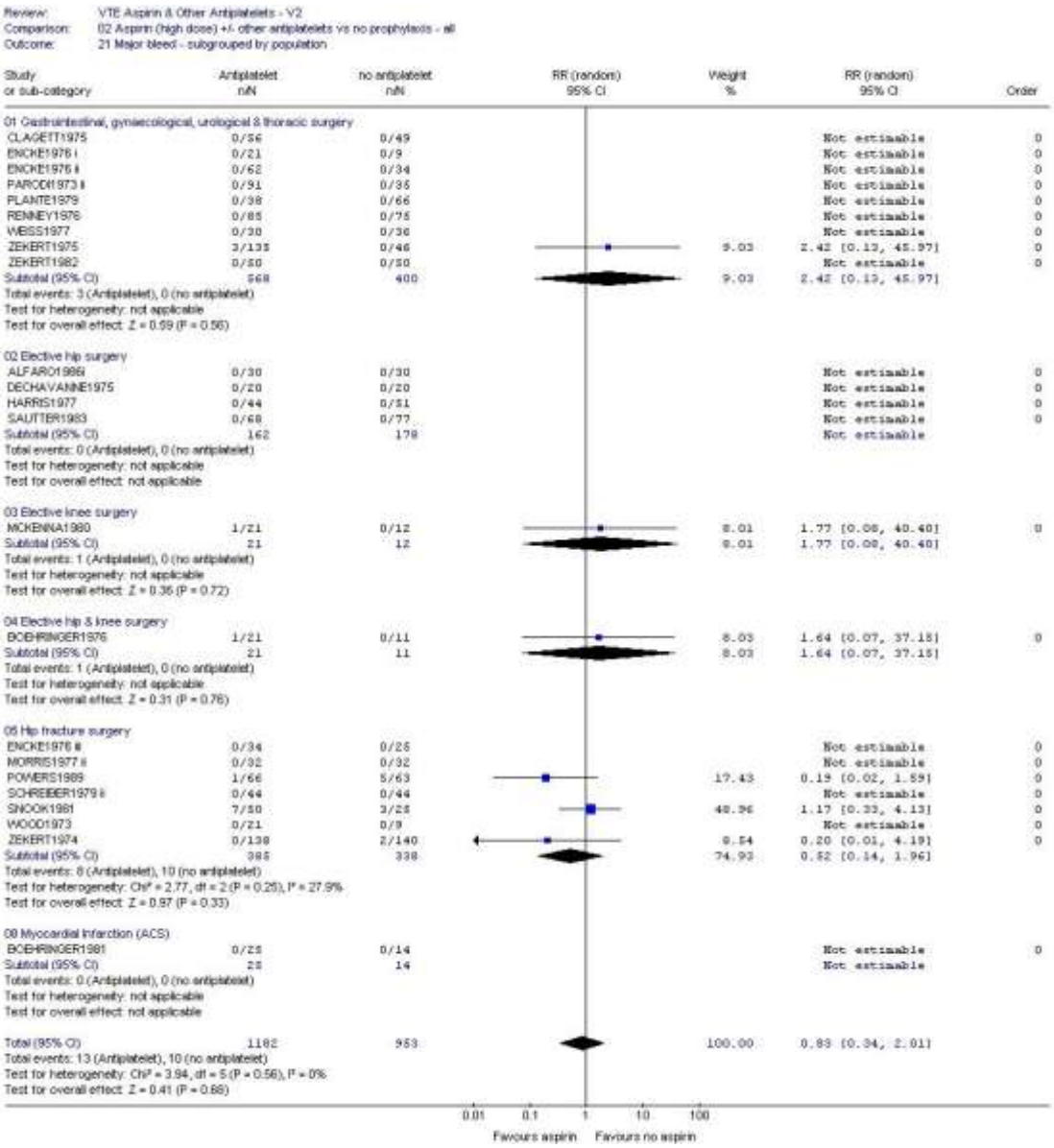
Forest Plot 28. Aspirin (High Dose) +/- Antiplatelet vs No Prophylaxis – DVT



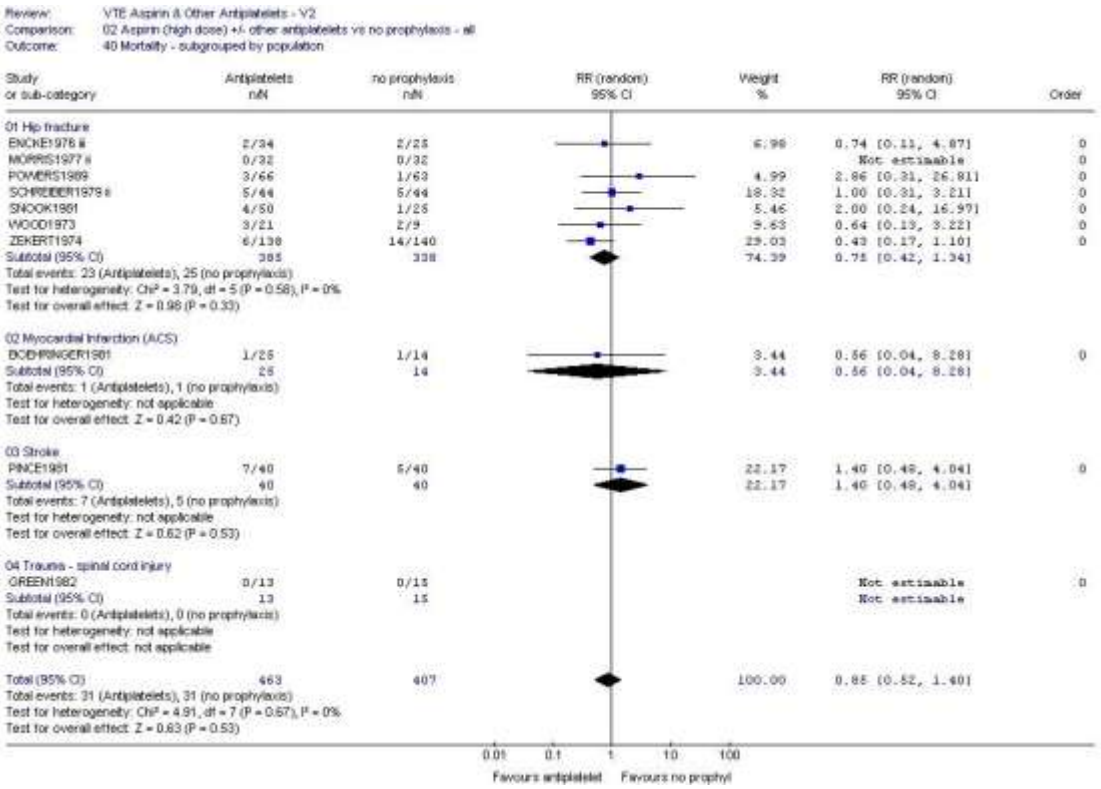
Forest Plot 29. Aspirin (High Dose) +/- Antiplatelet vs No Prophylaxis – Pulmonary Embolism



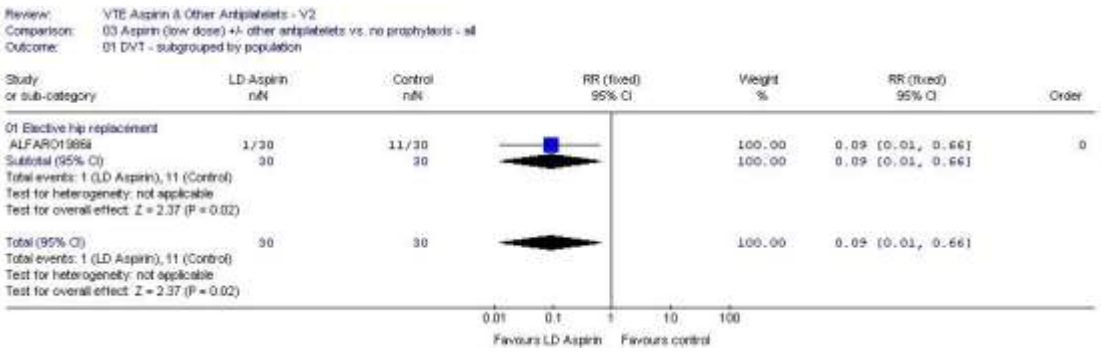
Forest Plot 30. Aspirin (High Dose) +/- Antiplatelet vs No Prophylaxis – Major Bleeding



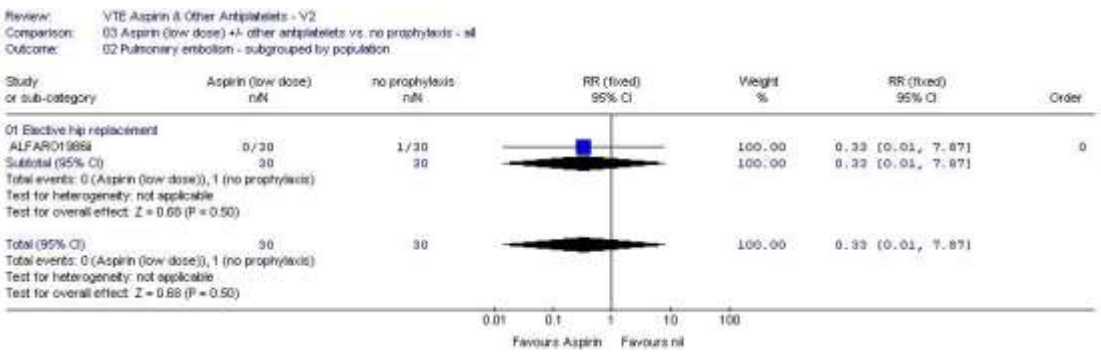
Forest Plot 31. Aspirin (High Dose) +/- Antiplatelet vs No Prophylaxis – Mortality



Forest Plot 32. Aspirin (Low Dose) +/- Antiplatelet vs No Prophylaxis – DVT

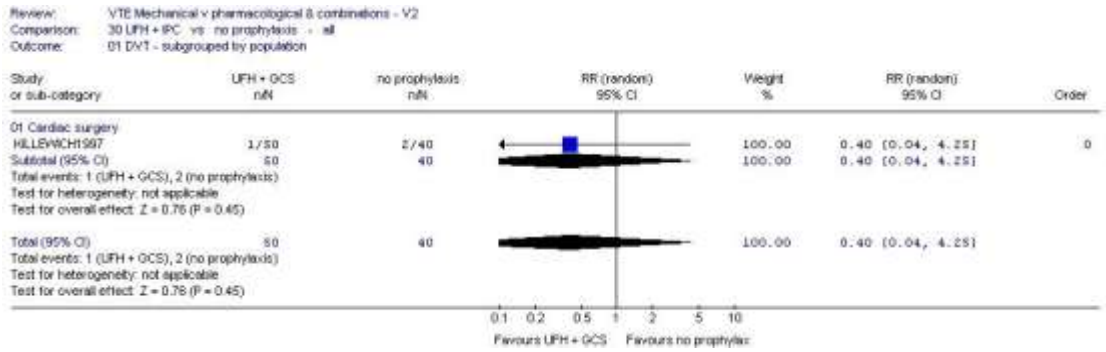


Forest Plot 33. Aspirin (Low Dose) +/- Antiplatelet vs No Prophylaxis – Pulmonary Embolism



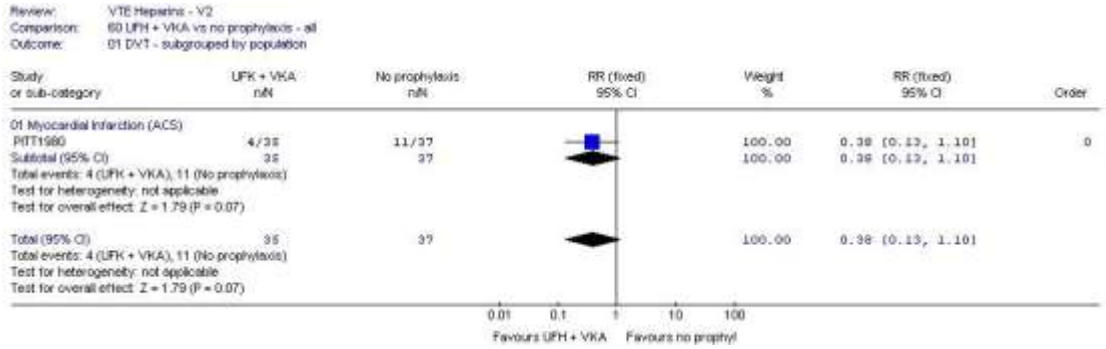
UFH + IPCD vs No Prophylaxis

Forest Plot 34. UFH + IPCD vs No Prophylaxis – DVT



VKA (Adjusted Dose) + UFH vs No Prophylaxis

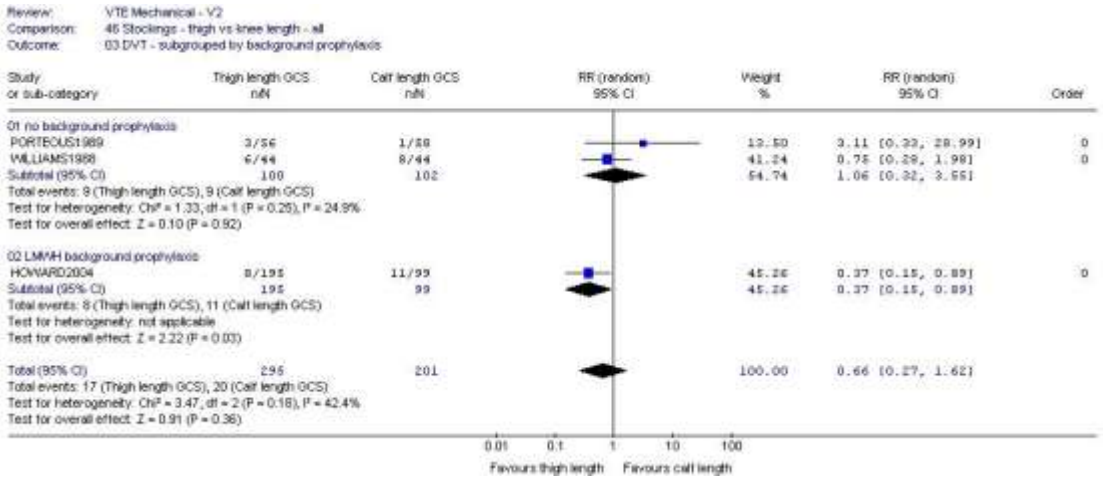
Forest Plot 35. VKA (Adjusted Dose) + UFH vs No Prophylaxis – DVT



Single Prophylaxis vs Single Prophylaxis

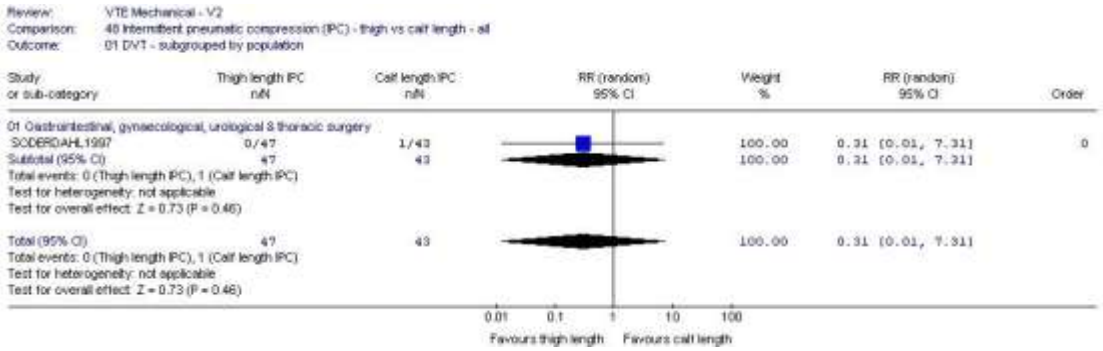
GCS – Thigh vs Knee Length

Forest Plot 36. GCS: Thigh vs Knee Length - DVT

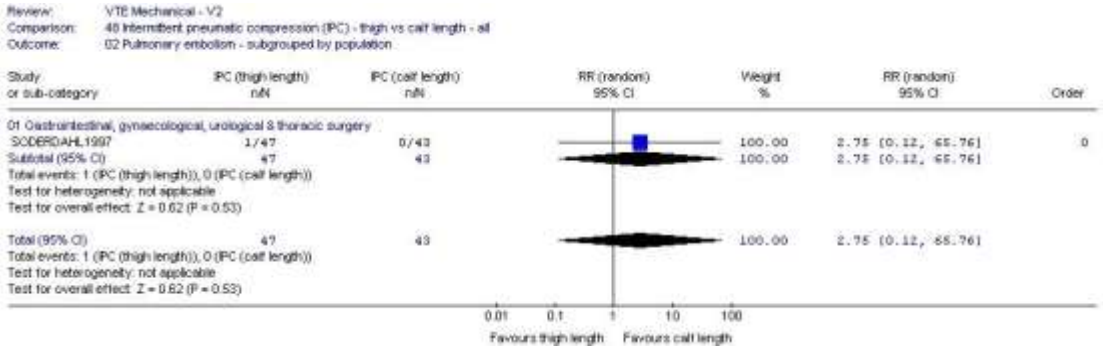


IPCD – Thigh vs Calf Length

Forest Plot 37. IPCD – Thigh vs Calf Length - DVT

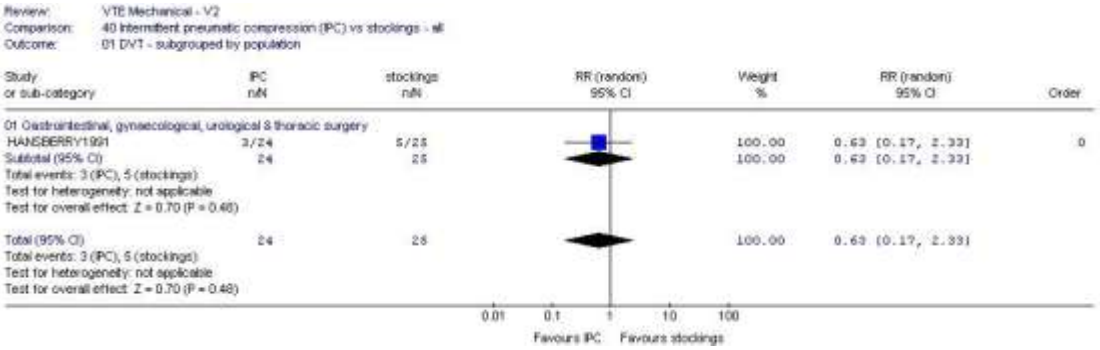


Forest Plot 38. IPCD – Thigh vs Calf Length – Pulmonary Embolism

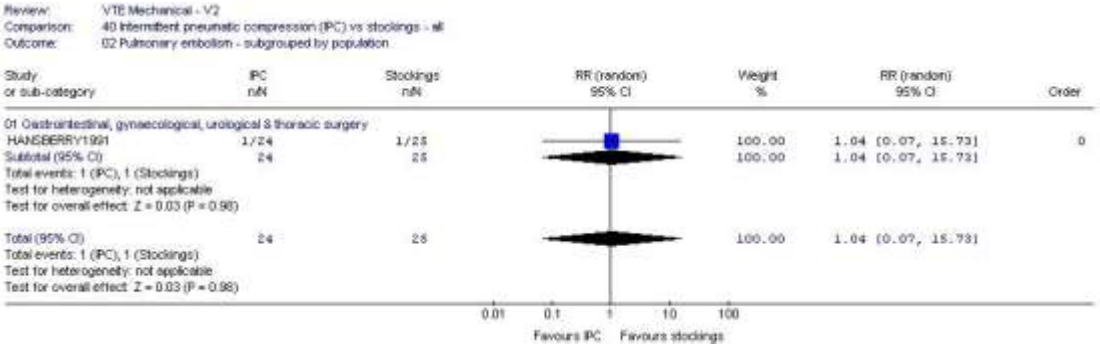


IPCD vs GCS

Forest Plot 39. IPCD vs GCS - DVT

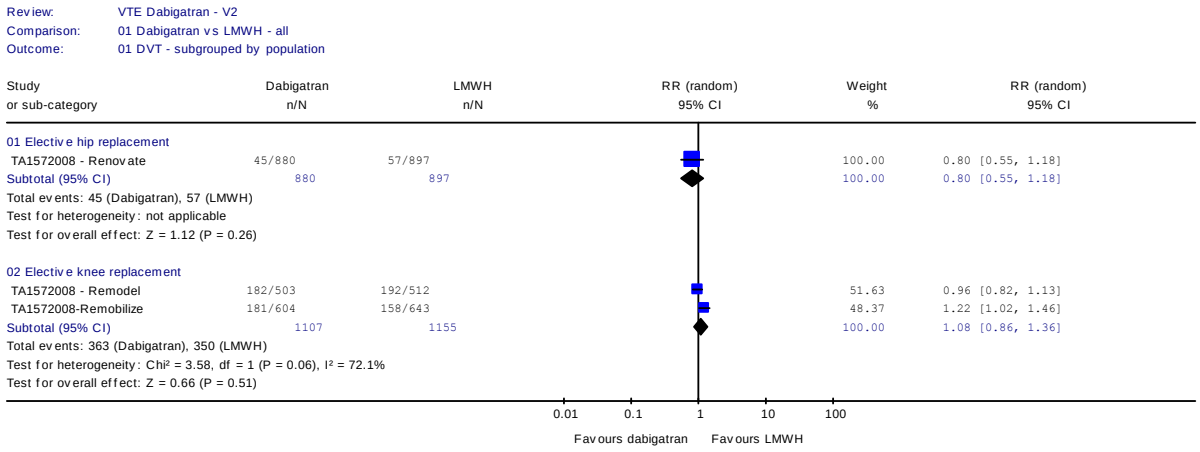


Forest Plot 40. IPCD vs GCS - Pulmonary Embolism

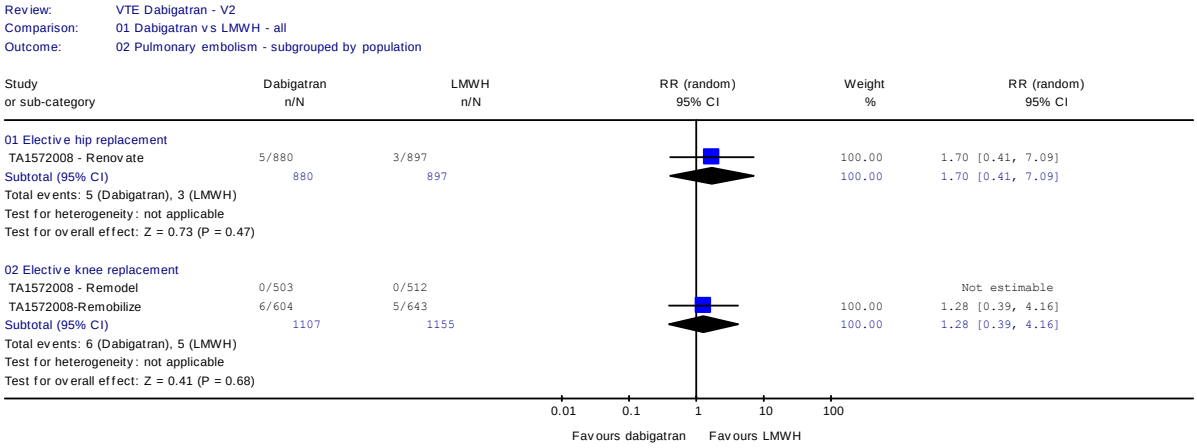


Dabigatran vs LMWH

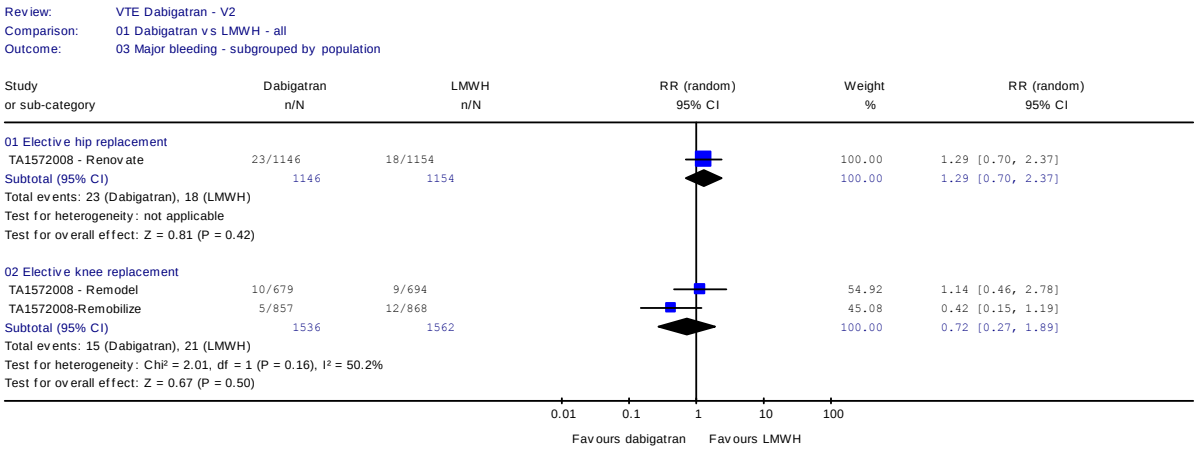
Forest Plot 41. Dabigatran vs LMWH – DVT



Forest Plot 42. Dabigatran vs LMWH – Pulmonary Embolism

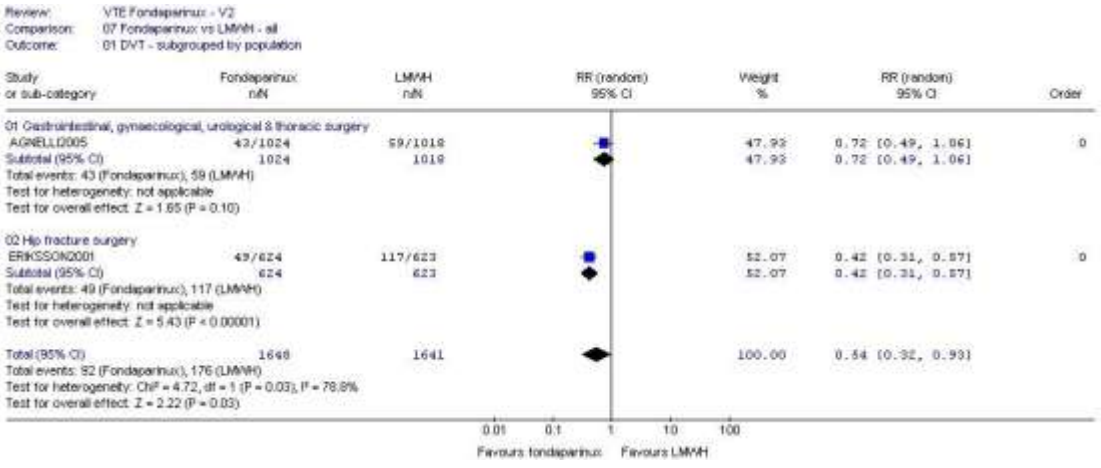


Forest Plot 43. Dabigatran vs LMWH – Major Bleeding

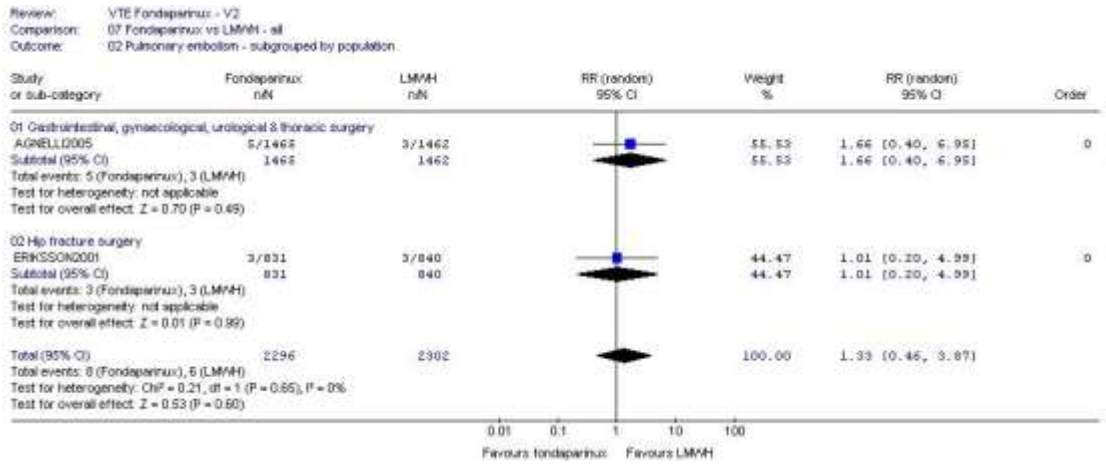


Fondaparinux vs LMWH

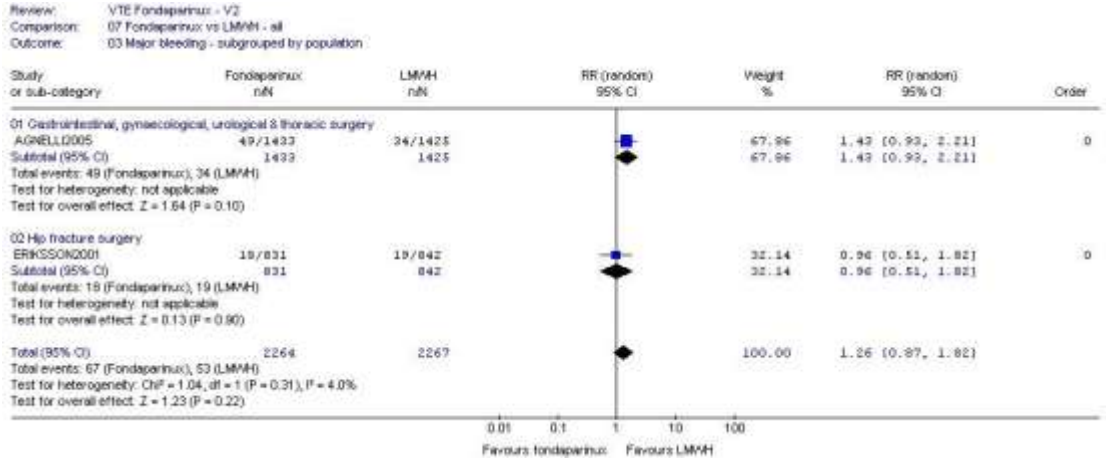
Forest Plot 44. Fondaparinux vs LMWH - DVT



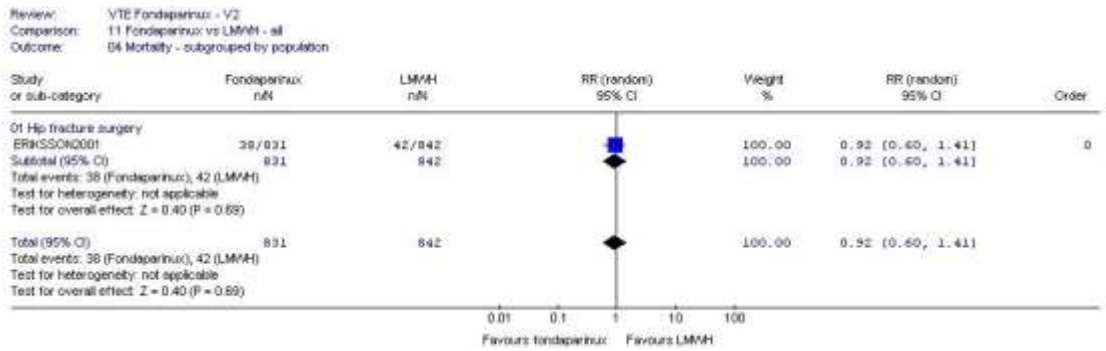
Forest Plot 45. Fondaparinux vs LMWH – Pulmonary Embolism



Forest Plot 46. Fondaparinux vs LMWH – Major Bleeding

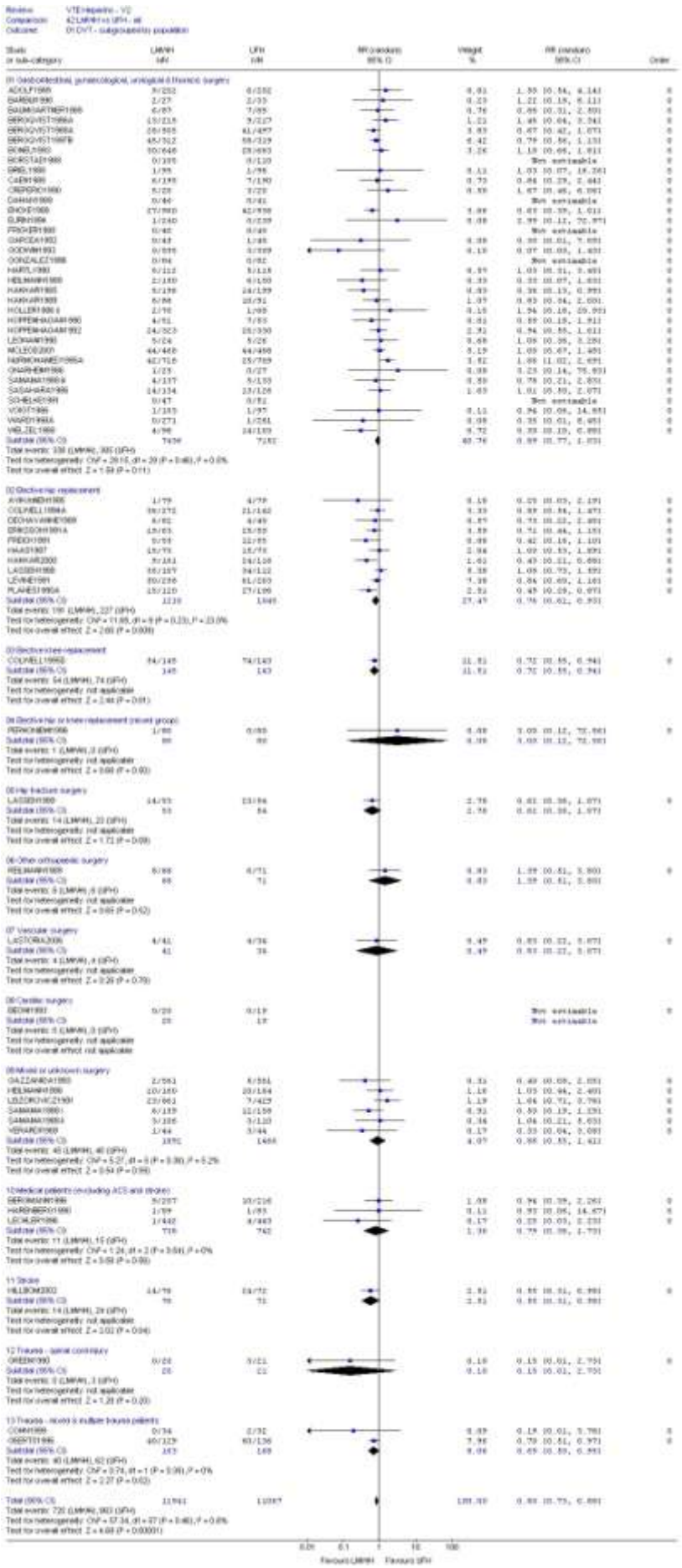


Forest Plot 47. Fondaparinux vs LMWH - Mortality

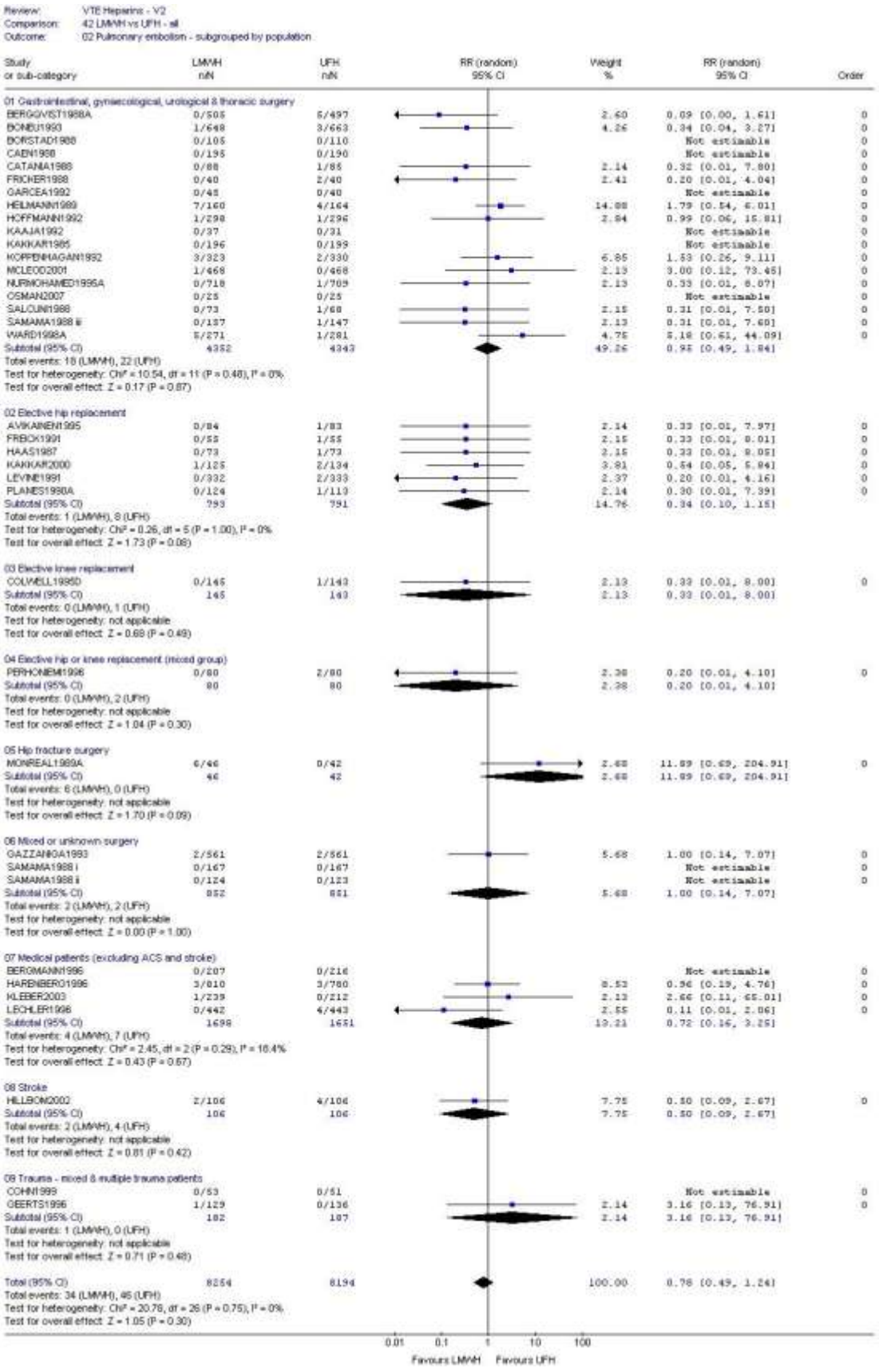


LMWH vs UFH

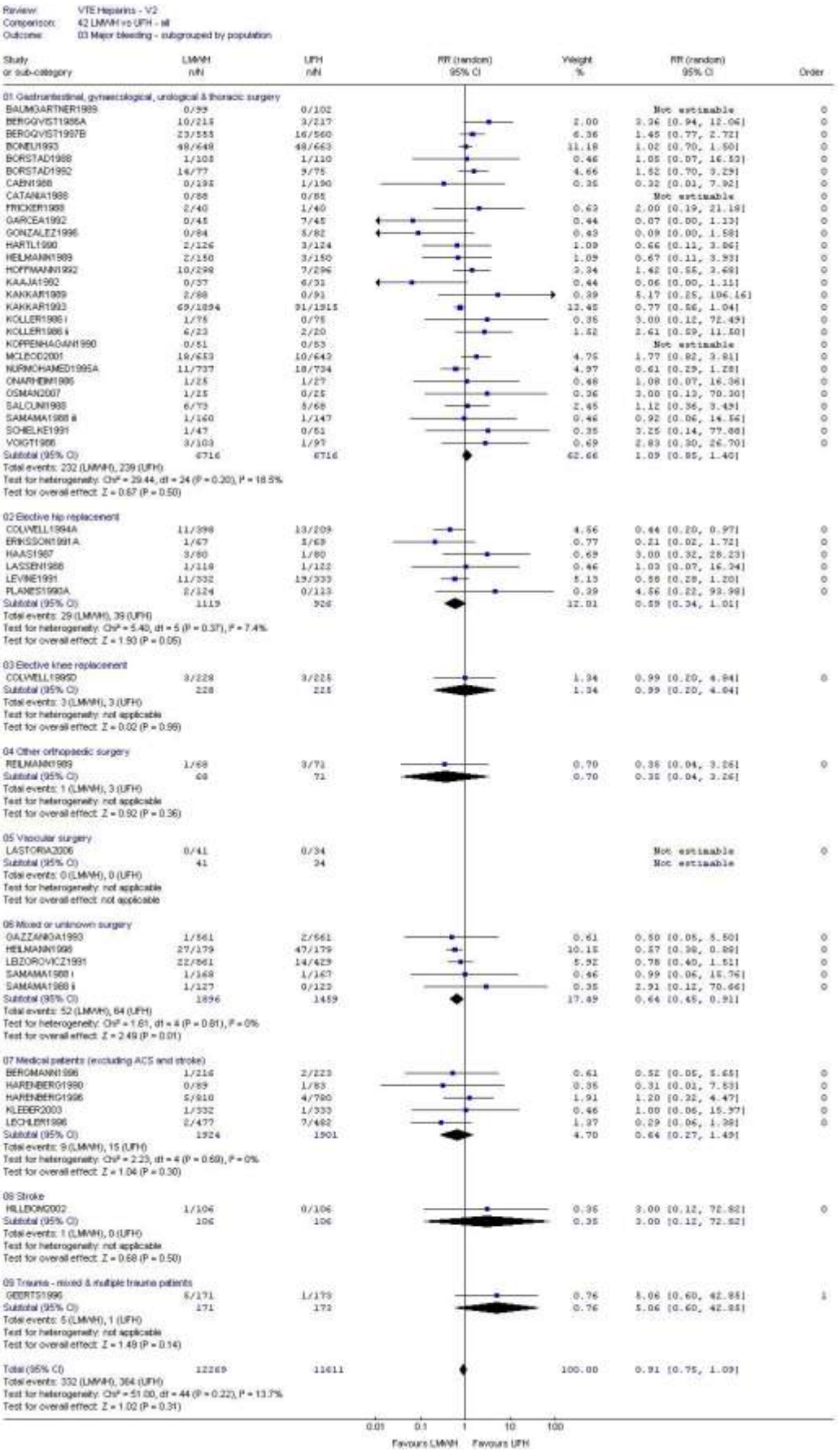
Forest Plot 48. LMWH vs UFH - DVT



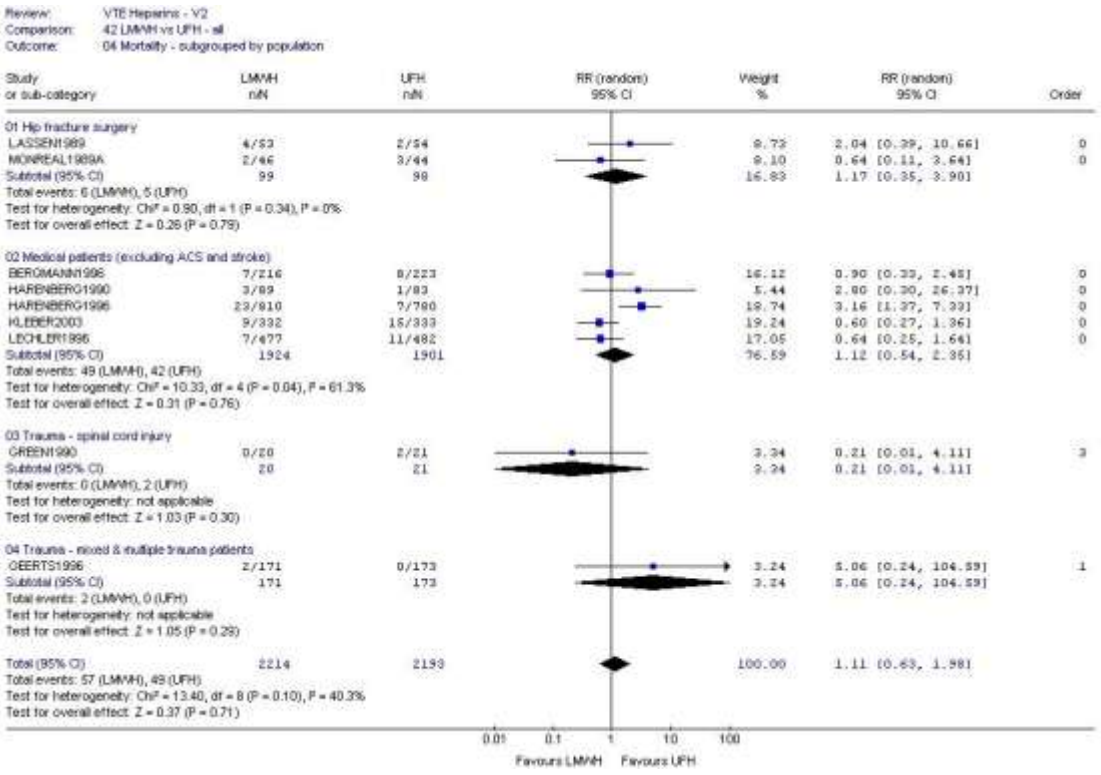
Forest Plot 49. LMWH vs UFH – Pulmonary Embolism



Forest Plot 50. LMWH vs UFH – Major Bleeding

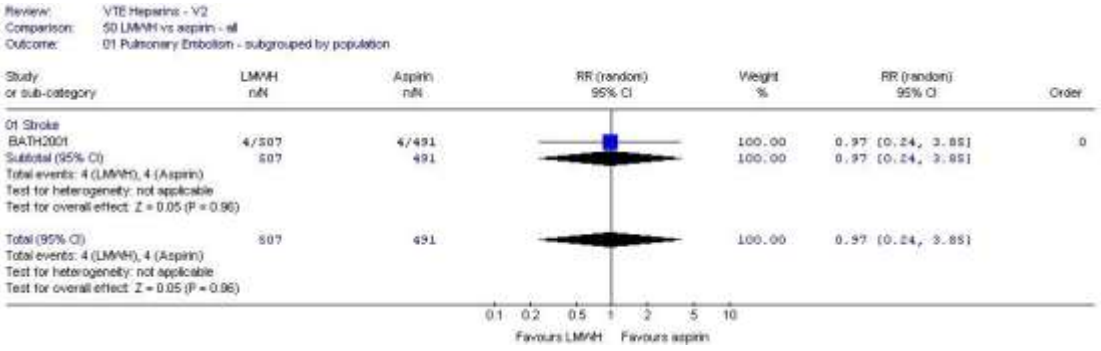


Forest Plot 51. LMWH vs UFH - Mortality

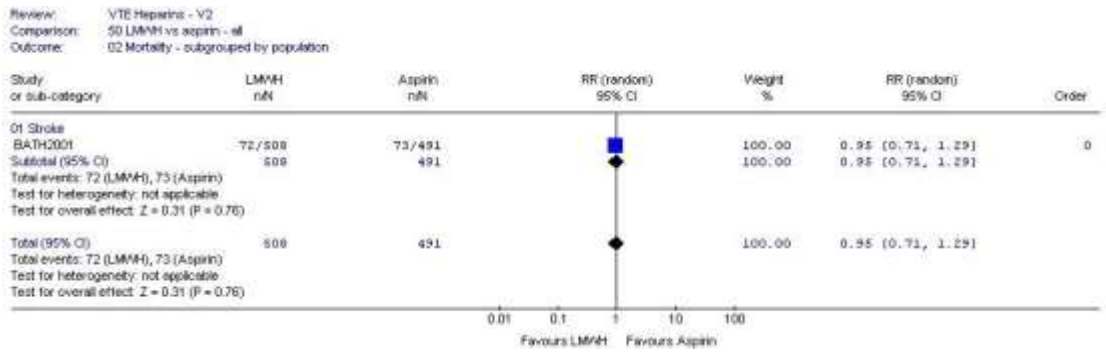


LMWH vs Aspirin (Low Dose)

Forest Plot 52. LMWH vs Aspirin (Low Dose) – Pulmonary Embolism

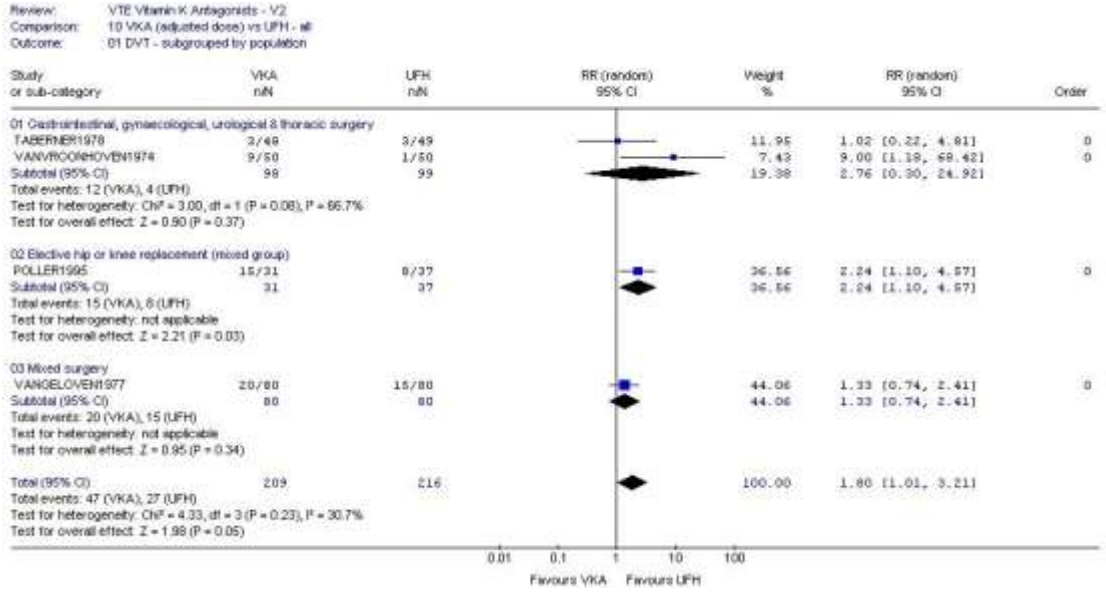


Forest Plot 53. LMWH vs Aspirin (Low Dose) – Mortality

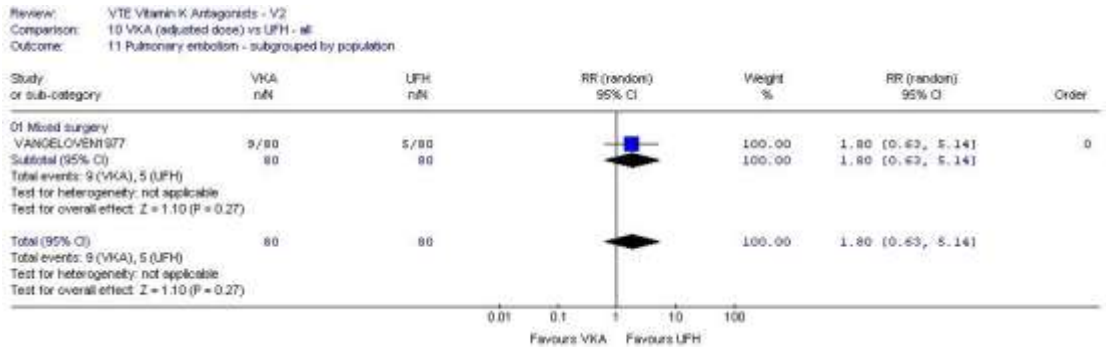


VKA (Adjusted Dose) vs Unfractionated Heparin

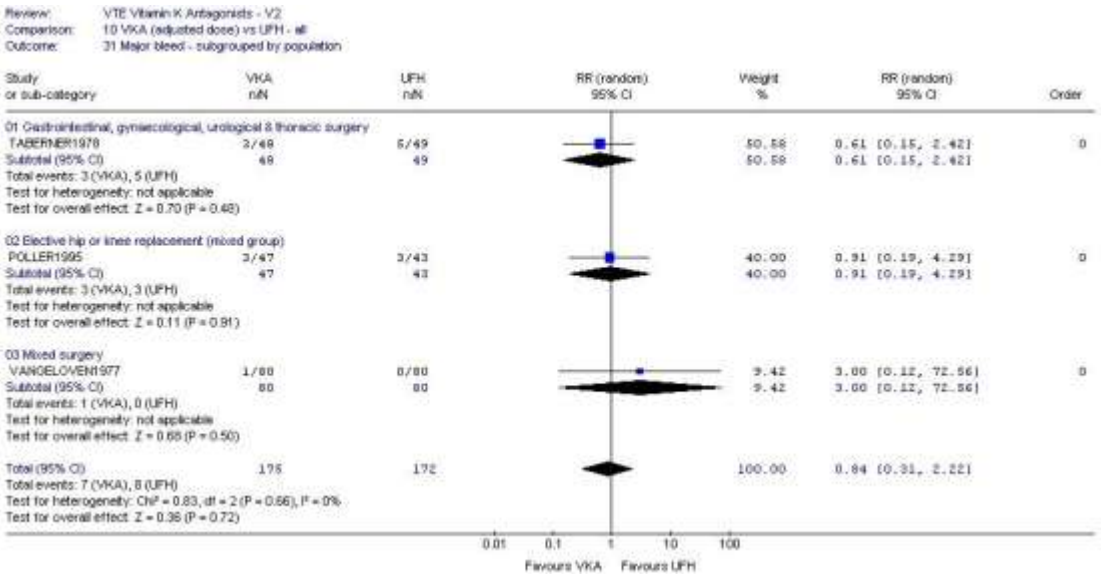
Forest Plot 54. VKA (Adjusted Dose) vs UFH- DVT



Forest Plot 55. VKA (Adjusted Dose) vs UFH– Pulmonary Embolism

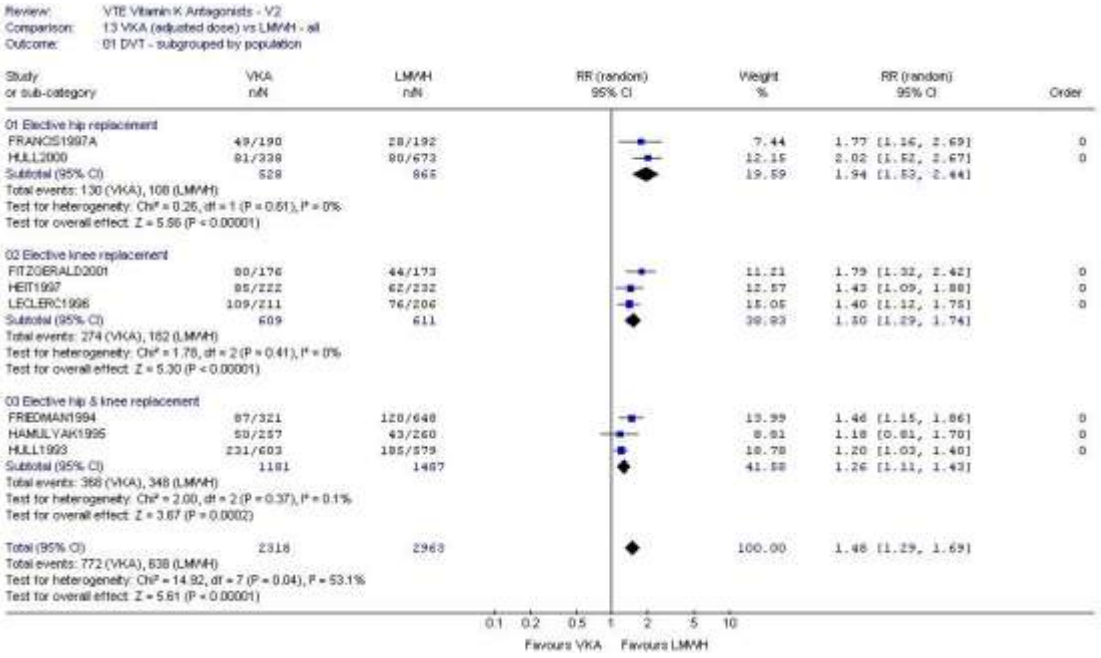


Forest Plot 56. VKA (Adjusted Dose) vs UFH– Major Bleeding

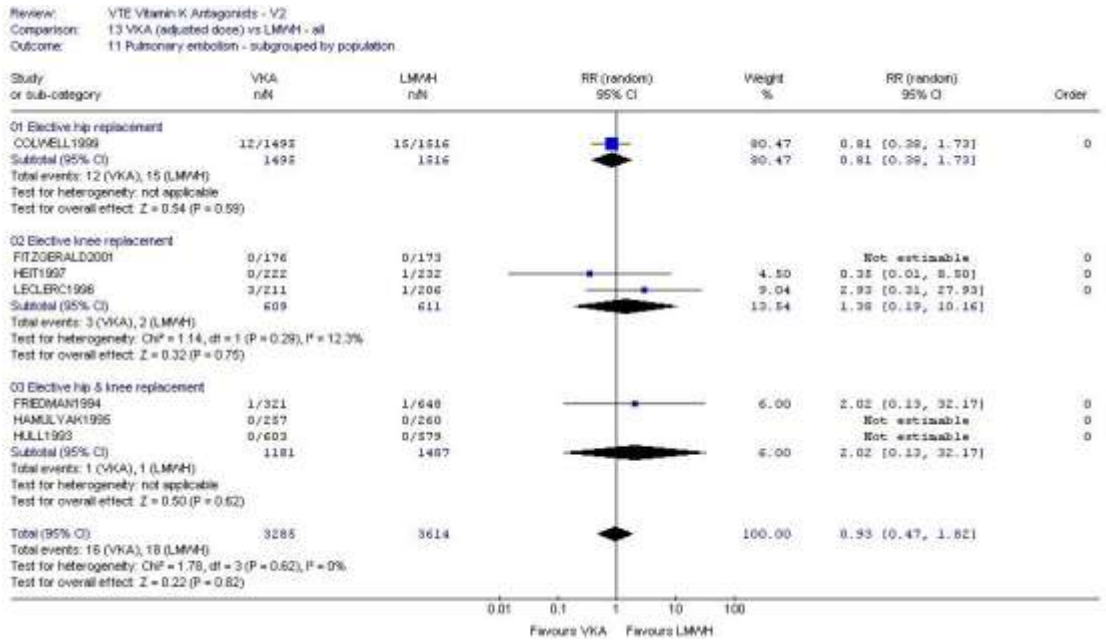


VKA (Adjusted Dose) vs LMWH

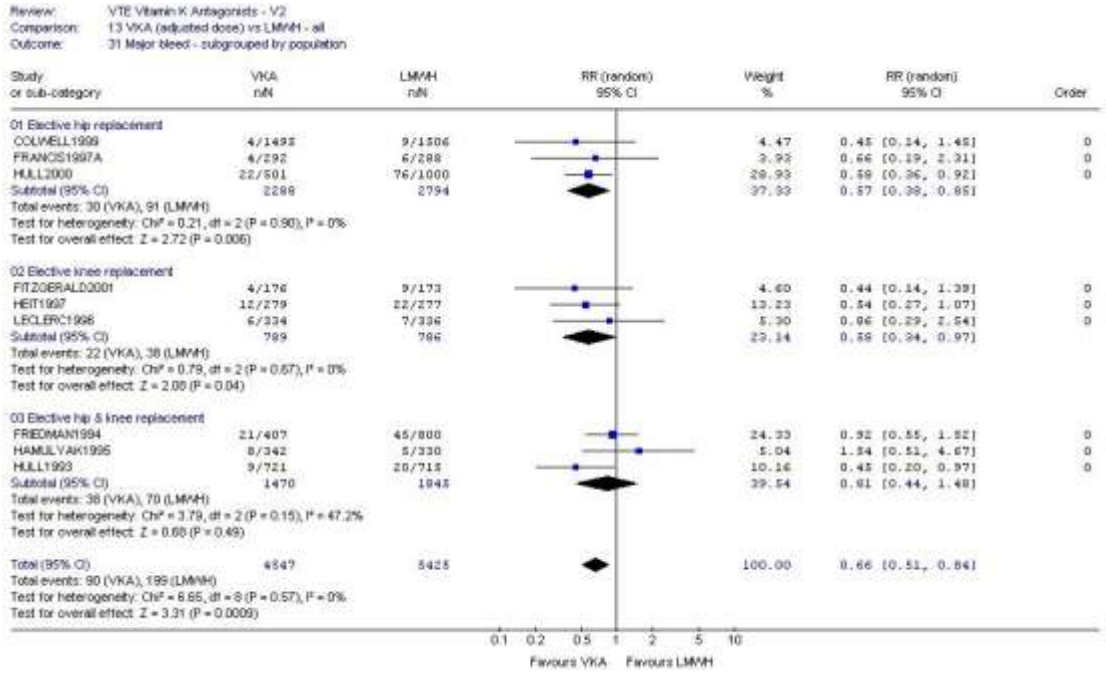
Forest Plot 57. VKA (Adjusted Dose) vs LMWH - DVT



Forest Plot 58. VKA (Adjusted Dose) vs LMWH – Pulmonary Embolism

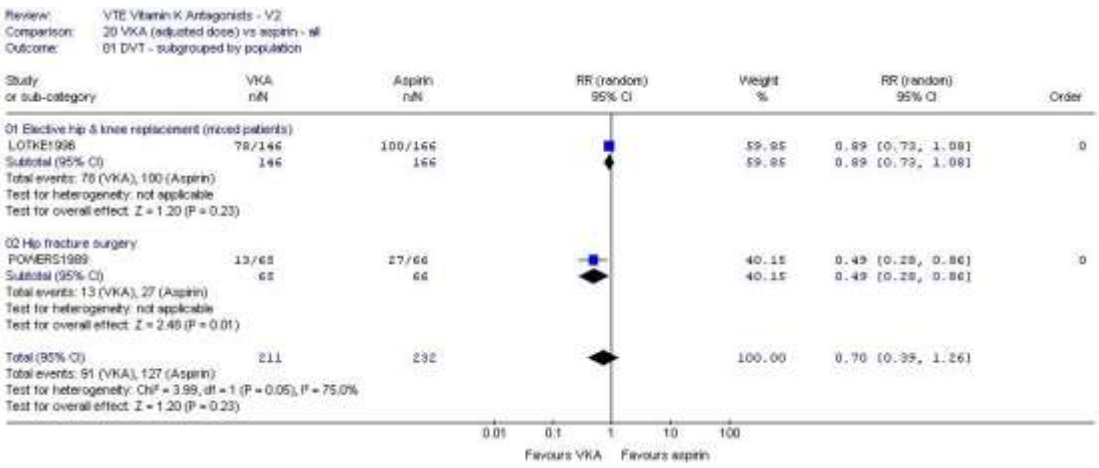


Forest Plot 59. VKA (Adjusted Dose) vs LMWH – Major Bleeding

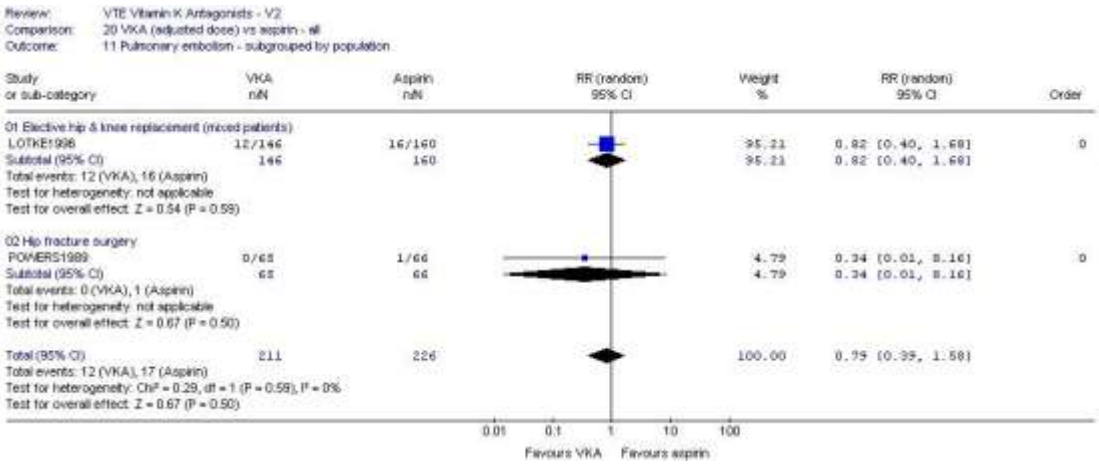


VKA (Adjusted Dose) vs Aspirin

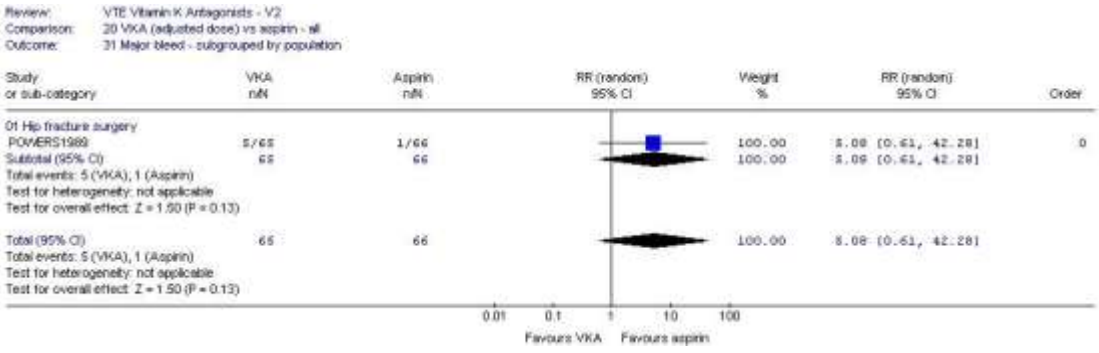
Forest Plot 60. VKA (Adjusted Dose) vs Aspirin - DVT



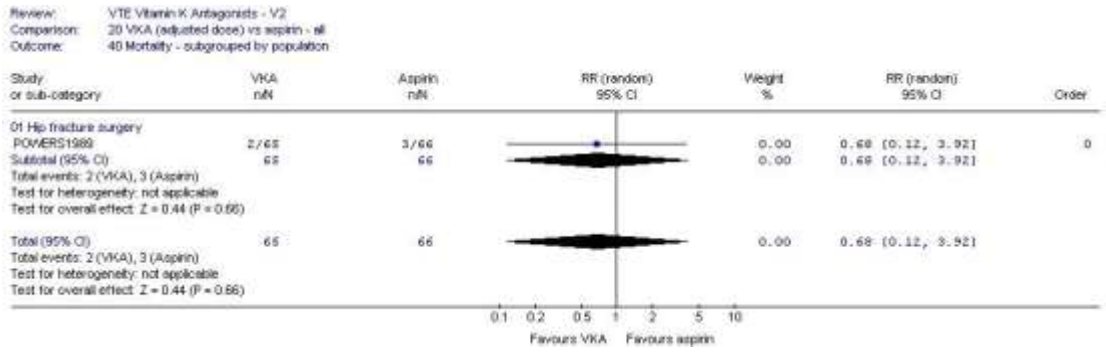
Forest Plot 61. VKA (Adjusted Dose) vs Aspirin – Pulmonary Embolism



Forest Plot 62. VKA (Adjusted Dose) vs Aspirin – Major Bleeding

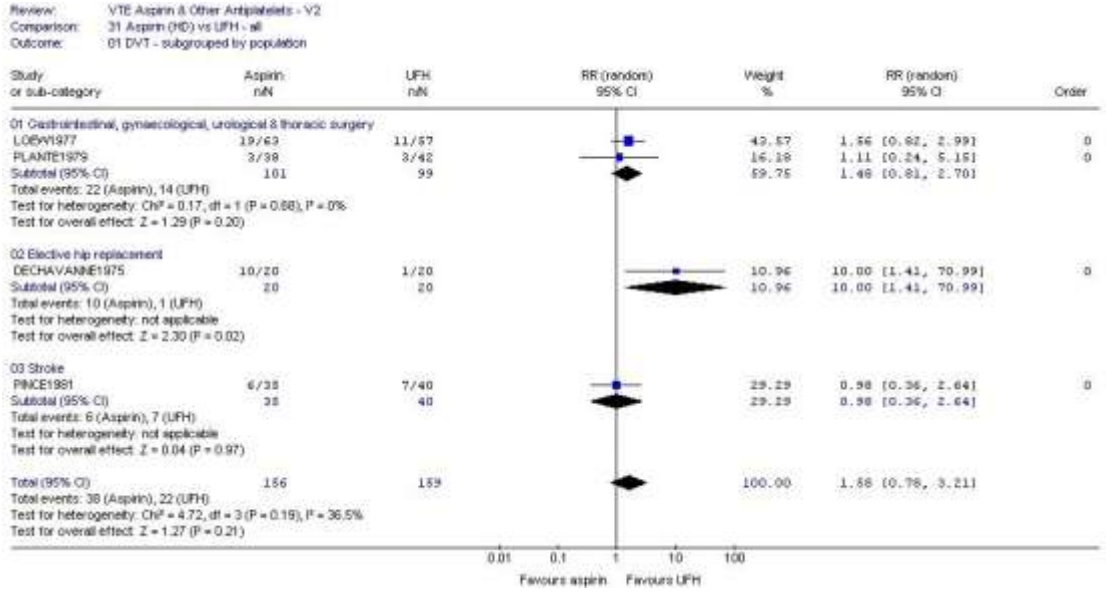


Forest Plot 63. VKA (Adjusted Dose) vs Aspirin – Mortality

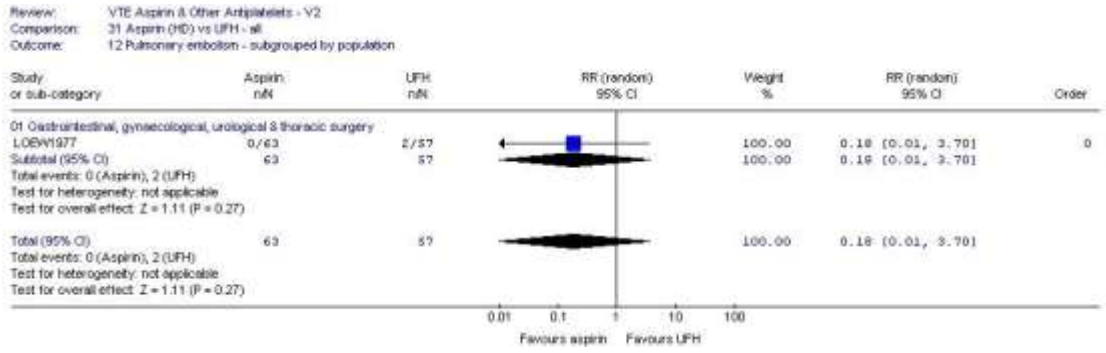


Aspirin (High Dose) vs Unfractionated Heparin

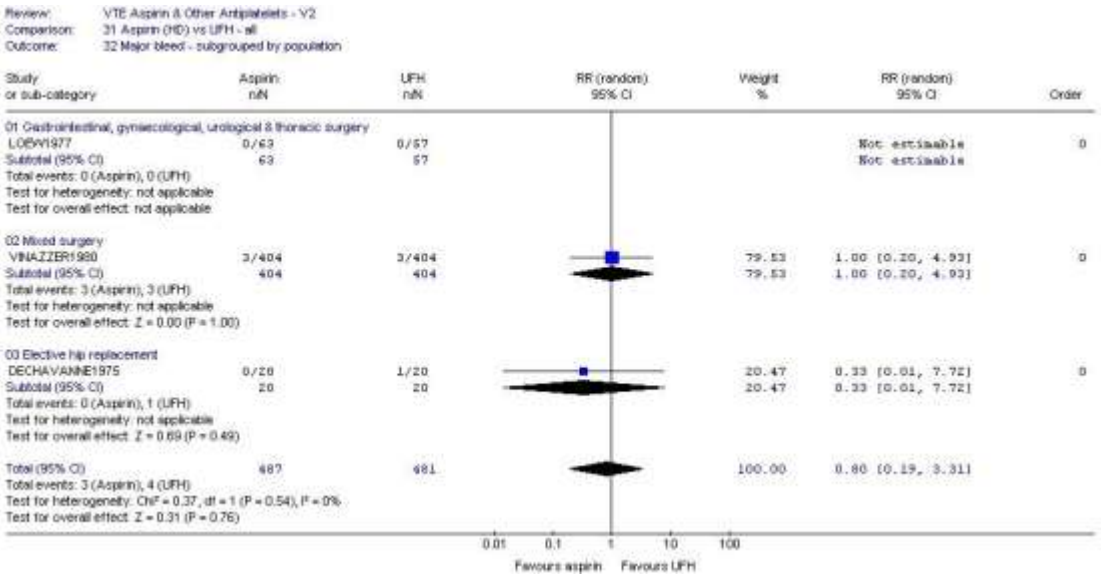
Forest Plot 64. Aspirin(High Dose) vs UFH- DVT



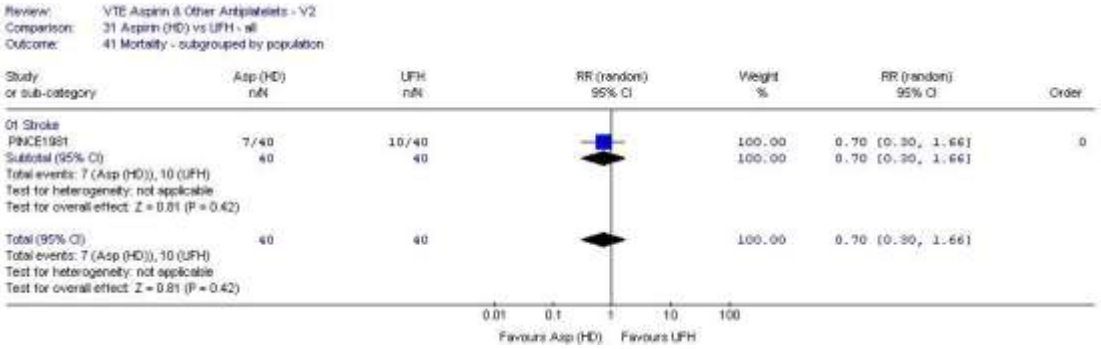
Forest Plot 65. Aspirin (High Dose) vs UFH– Pulmonary Embolism



Forest Plot 66. Aspirin (High Dose) vs UFH– Major Bleeding

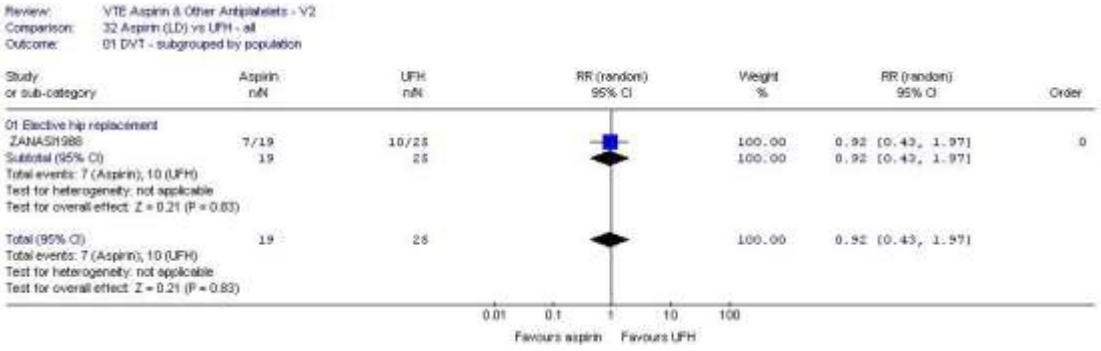


Forest Plot 67. Aspirin (High Dose) vs UFH– Mortality



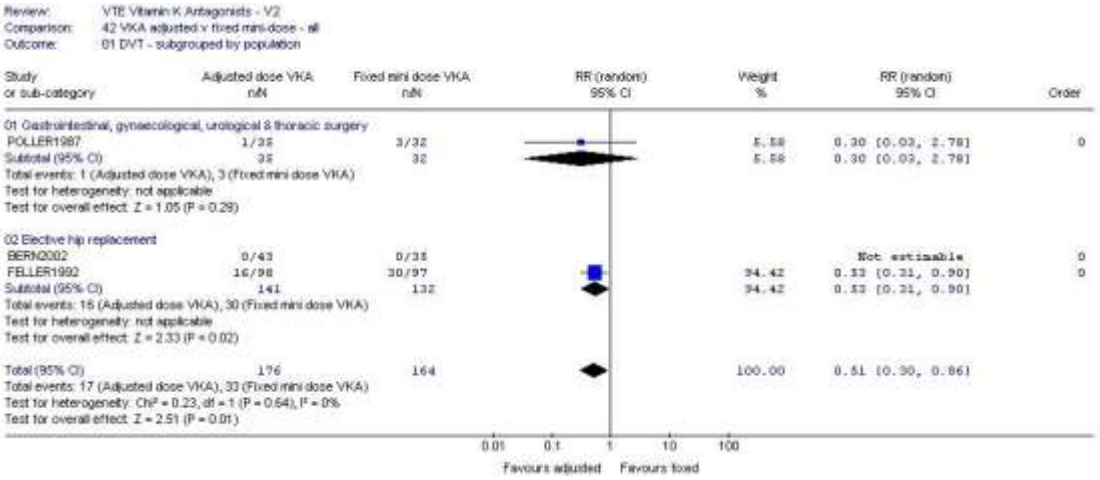
Aspirin (Low Dose) vs Unfractionated Heparin

Forest Plot 68. Aspirin(Low Dose) vs UFH- DVT

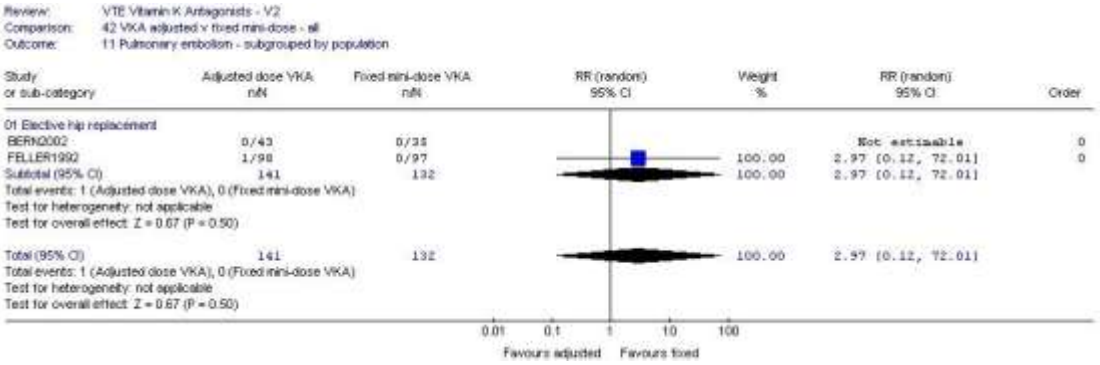


Adjusted vs Fixed (Lower) Dose VKA

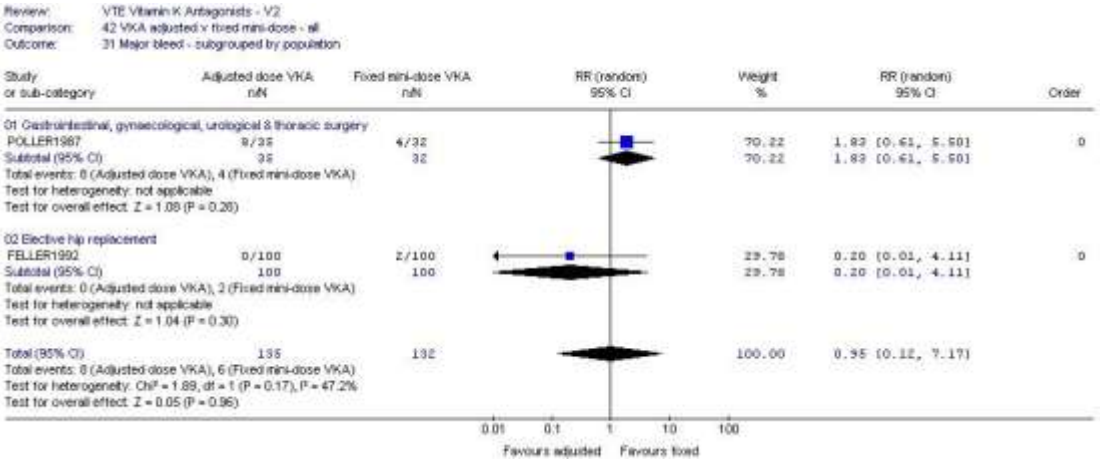
Forest Plot 69. Adjusted vs Fixed Dose VKA – DVT



Forest Plot 70. Adjusted vs Fixed Dose VKA – Pulmonary Embolism

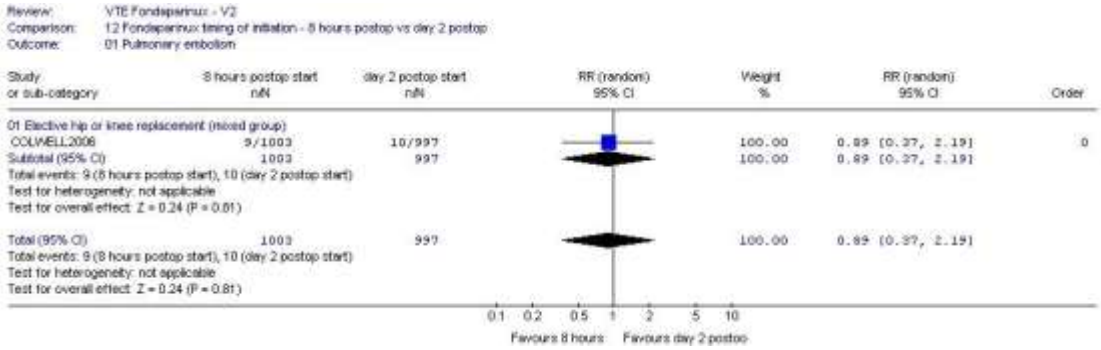


Forest Plot 71. Adjusted vs Fixed Dose VKA – Major Bleeding

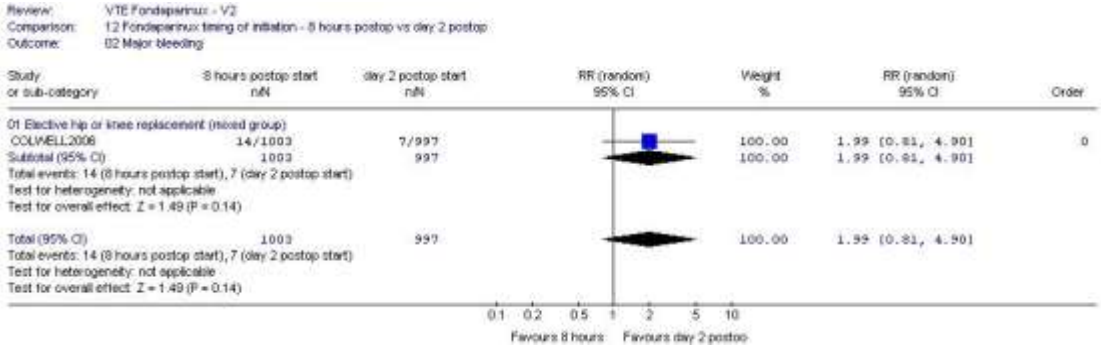


Fondaparinux Timing Of Initiation (8 Hours Postop vs 2nd Day Postop)

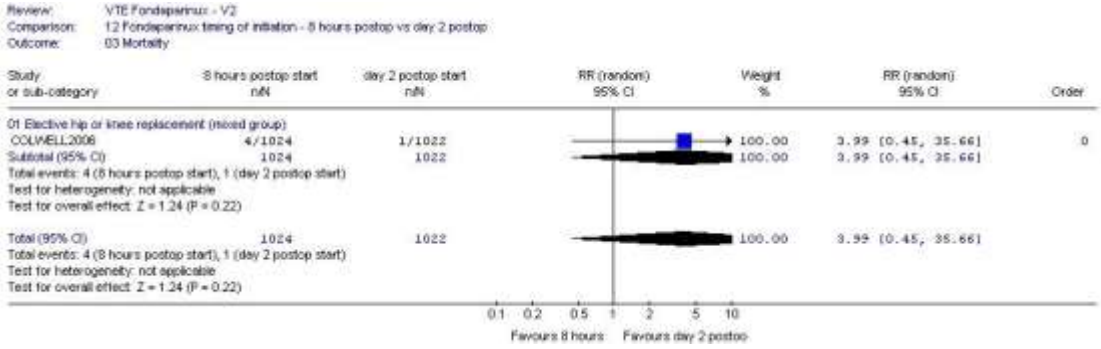
Forest Plot 72. Fondaparinux Timing Of Initiation – Pulmonary Embolism



Forest Plot 73. Fondaparinux Timing Of Initiation – Major Bleeding

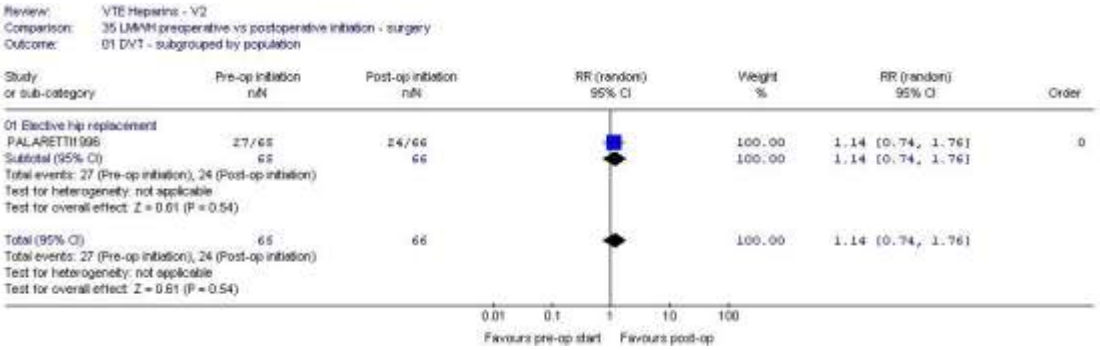


Forest Plot 74. Fondaparinux Timing Of Initiation – Mortality

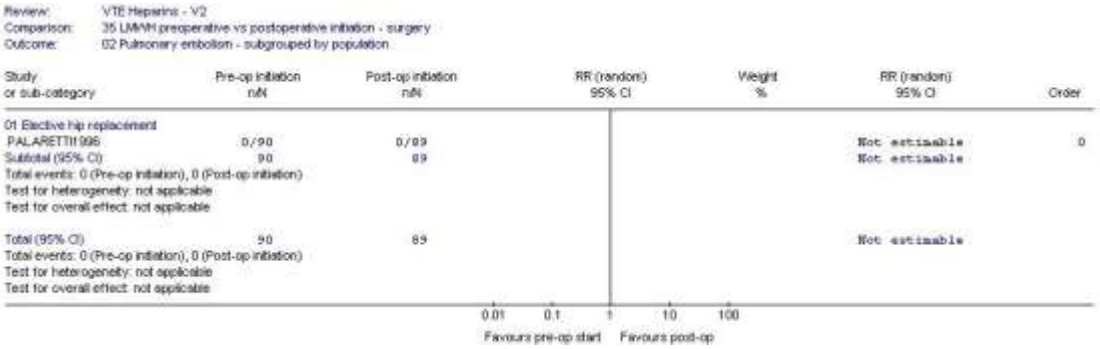


LMWH Preoperative vs Postoperative Initiation

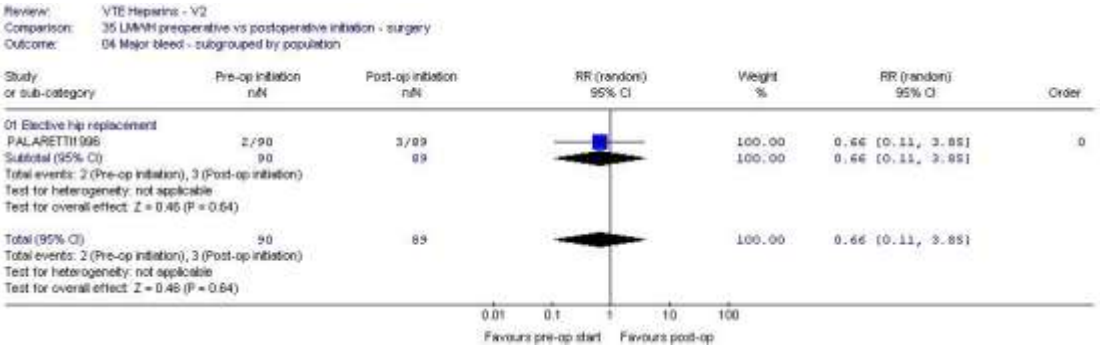
Forest Plot 75. LMWH Preoperative vs Postoperative Initiation – DVT



Forest Plot 76. LMWH Preoperative vs Postoperative Initiation – Pulmonary Embolism

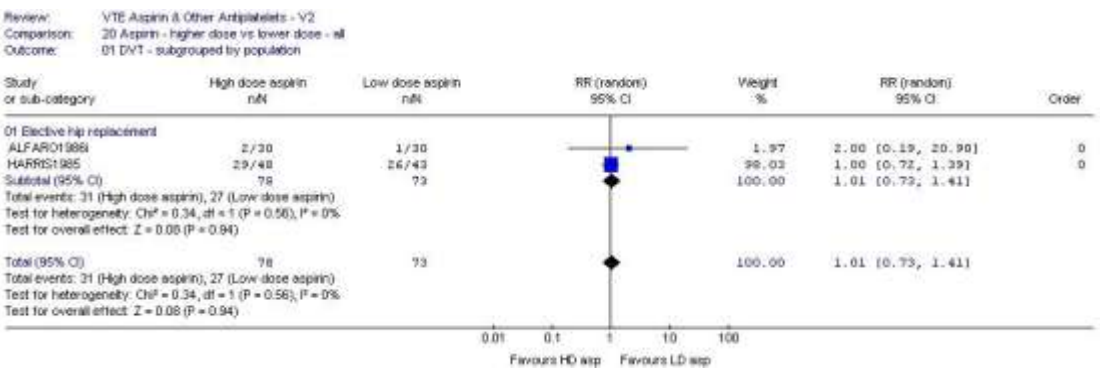


Forest Plot 77. LMWH Preoperative vs Postoperative Initiation – Major Bleeding

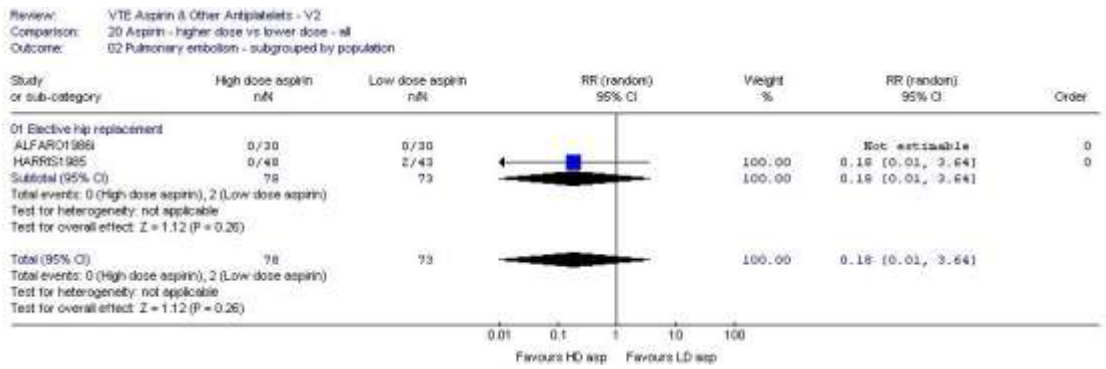


Aspirin (High Dose) vs Aspirin (Low Dose)

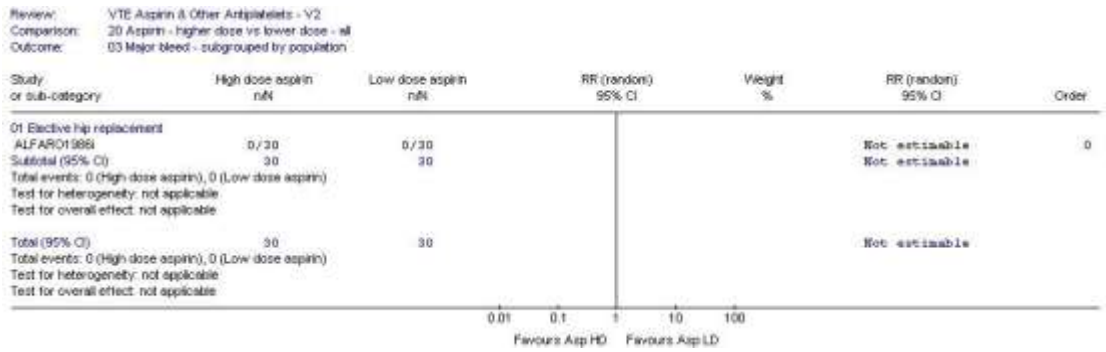
Forest Plot 78. Aspirin (High Dose) vs Aspirin (Low Dose) - DVT



Forest Plot 79. Aspirin (High Dose) vs Aspirin (Low Dose) – Pulmonary Embolism



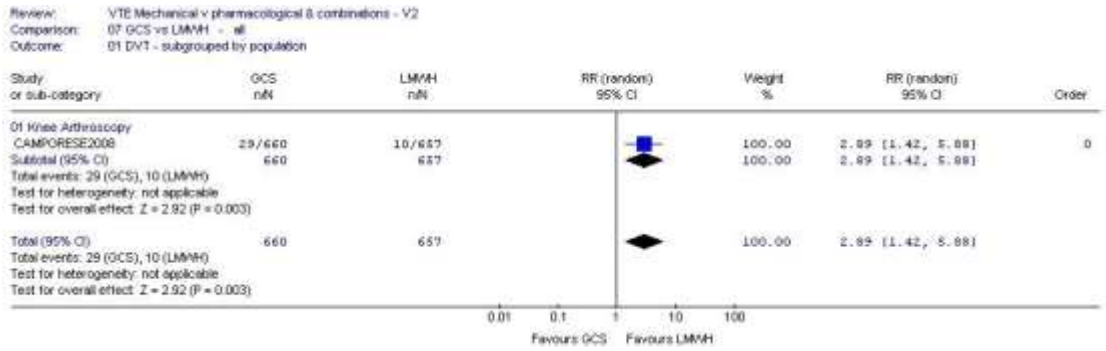
Forest Plot 80. Aspirin (High Dose) vs Aspirin (Low Dose) – Major Bleeding



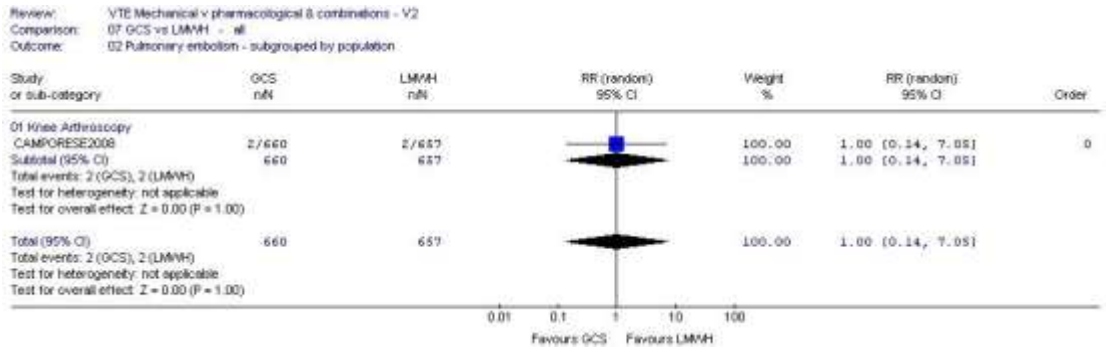
Mechanical vs Pharmacological Prophylaxis

GCS vs LMWH

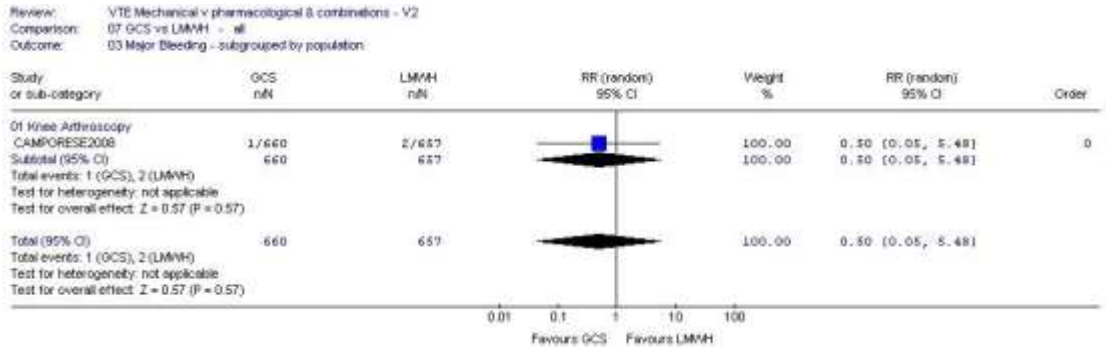
Forest Plot 81. GCS vs LMWH - DVT



Forest Plot 82. GCS vs LMWH – Pulmonary Embolism

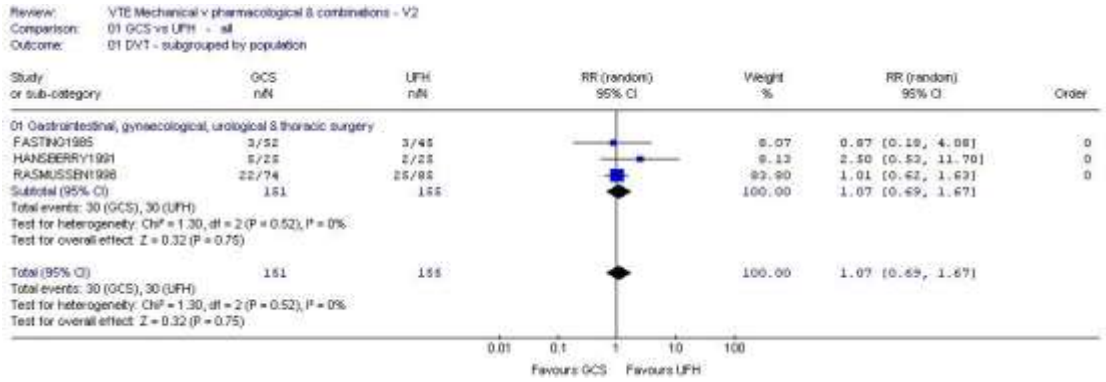


Forest Plot 83. GCS vs LMWH – Major Bleeding

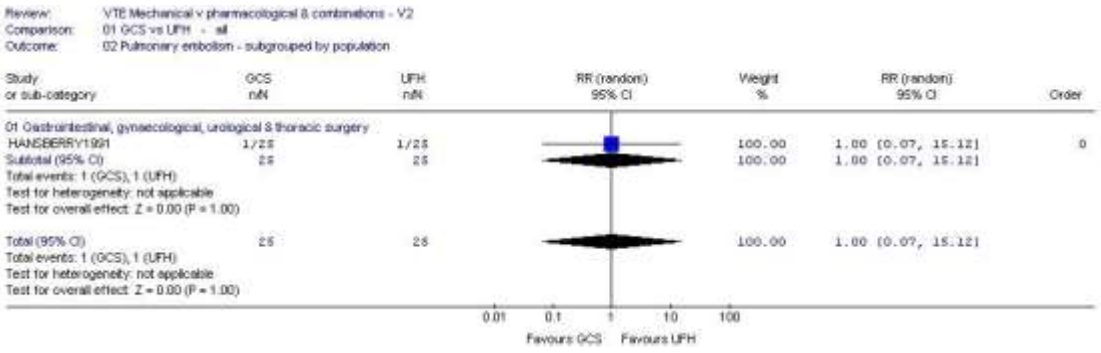


GCS vs UFH

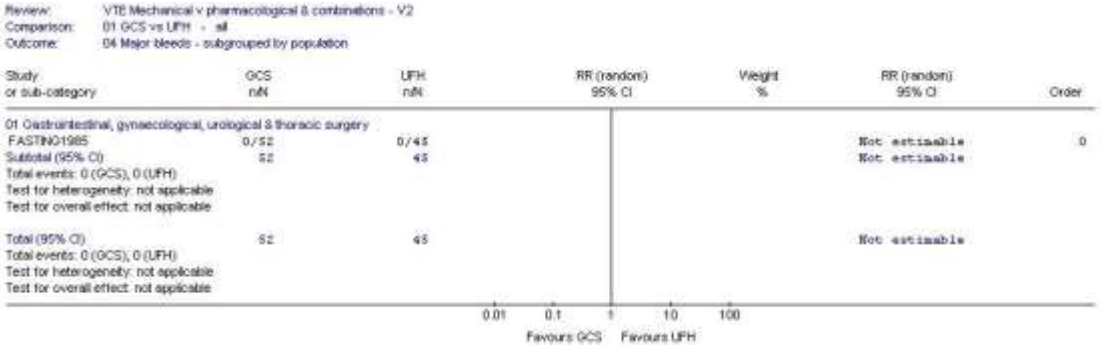
Forest Plot 84. GCS vs UFH - DVT



Forest Plot 85. GCS vs UFH – Pulmonary Embolism

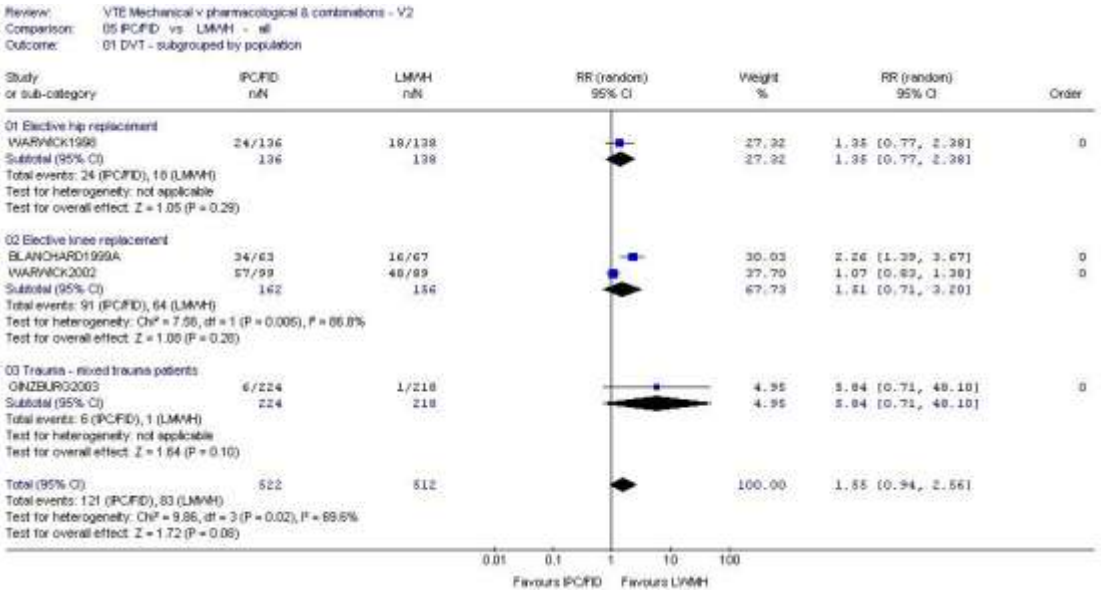


Forest Plot 86. GCS vs UFH – Major Bleeding

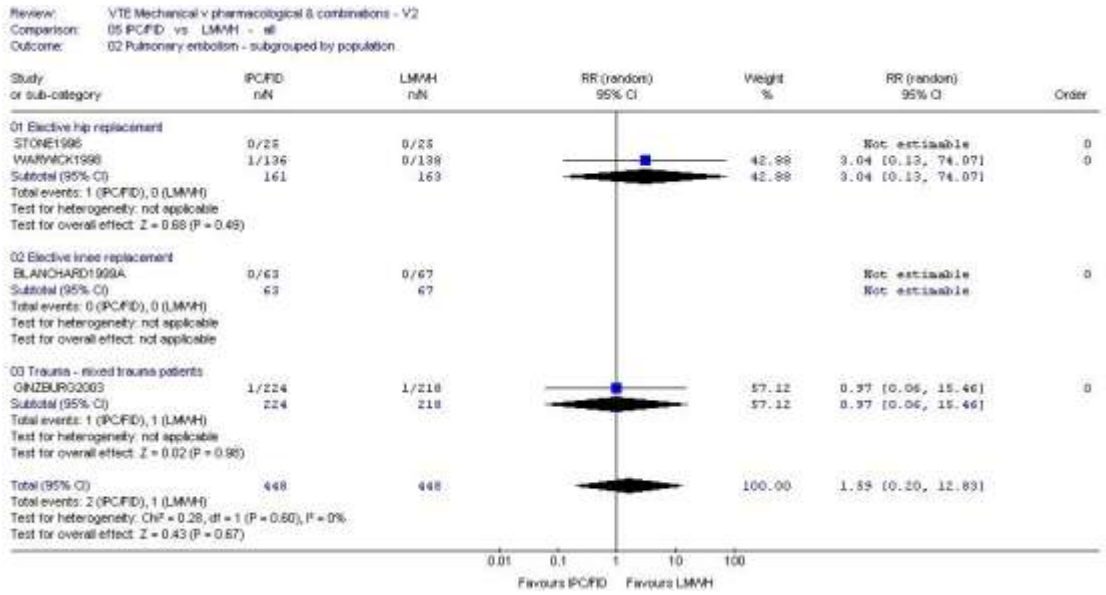


IPCD or FID (FID) vs LMWH

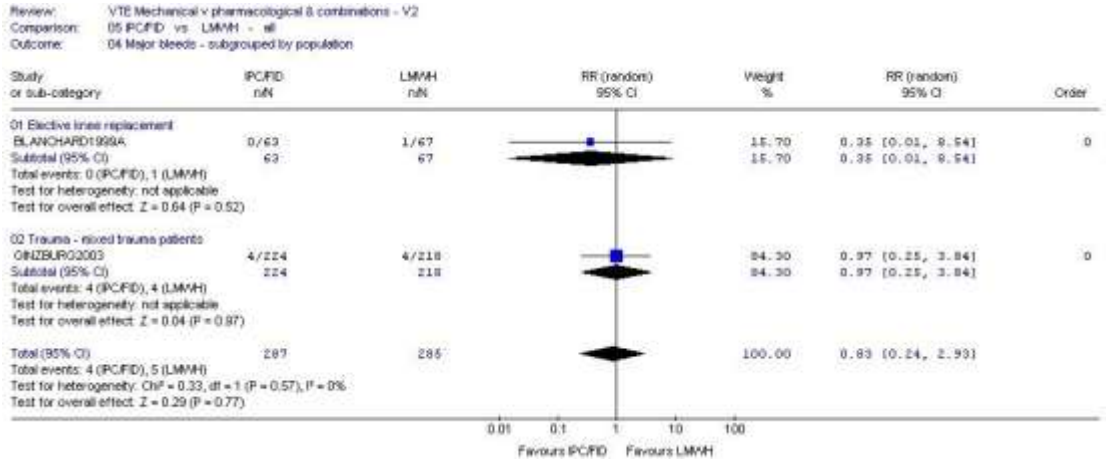
Forest Plot 87. IPCD/FID vs LMWH - DVT



Forest Plot 88. IPCD/FID vs LMWH – Pulmonary Embolism

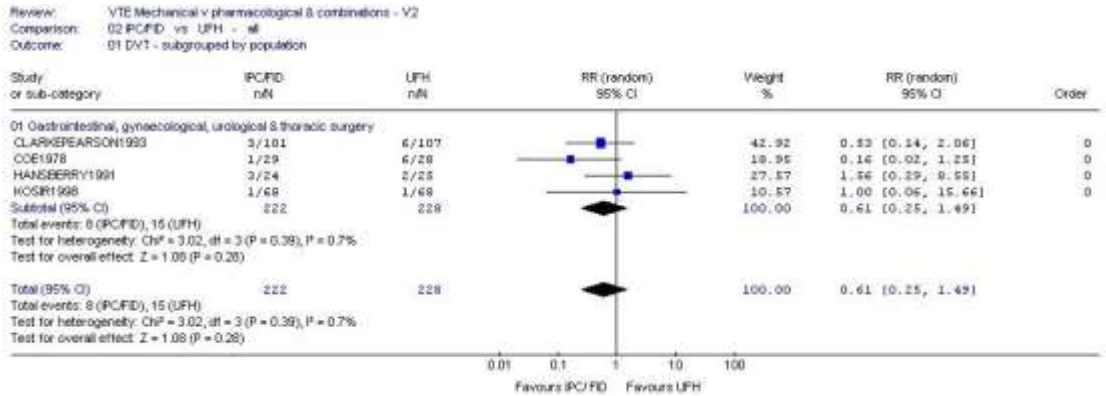


Forest Plot 89. IPCD/FID vs LMWH – Major Bleeding

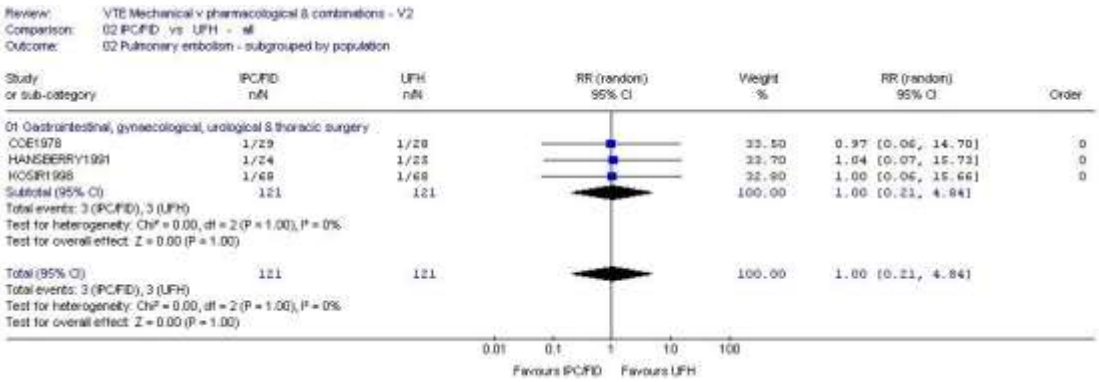


IPCD or FID (FID) vs UFH

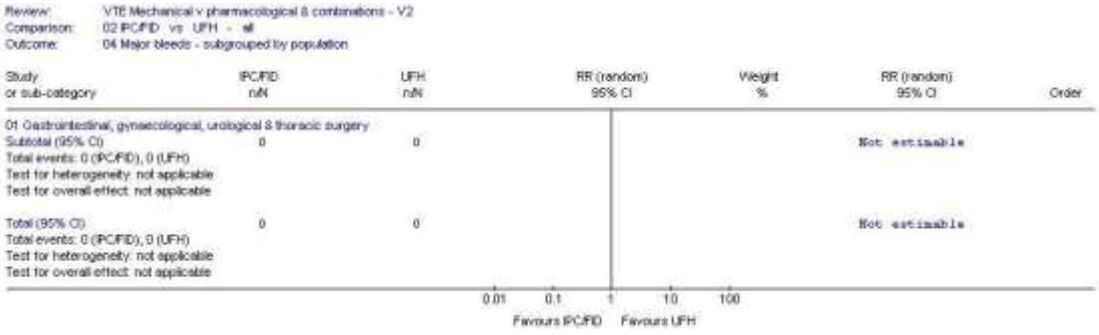
Forest Plot 90. IPCD/FID vs UFH - DVT



Forest Plot 91. IPCD/FID vs UFH – Pulmonary Embolism

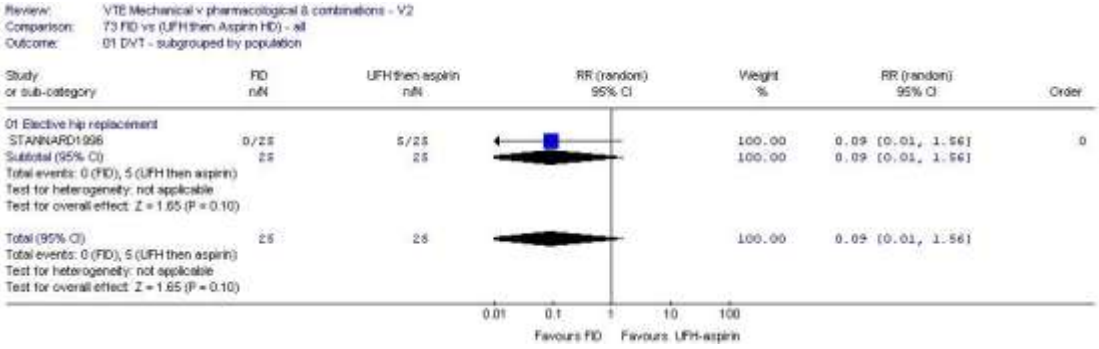


Forest Plot 92. IPCD/FID vs UFH – Major Bleeding

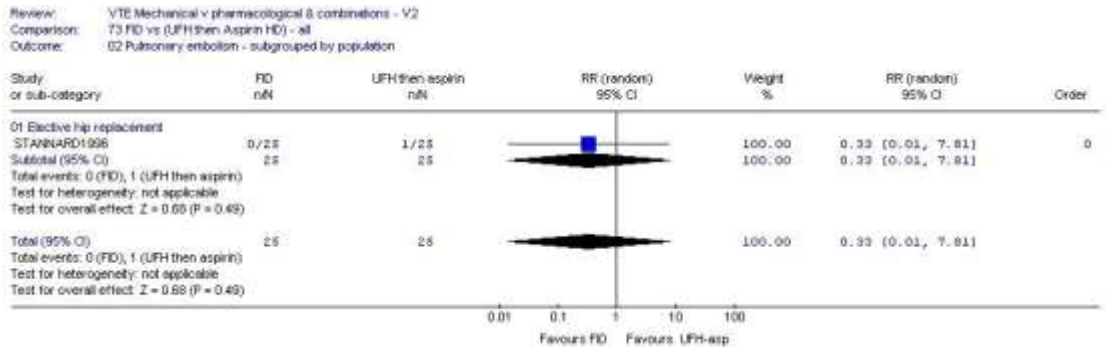


IPCD or FID (FID) vs UFH then aspirin

Forest Plot 93. IPCD/FID vs UFH then aspirin - DVT

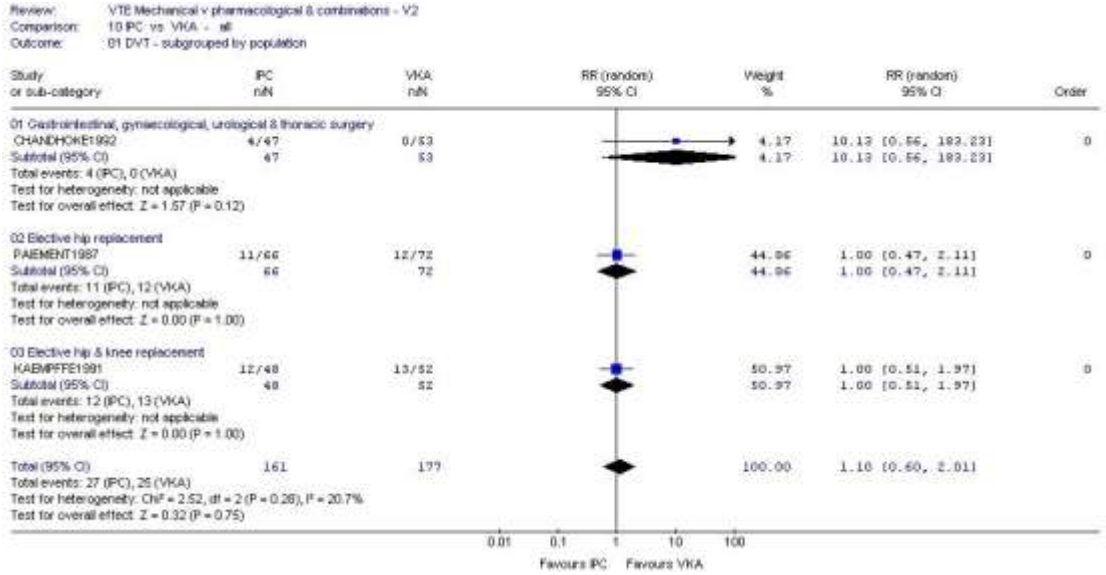


Forest Plot 94. IPCD/FID vs UFH then aspirin – pulmonary embolism

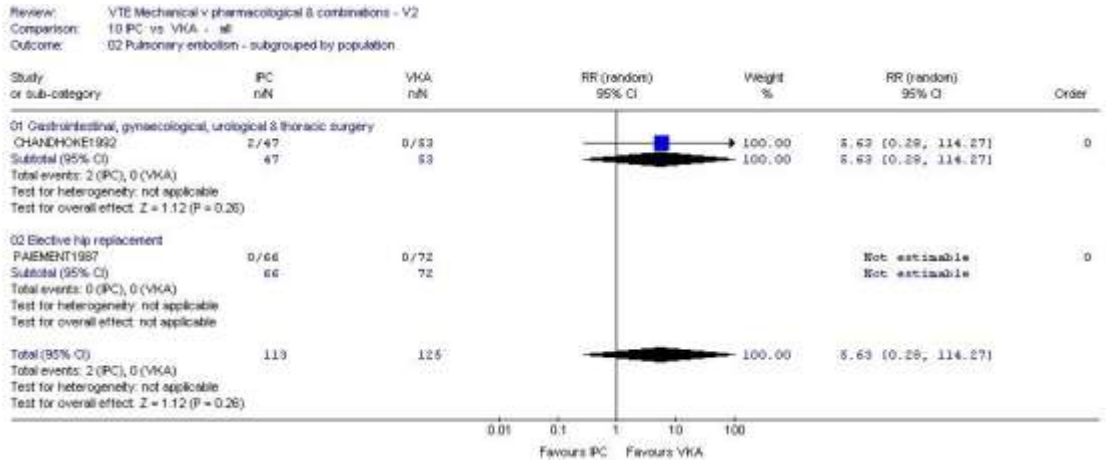


IPCD or FID (FID) vs VKA

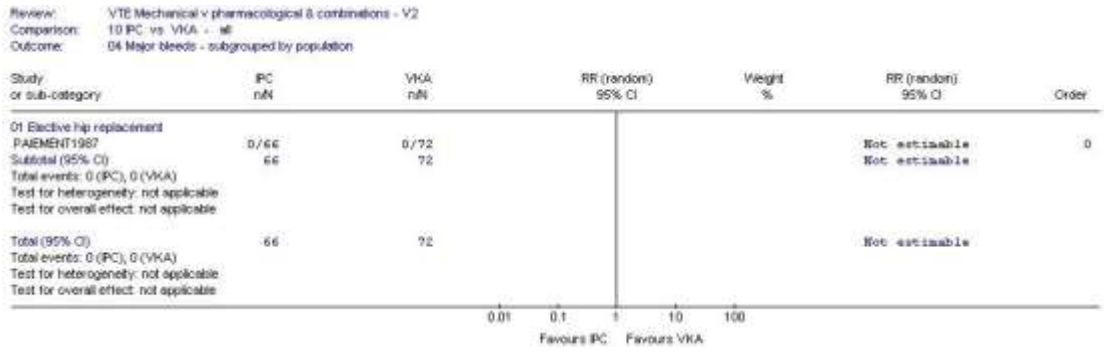
Forest Plot 95. IPCD/FID vs VKA - DVT



Forest Plot 96. IPCD/FID vs VKA – Pulmonary Embolism

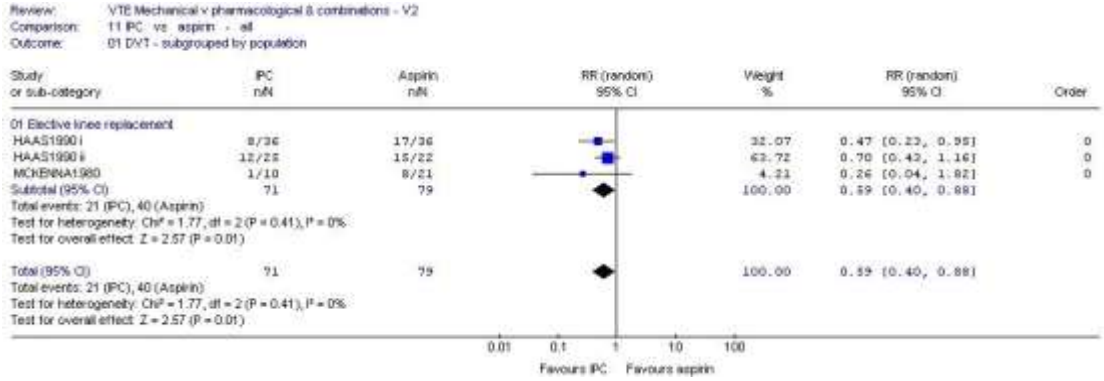


Forest Plot 97. IPCD/FID vs VKA – Major Bleeding

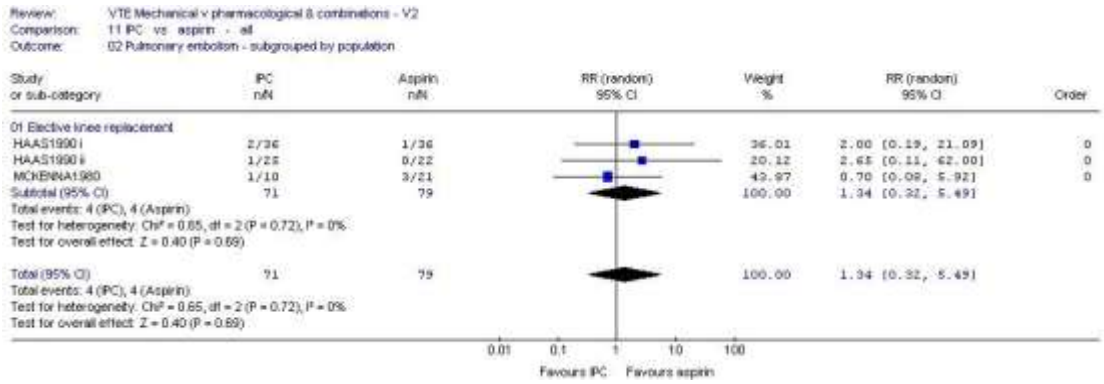


IPCD or FID (FID) vs Aspirin

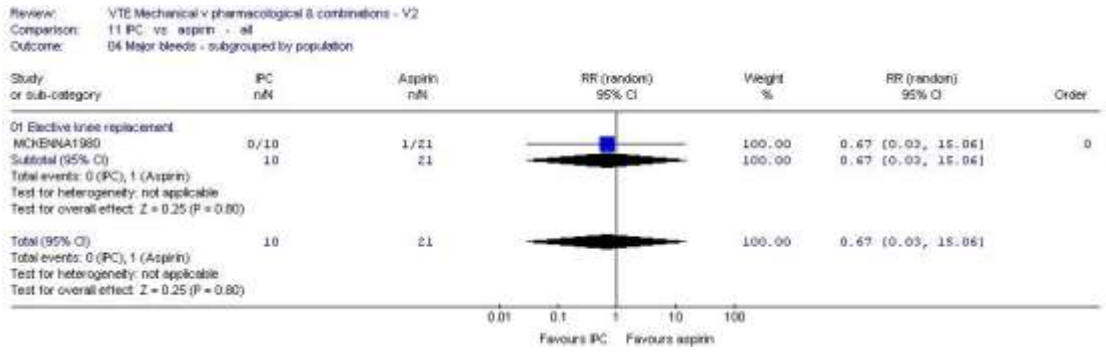
Forest Plot 98. IPCD/FID vs Aspirin- DVT



Forest Plot 99. IPCD/FID vs Aspirin – Pulmonary Embolism

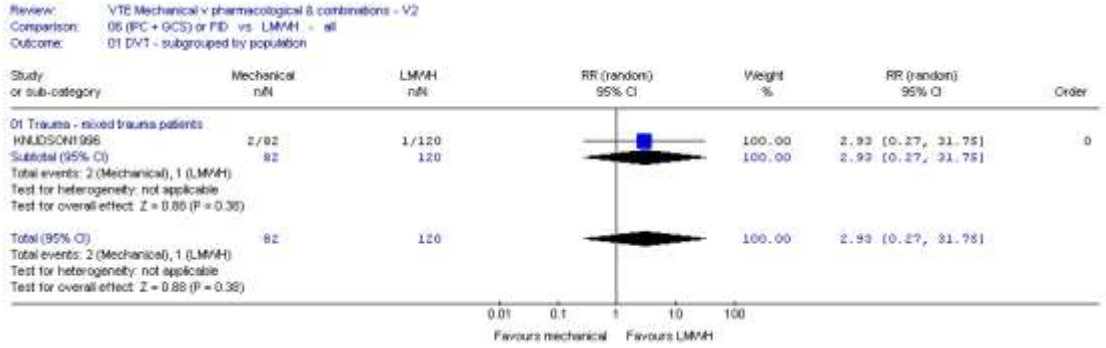


Forest Plot 100. IPCD/FID vs Aspirin – Major Bleeding

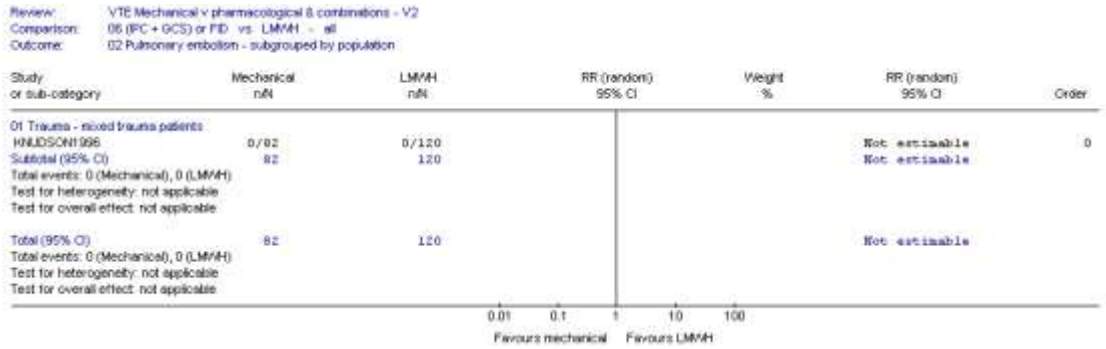


IPCD + GCS or FID (FID) vs LMWH

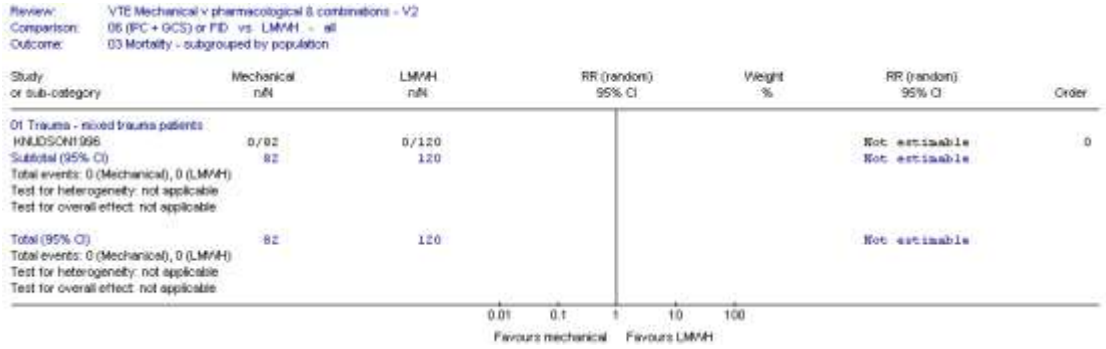
Forest Plot 101. (IPCD + GCS) or FID vs LMWH - DVT



Forest Plot 102. (IPCD + GCS) or FID vs LMWH – Pulmonary Embolism

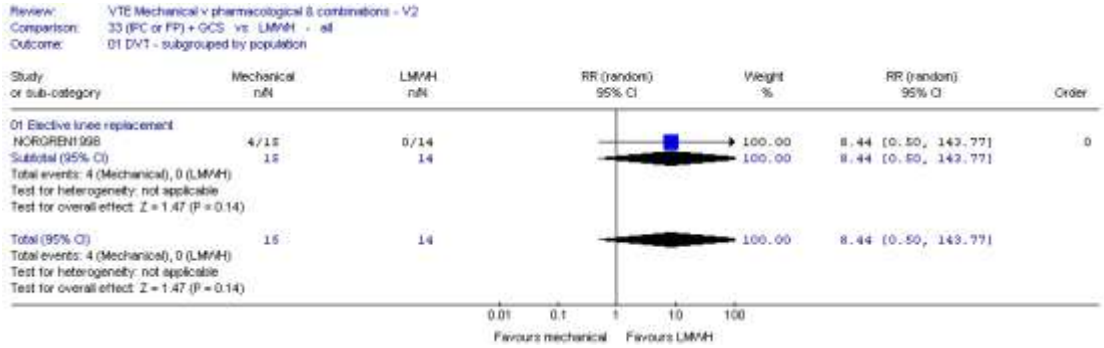


Forest Plot 103. (IPCD + GCS) or FID vs LMWH - Mortality



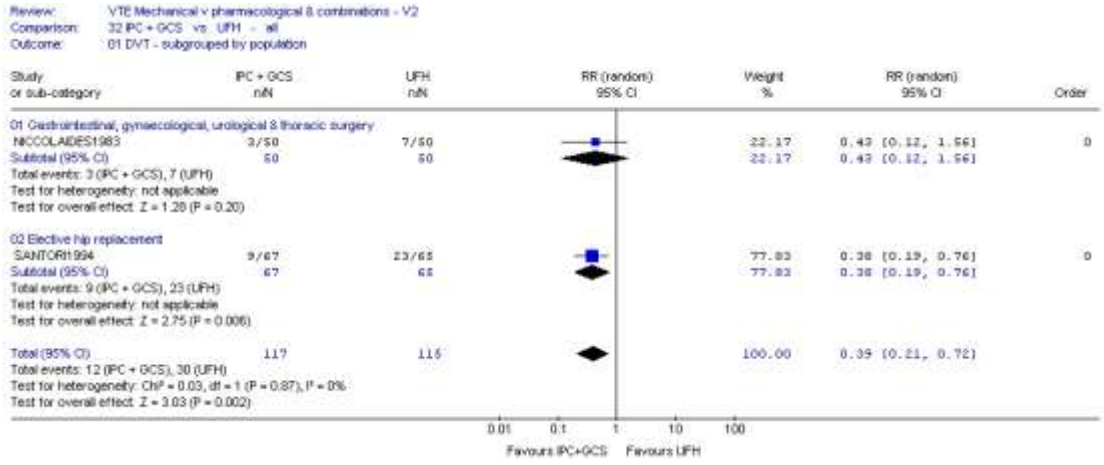
IPCD or FID (FID) + GCS vs LMWH

Forest Plot 104. (IPCD/FID) + GCS vs LMWH - DVT



IPCD + GCS vs UFH

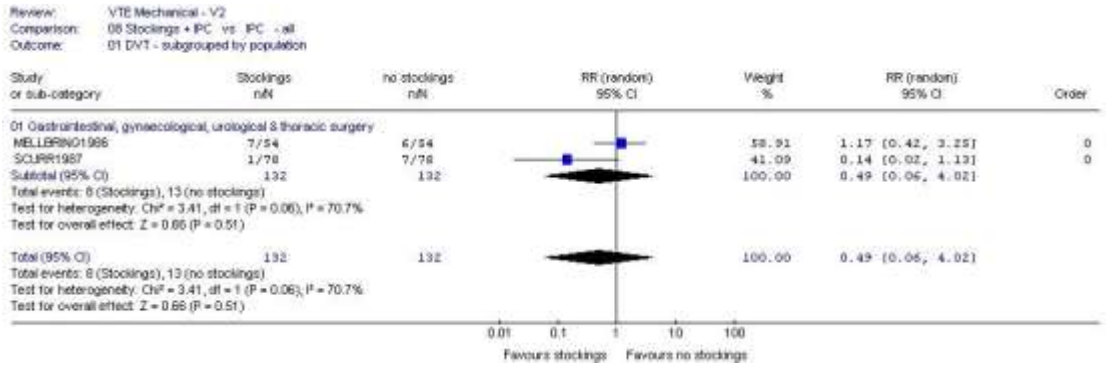
Forest Plot 105. (IPCD + GCS) vs UFH - DVT



Mechanical Adjuvant Studies

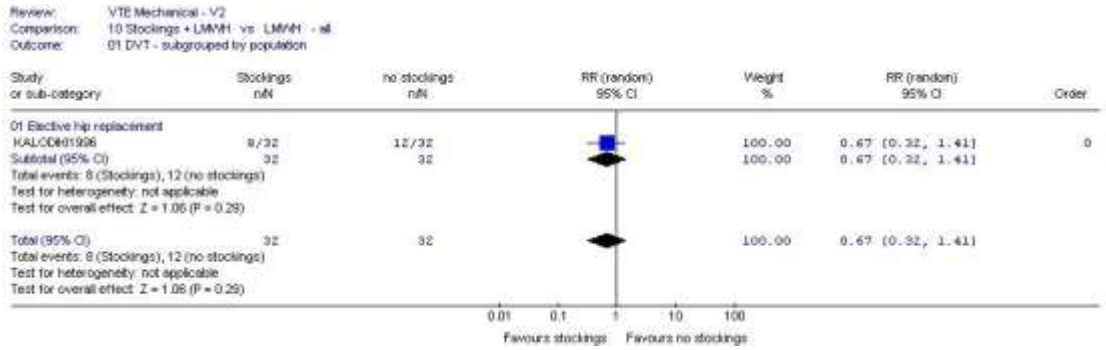
GCS + IPCD vs IPCD

Forest Plot 106. GCS + IPCD vs IPCD - DVT

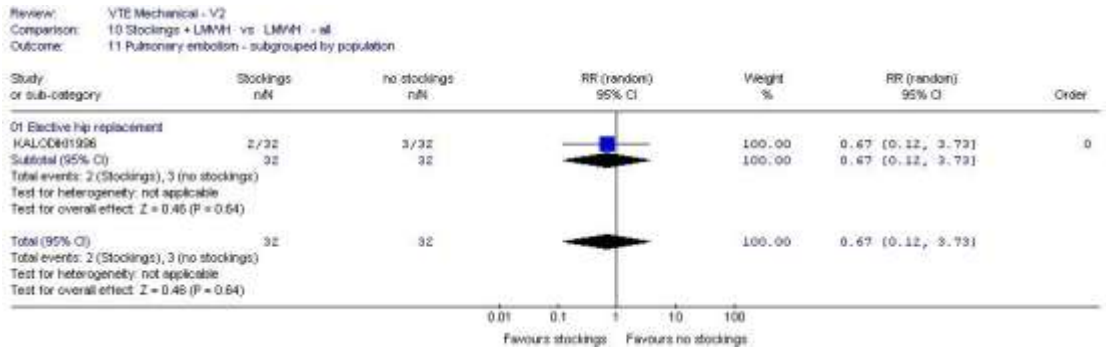


GCS + LMWH vs LMWH

Forest Plot 107. GCS + LMWH vs LMWH - DVT

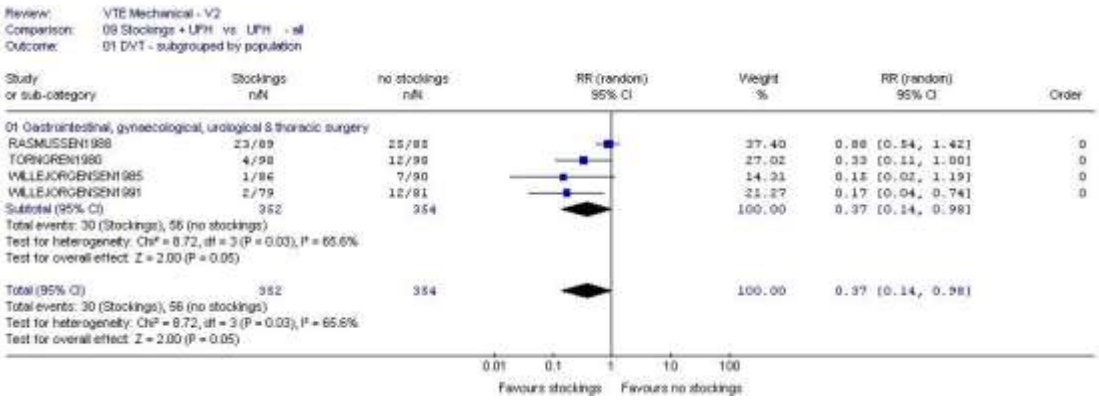


Forest Plot 108. GCS + LMWH vs LMWH – Pulmonary Embolism

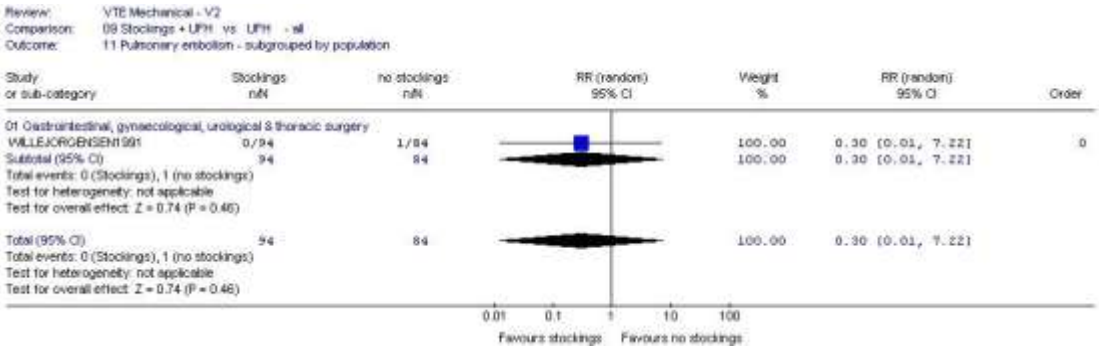


GCS + UFH vs UFH

Forest Plot 109. GCS + UFH vs UFH - DVT

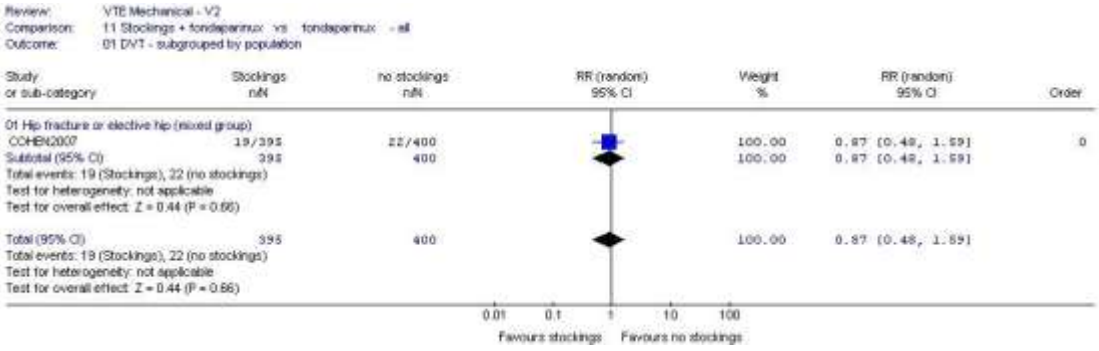


Forest Plot 110. GCS + UFH vs UFH – Pulmonary Embolism

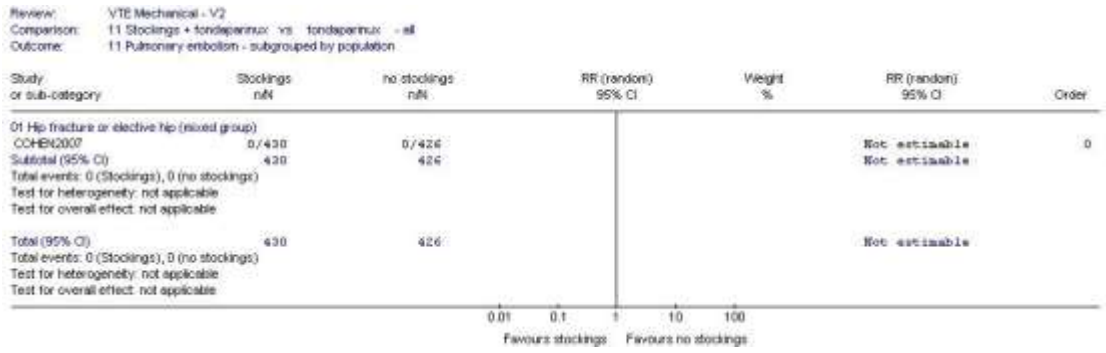


GCS + Fondaparinux vs Fondaparinux

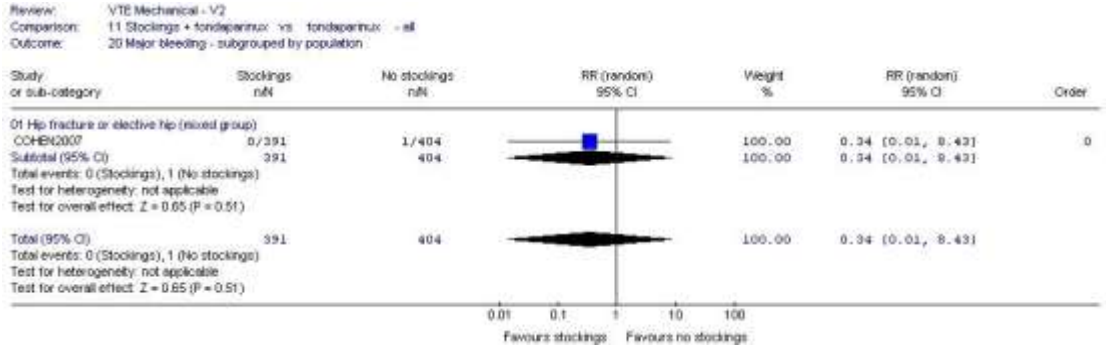
Forest Plot 111. GCS + Fondaparinux vs Fondaparinux - DVT



Forest Plot 112. GCS + Fondaparinux vs Fondaparinux – Pulmonary Embolism

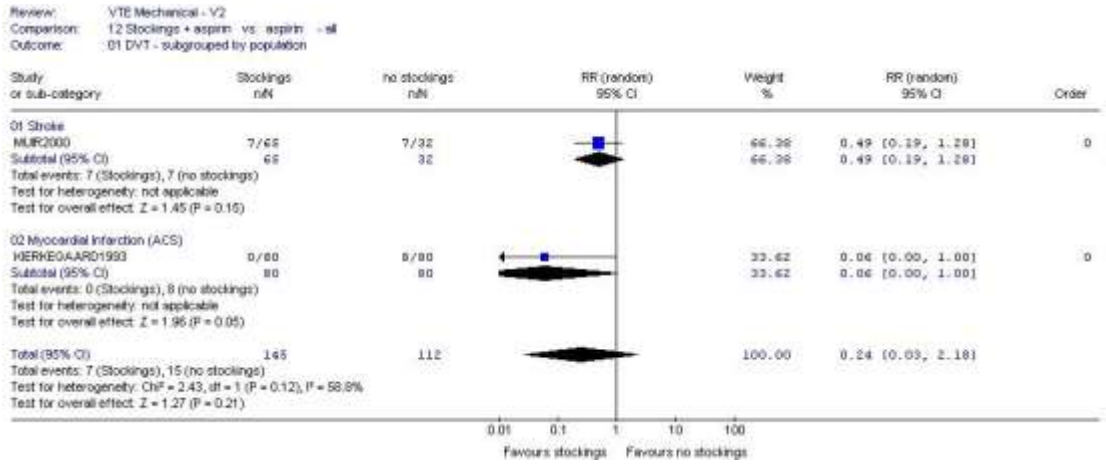


Forest Plot 113. GCS + Fondaparinux vs Fondaparinux – Major Bleeding

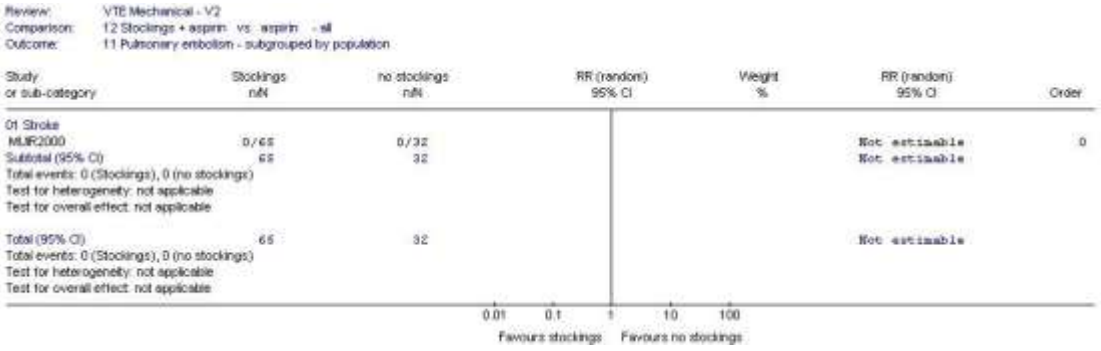


GCS + Aspirin vs Aspirin

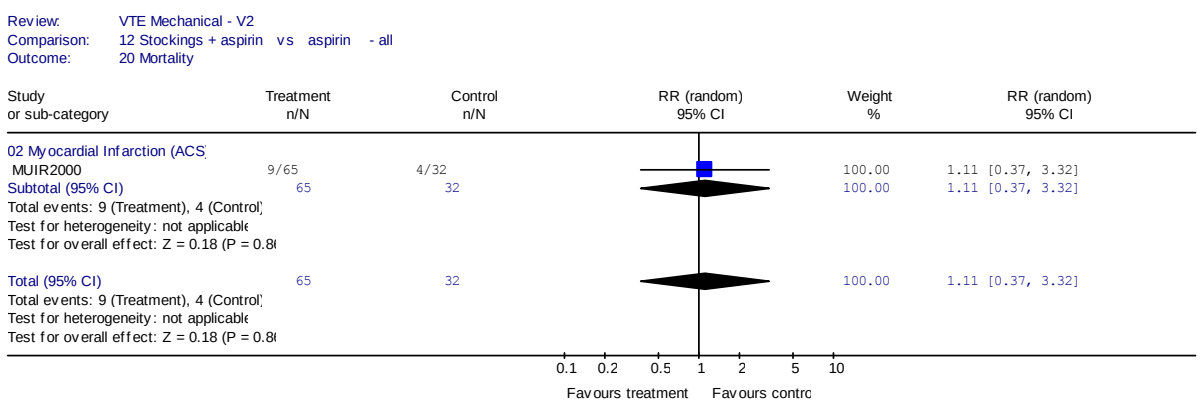
Forest Plot 114. GCS + Aspirin vs Aspirin - DVT



Forest Plot 115. GCS + Aspirin vs Aspirin – Pulmonary Embolism

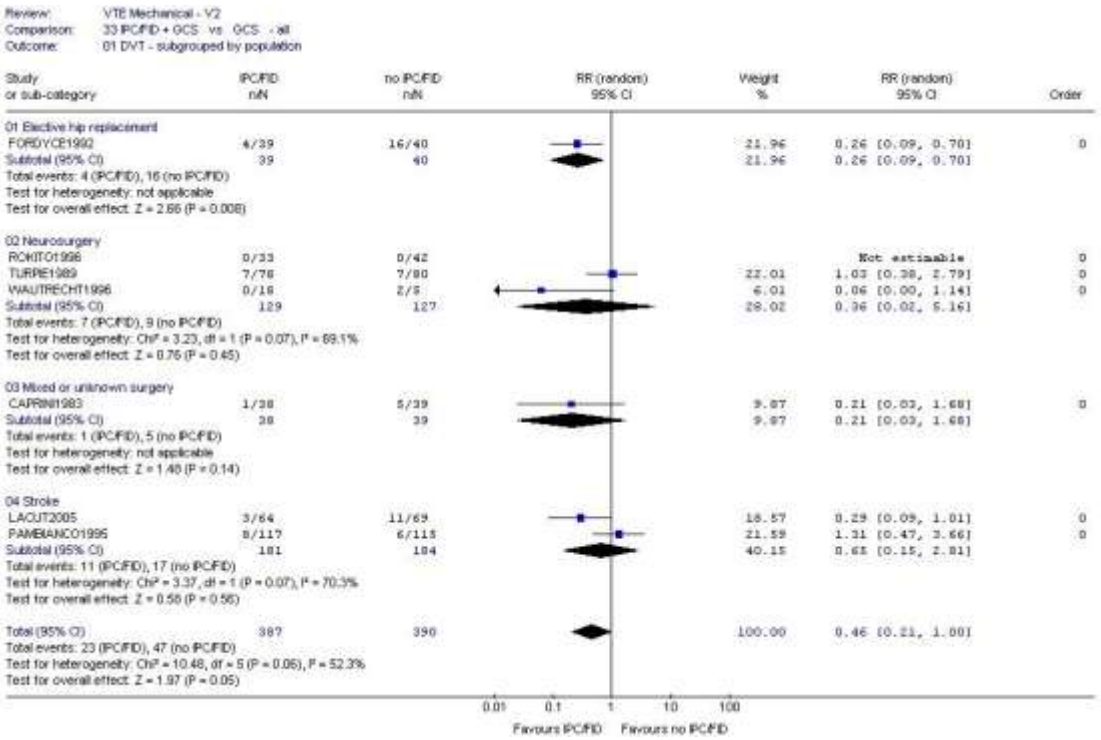


Forest Plot 116. GCS + Aspirin vs Aspirin – Mortality

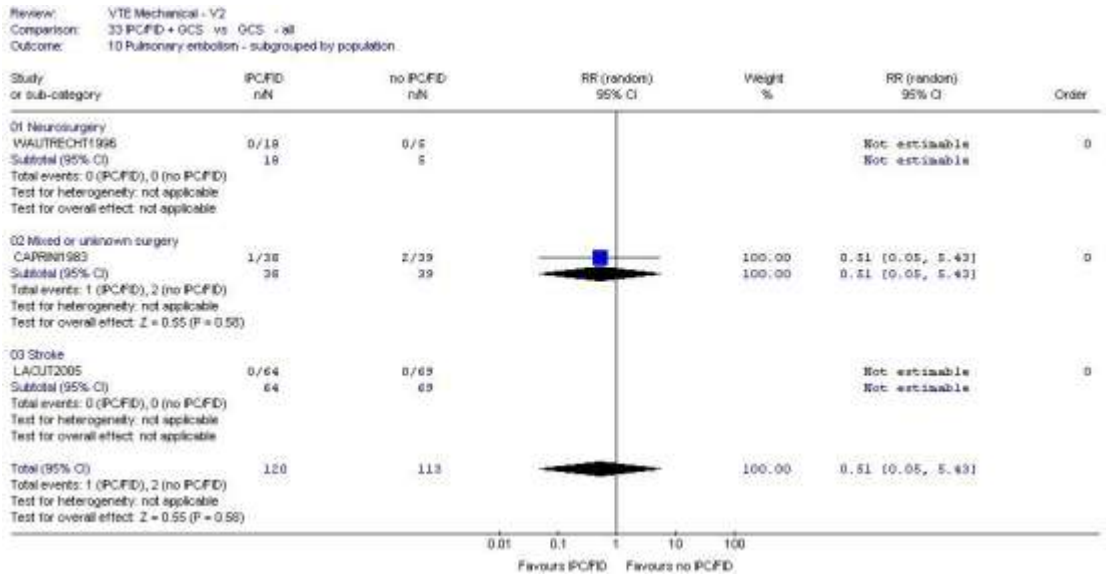


Intermittent Pneumatic Compression Devices or FID (IPCD/FID) plus GCS vs GCS

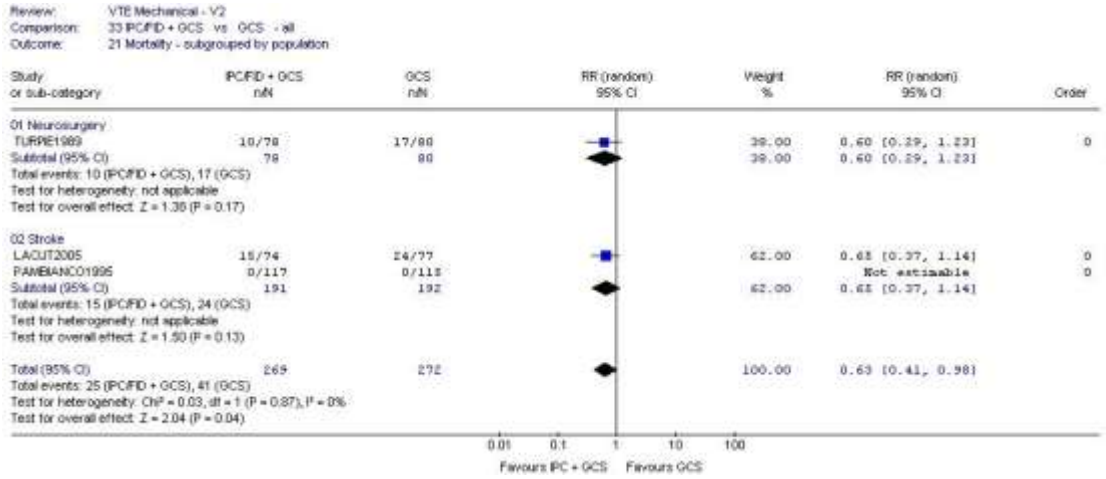
Forest Plot 117. IPCD/FID + GCS vs GCS - DVT



Forest Plot 118. IPCD/FID + GCS vs GCS - Pulmonary Embolism

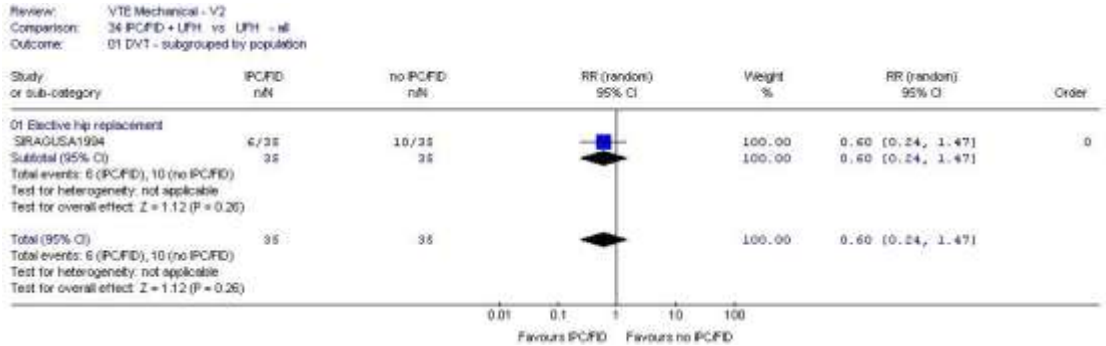


Forest Plot 119. IPCD/FID + GCS vs GCS - Mortality

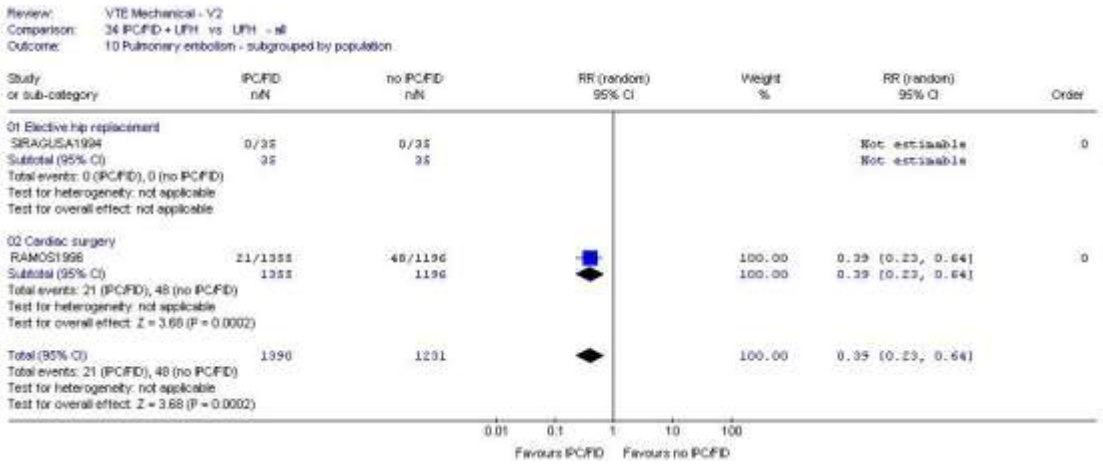


Intermittent Pneumatic Compression Devices or FID (IPCD/FID) + UFH vs UFH

Forest Plot 120. IPCD/FID + UFH vs UFH - DVT

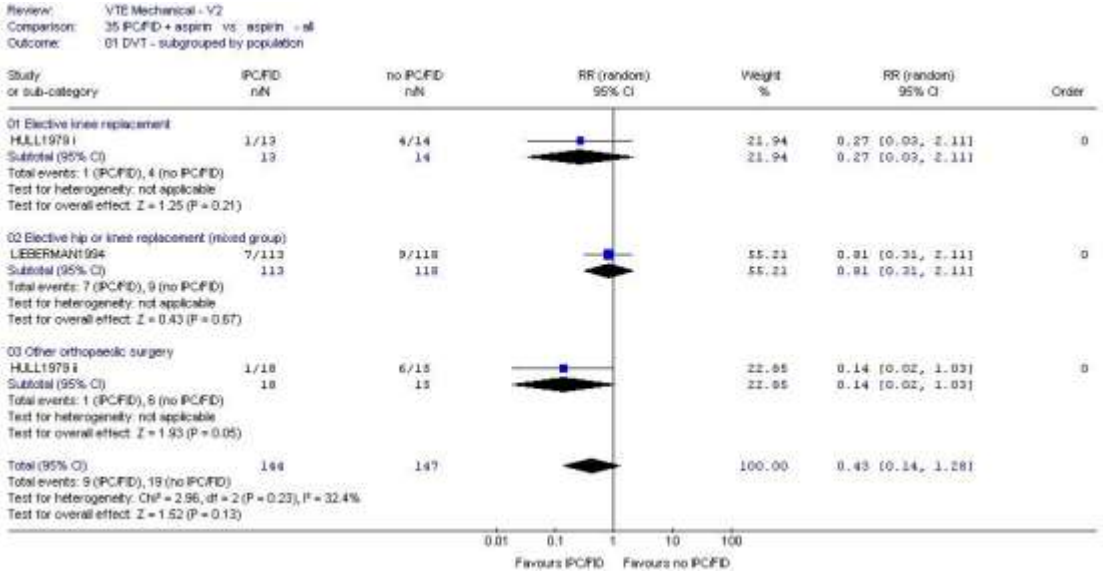


Forest Plot 121. IPCD/FID + UFH vs UFH - Pulmonary Embolism



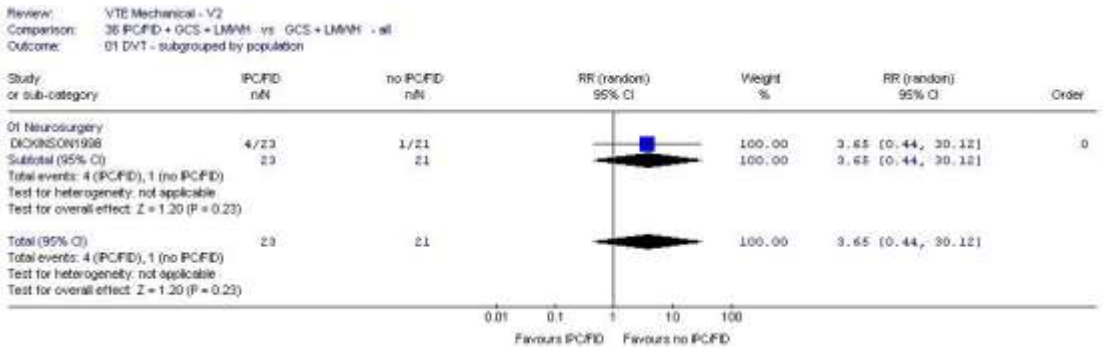
Intermittent Pneumatic Compression Devices or FID (IPCD/FID) + Aspirin vs Aspirin

Forest Plot 122. IPCD/FID + Aspirin vs Aspirin- DVT

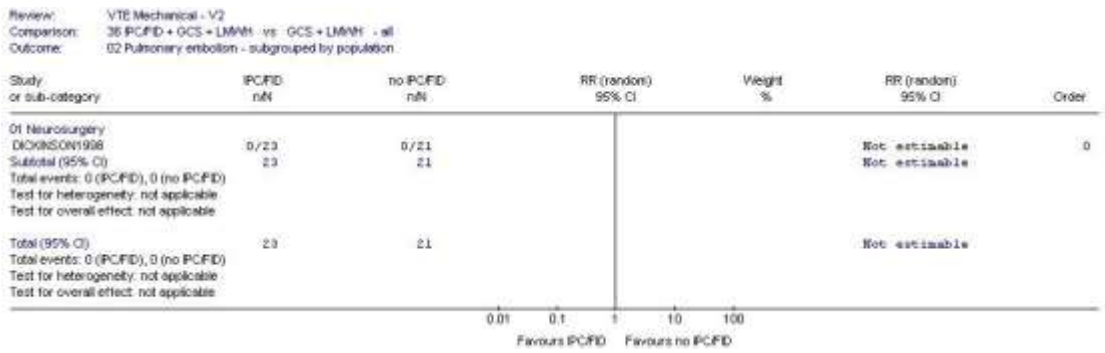


Intermittent Pneumatic Compression Devices or FID (IPCD/FID) + GCS + LMWH vs GCS + LMWH

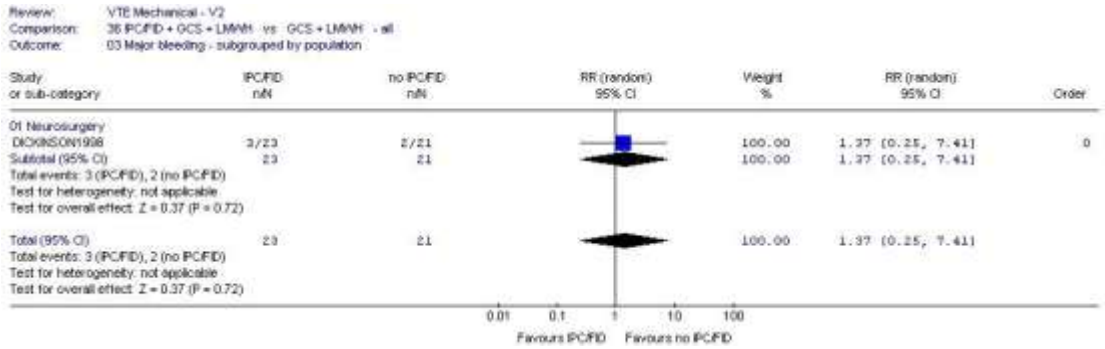
Forest Plot 123. IPCD/FID + GCS +LMWH vs GCS +LMWH - DVT



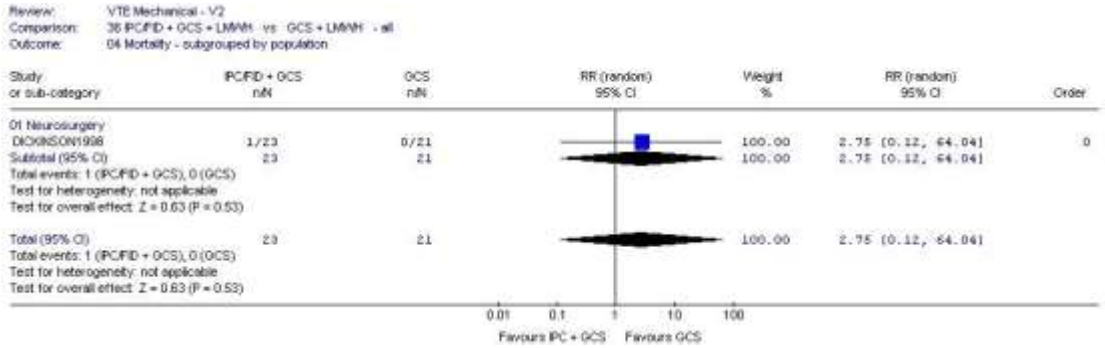
Forest Plot 124. IPCD/FID + GCS +LMWH vs GCS +LMWH - Pulmonary Embolism



Forest Plot 125. IPCD/FID + GCS +LMWH vs GCS +LMWH – Major Bleeding

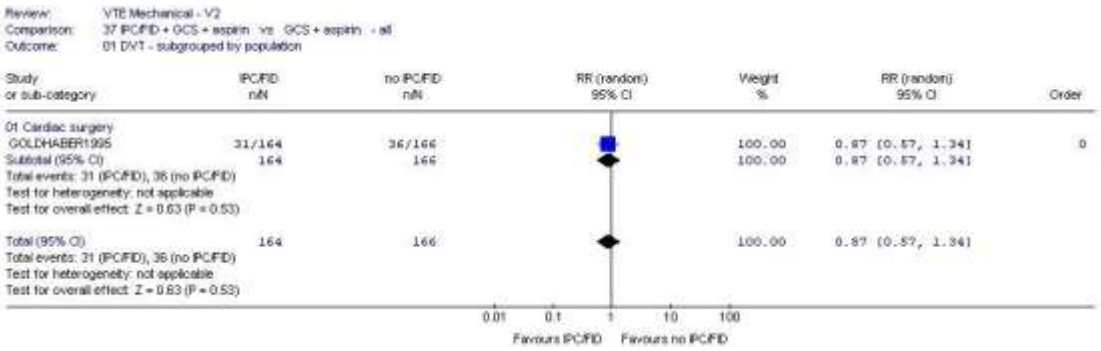


Forest Plot 126. IPCD/FID + GCS +LMWH vs GCS +LMWH – Mortality

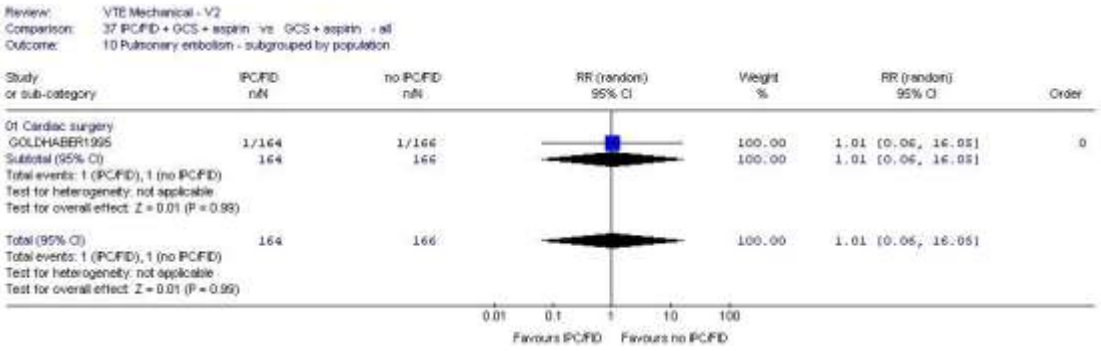


Intermittent Pneumatic Compression Devices or FID (IPCD/FID) + GCS + Aspirin vs GCS + Aspirin

Forest Plot 127. IPCD/FID + GCS + Aspirin vs GCS + Aspirin - DVT

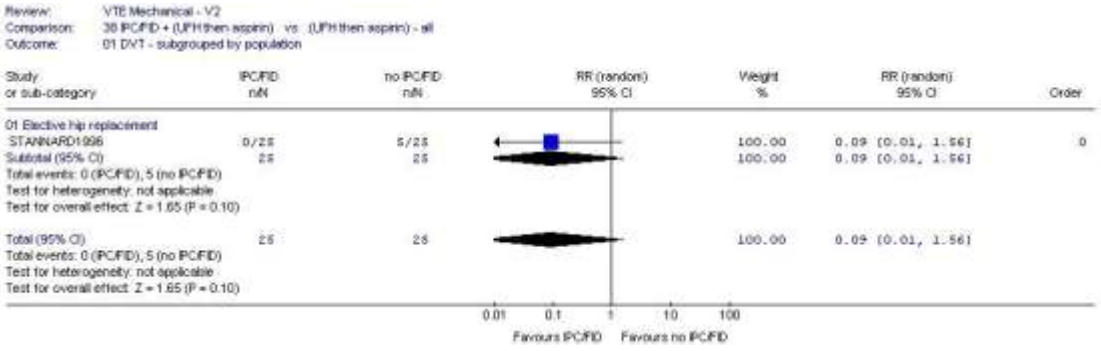


Forest Plot 128. IPCD/FID + GCS + Aspirin vs GCS + Aspirin - Pulmonary Embolism



Intermittent Pneumatic Compression Devices or FID (IPCD/FID) + UFH Then Aspirin vs UFH Then Aspirin

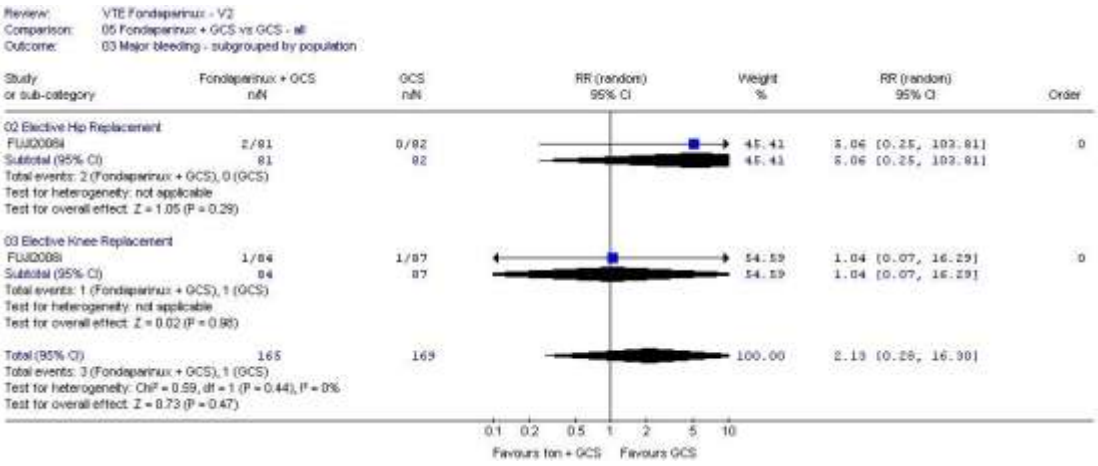
Forest Plot 129. IPCD/FID + UFH Then Aspirin vs UFH Then Aspirin - DVT



Pharmacological Adjuvant Studies

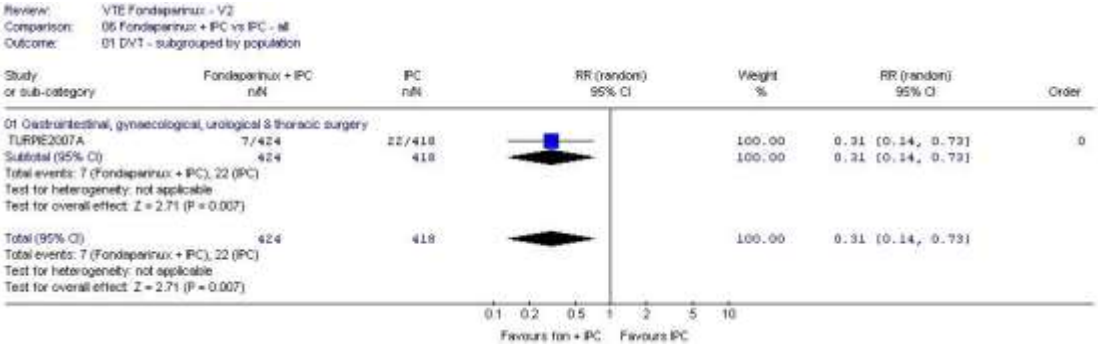
Fondaparinux + GCS vs GCS

Forest Plot 130. Fondaparinux + GCS vs GCS – major bleeding

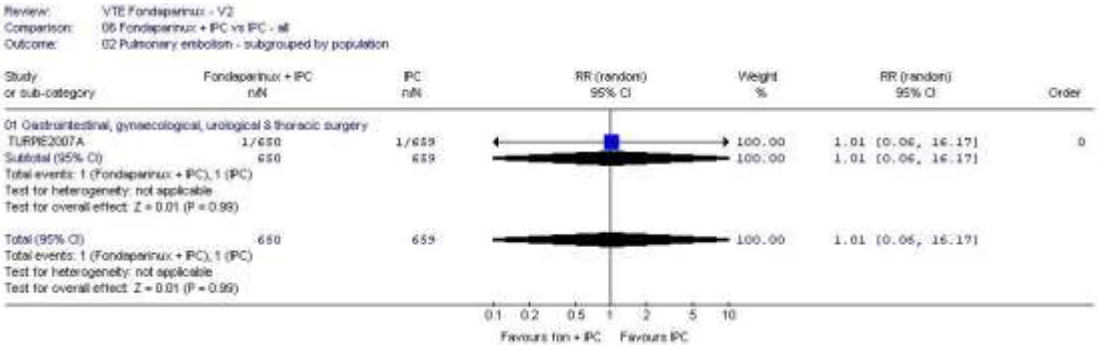


Fondaparinux + IPCD vs IPCD

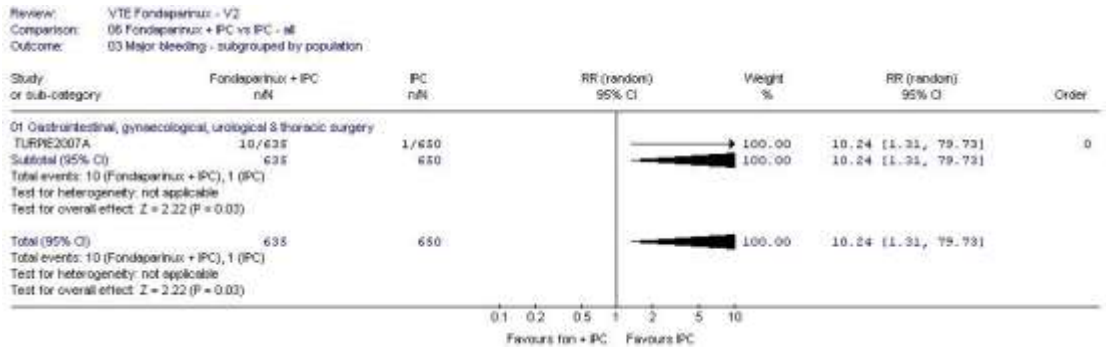
Forest Plot 131. Fondaparinux + IPCD vs IPCD – DVT



Forest Plot 132. Fondaparinux + IPCD vs IPCD – pulmonary embolism

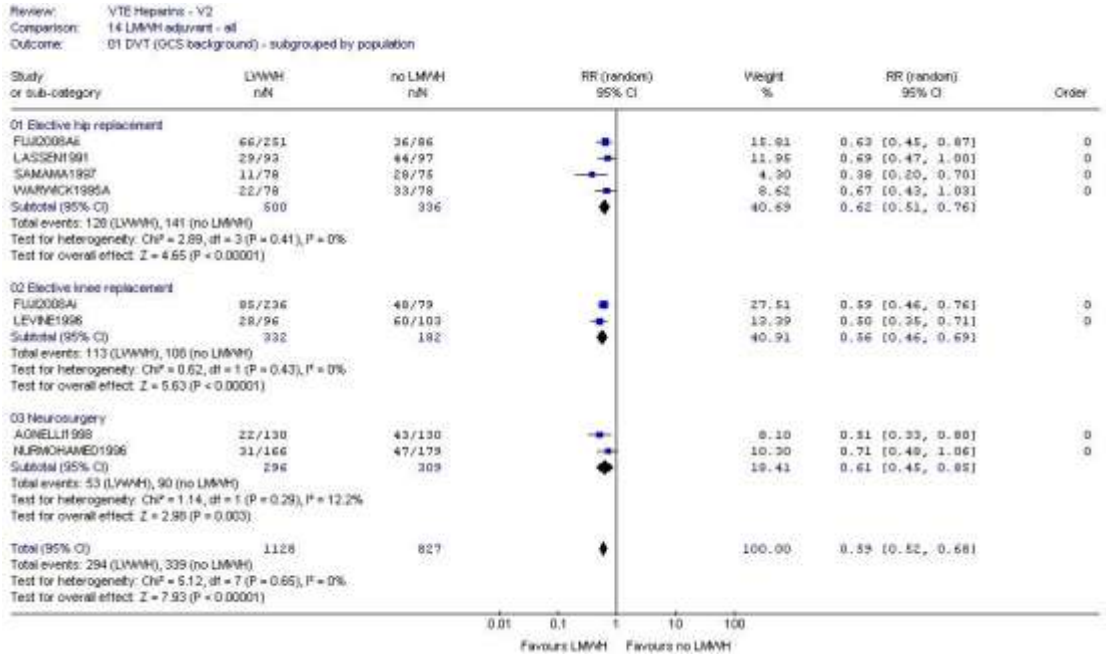


Forest Plot 133. Fondaparinux + IPCD vs IPCD – major bleeding

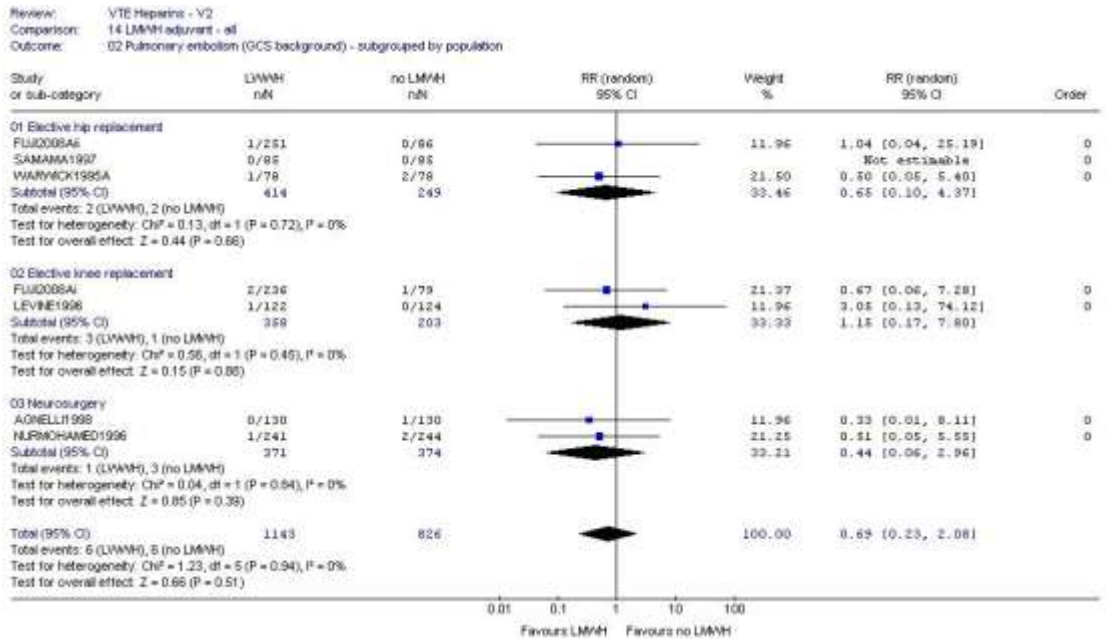


LMWH + GCS vs GCS

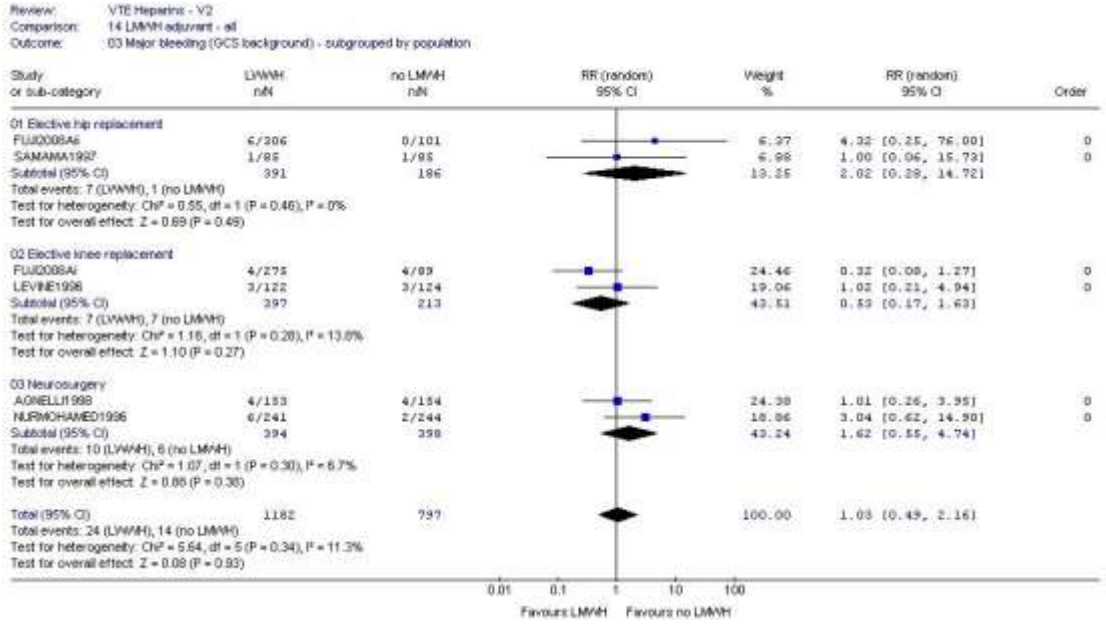
Forest Plot 134. LMWH + GCS vs GCS – DVT



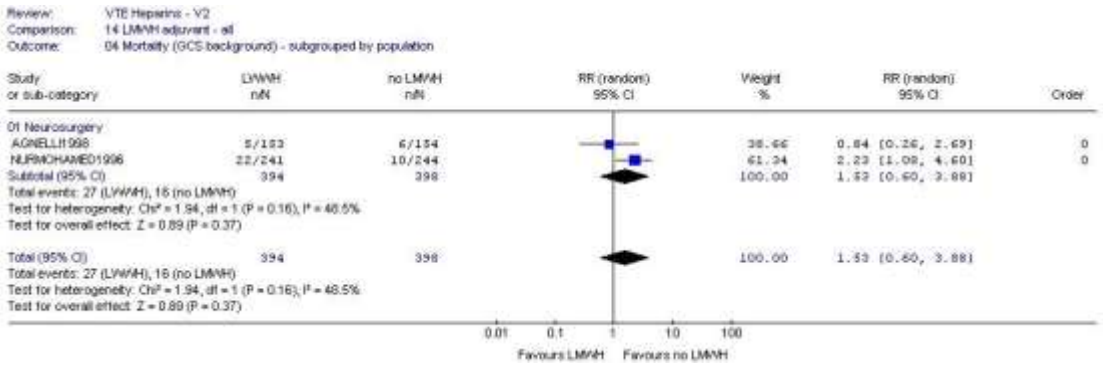
Forest Plot 135. LMWH + GCS vs GCS – Pulmonary Embolism



Forest Plot 136. LMWH + GCS vs GCS – Major Bleeding

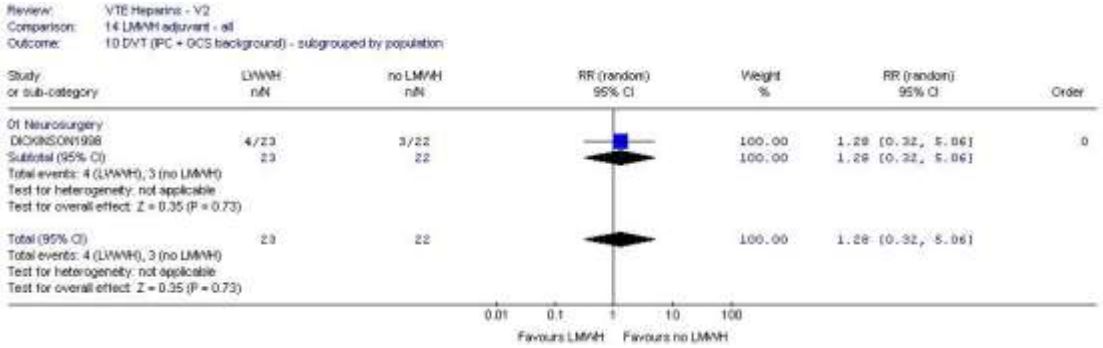


Forest Plot 137. LMWH + GCS vs GCS – Mortality

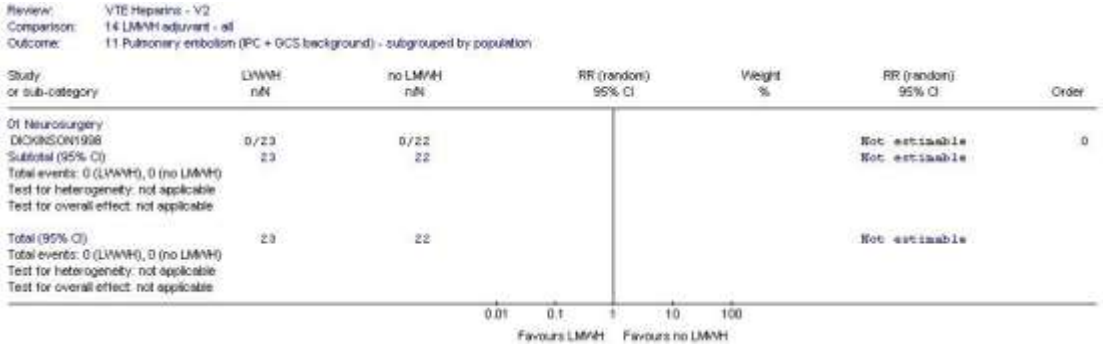


LMWH + IPCD + GCS vs IPCD + GCS

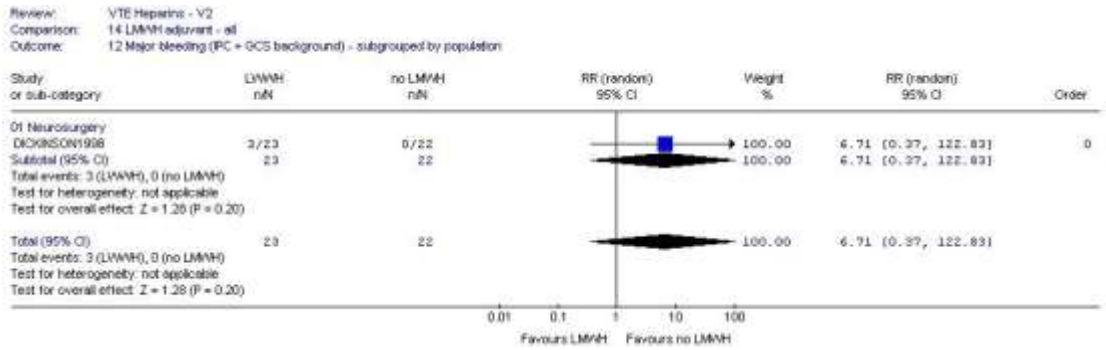
Forest Plot 138. LMWH + IPCD + GCS vs IPCD + GCS – DVT



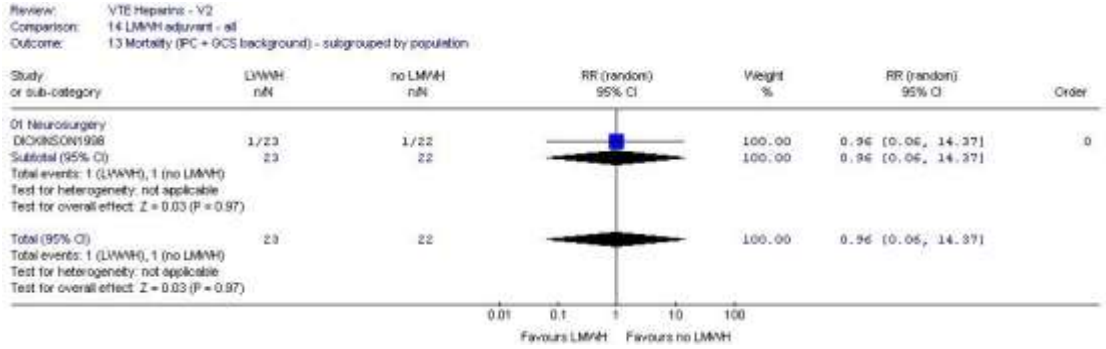
Forest Plot 139. LMWH + IPCD + GCS vs IPCD + GCS – Pulmonary Embolism



Forest Plot 140. LMWH + IPCD + GCS vs IPCD + GCS – Major Bleeding

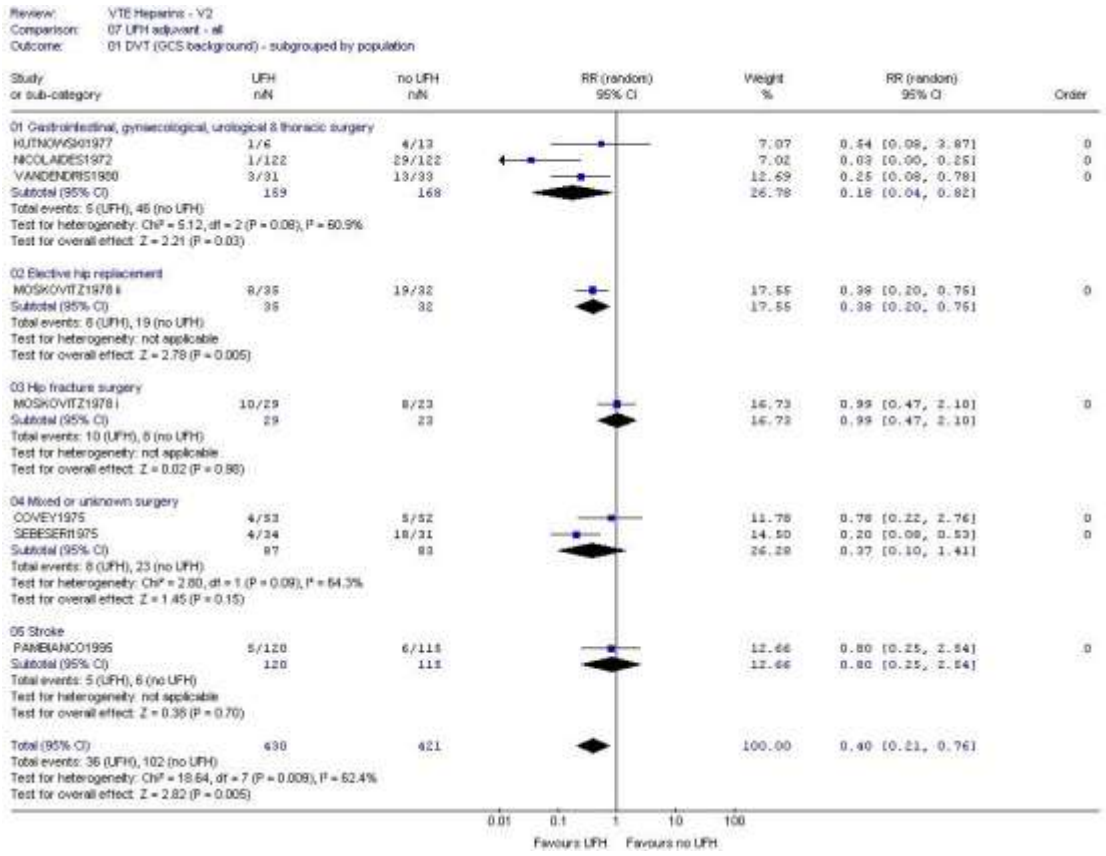


Forest Plot 141. LMWH + IPCD + GCS vs IPCD + GCS – Mortality

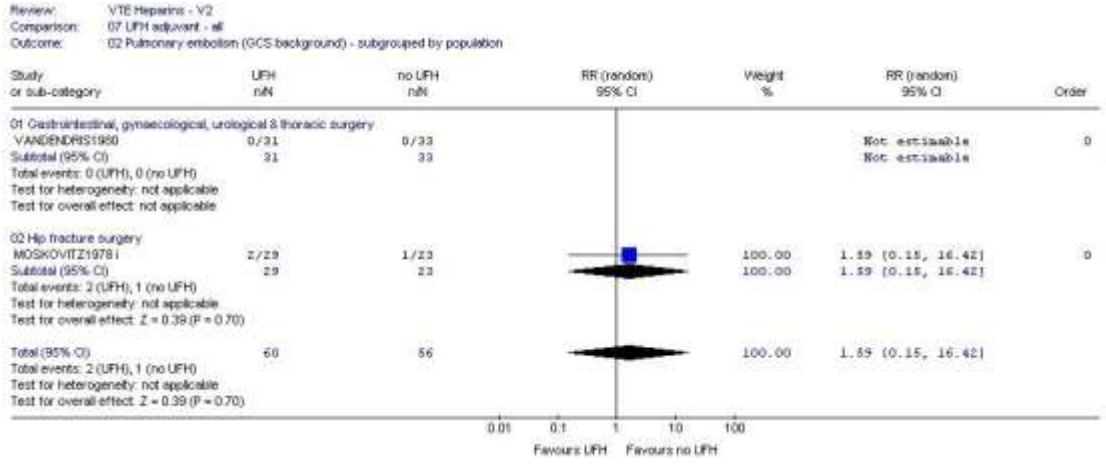


UFH + GCS vs GCS

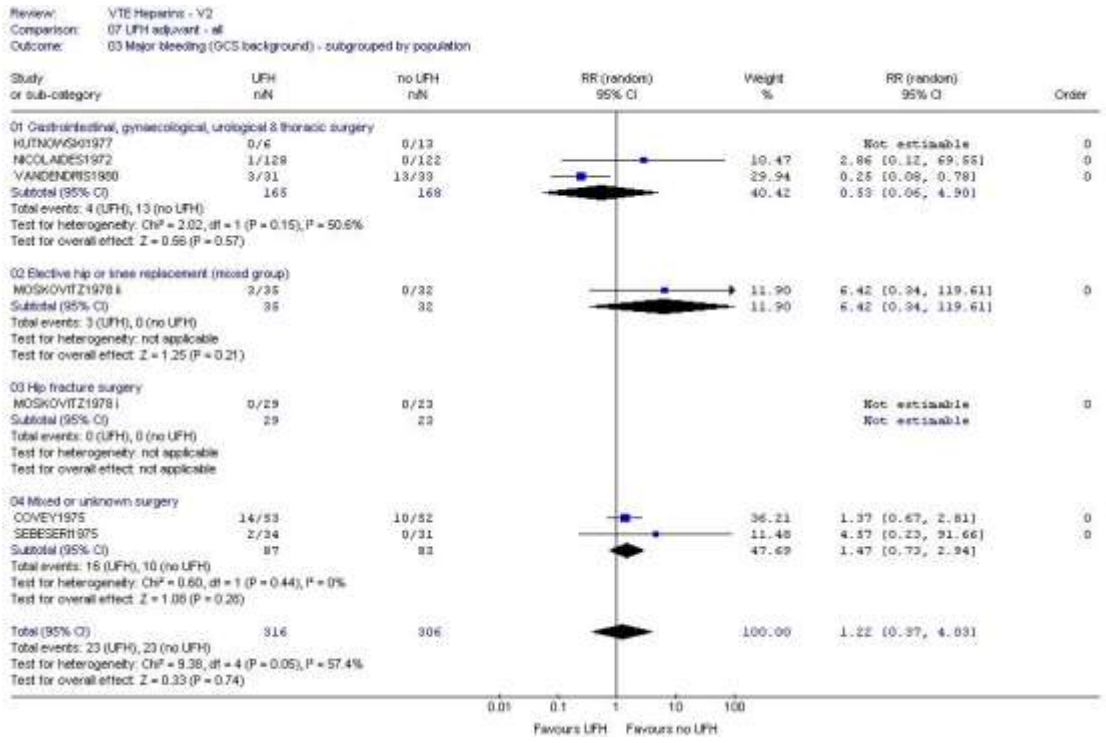
Forest Plot 142. UFH + GCS vs GCS – DVT



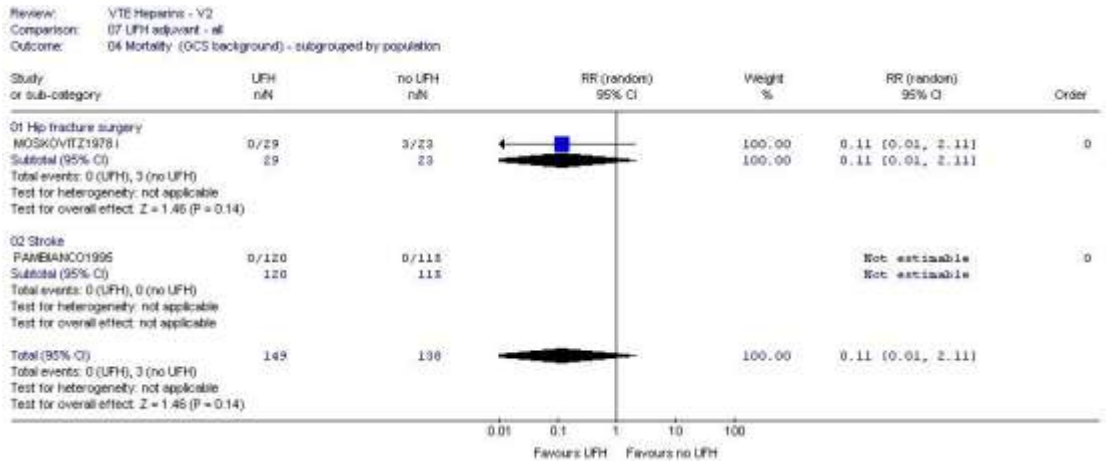
Forest Plot 143. UFH + GCS vs GCS – Pulmonary Embolism



Forest Plot 144. UFH + GCS vs GCS – Major Bleeding

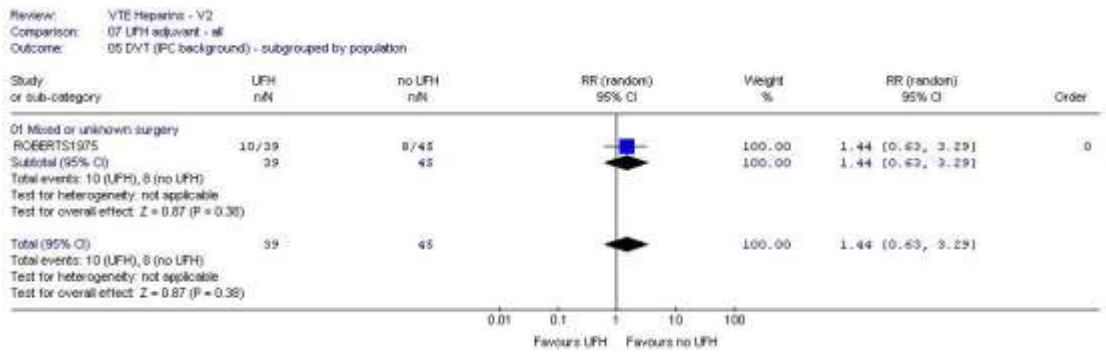


Forest Plot 145. UFH + GCS vs GCS – Mortality



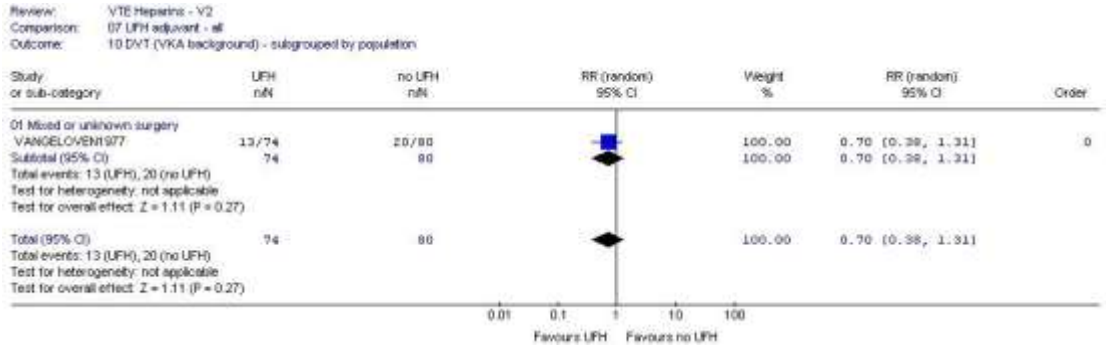
UFH + IPCD vs IPCD

Forest Plot 146. UFH + IPCD vs IPCD – DVT

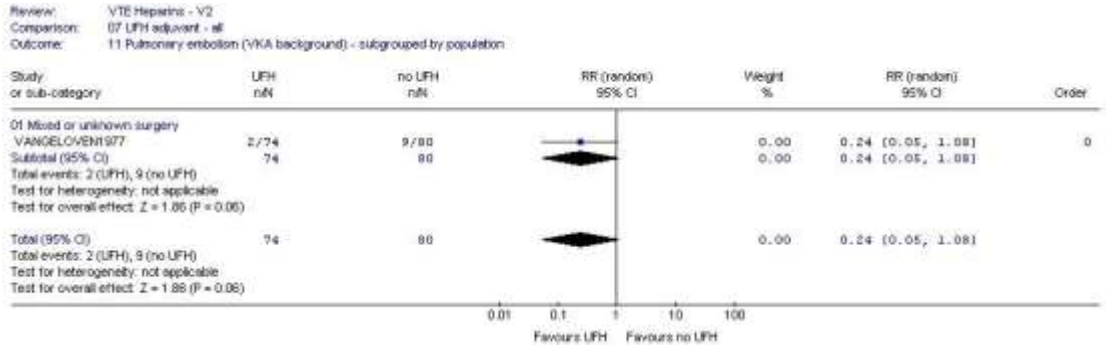


UFH + VKA vs VKA

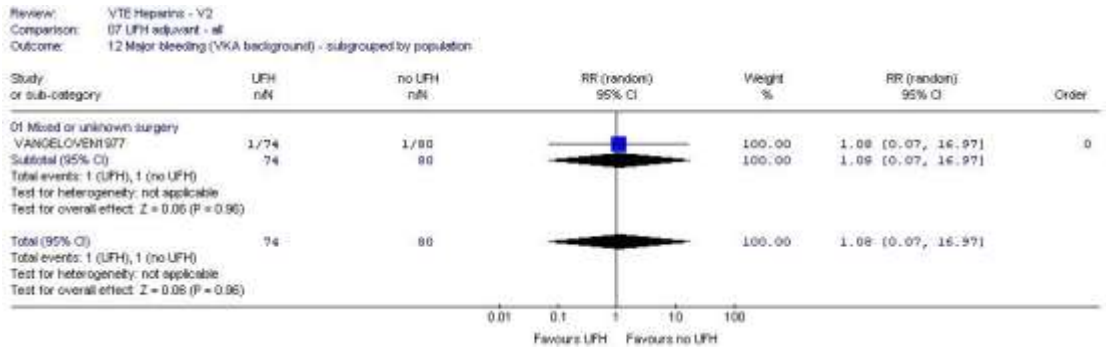
Forest Plot 147. UFH + VKA vs VKA – DVT



Forest Plot 148. UFH + VKA vs VKA – Pulmonary Embolism

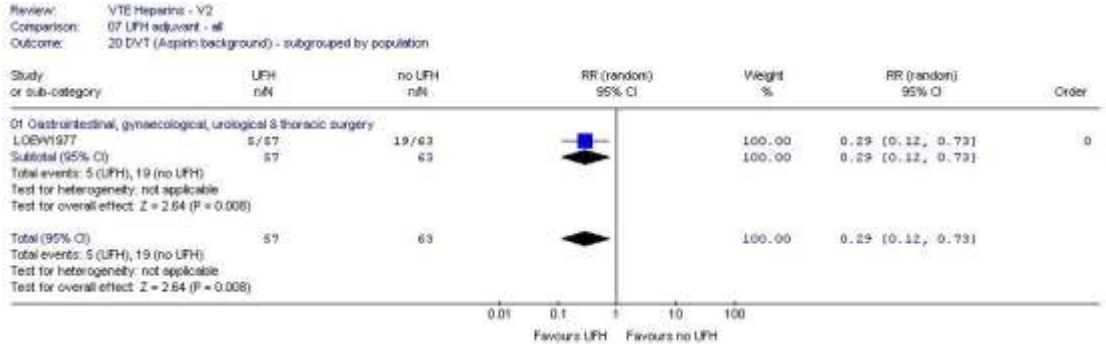


Forest Plot 149. UFH + VKA vs VKA – Major Bleeding

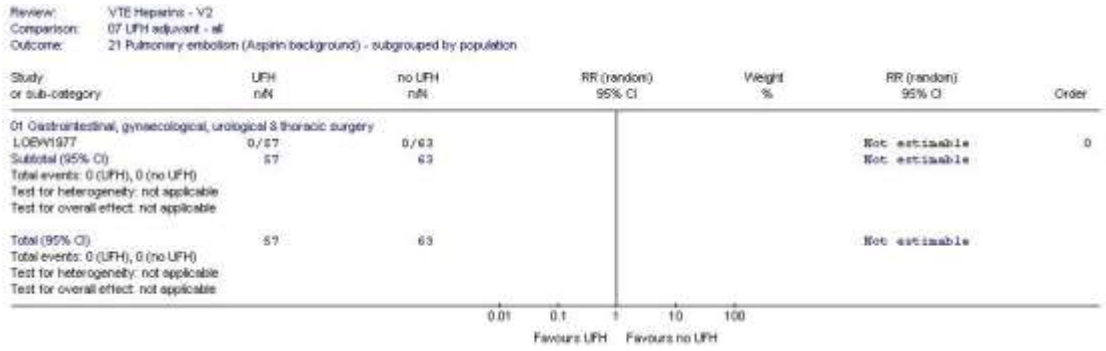


UFH + Aspirin vs Aspirin

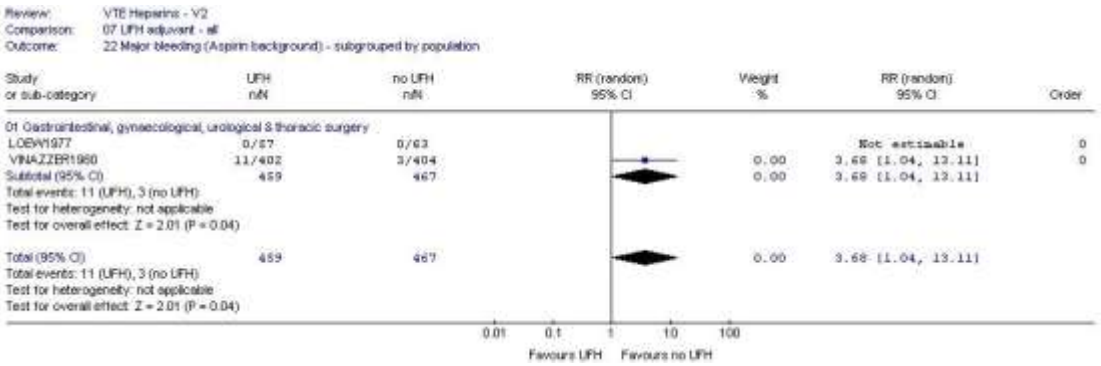
Forest Plot 150. UFH + Aspirin vs Aspirin – DVT



Forest Plot 151. UFH + Aspirin vs Aspirin – Pulmonary Embolism

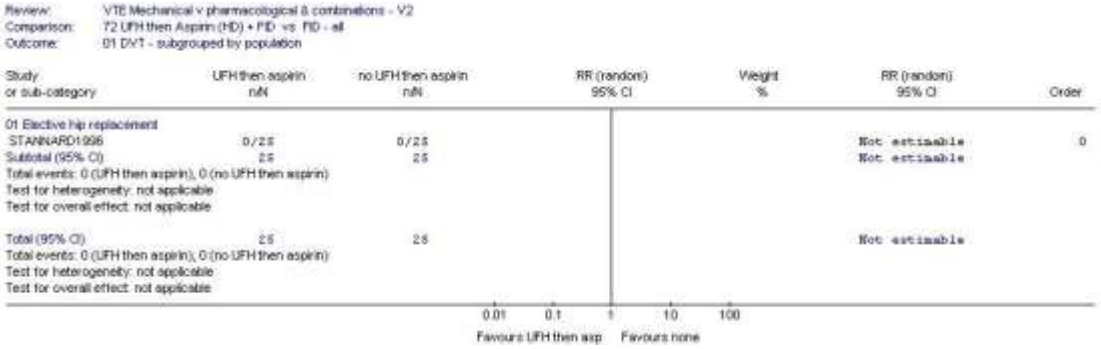


Forest Plot 152. UFH + Aspirin vs Aspirin – Major Bleeding

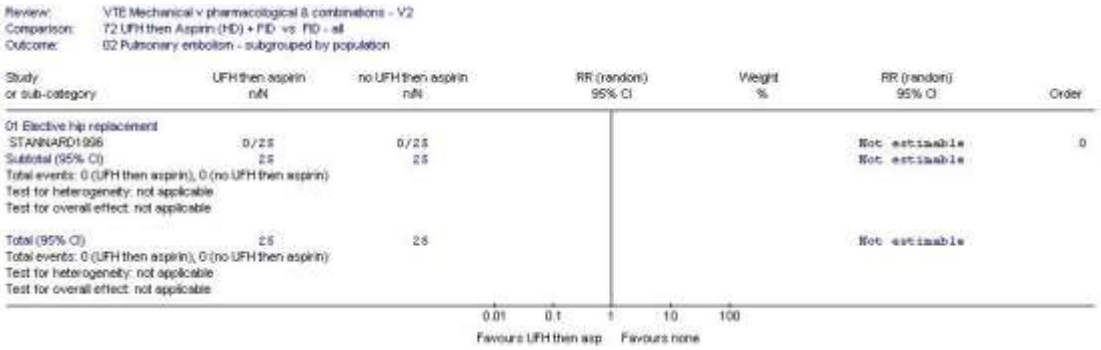


UFH then Aspirin + IPCD/FID vs IPCD/FID

Forest Plot 153. UFH then Aspirin + IPCD/FID vs IPCD/FID – DVT

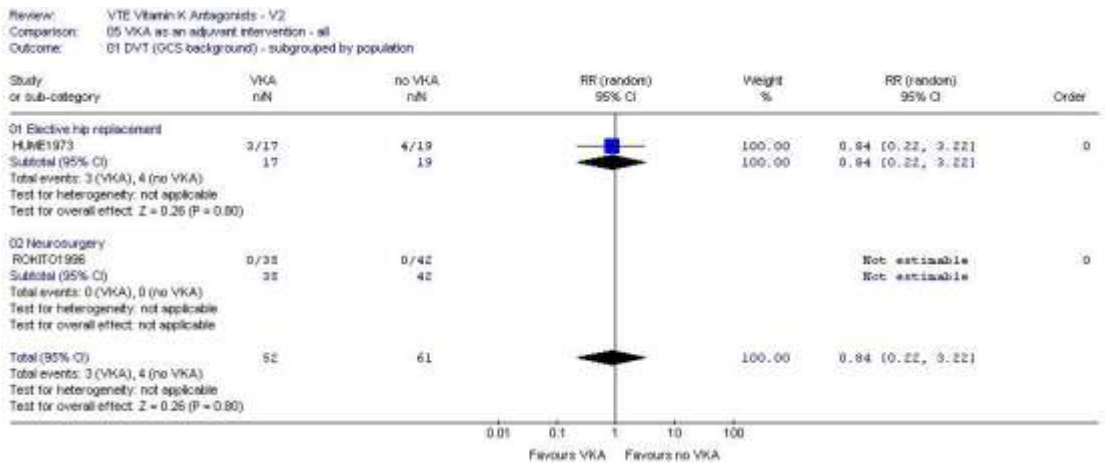


Forest Plot 154. UFH then Aspirin + IPCD/FID vs IPCD/FID – Pulmonary Embolism

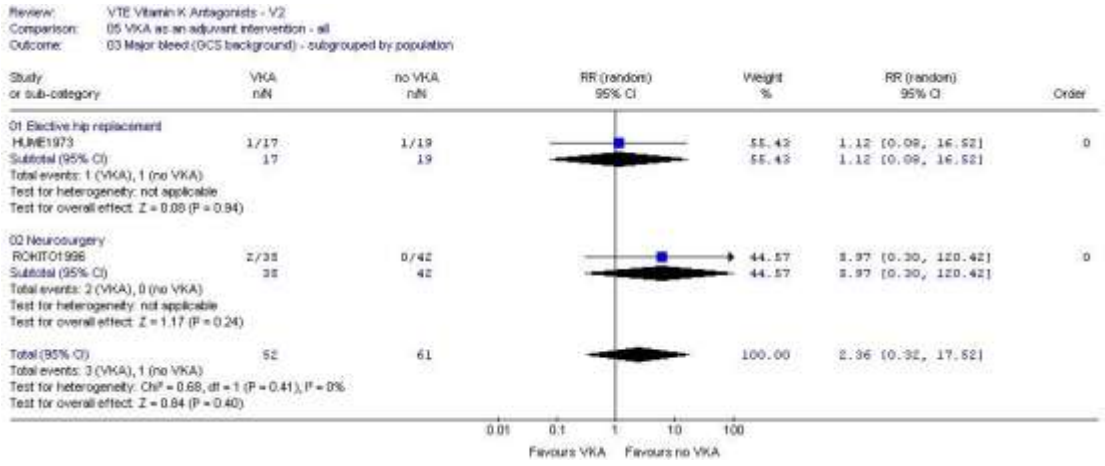


VKA + GCS vs GCS

Forest Plot 155. VKA + GCS vs GCS – DVT

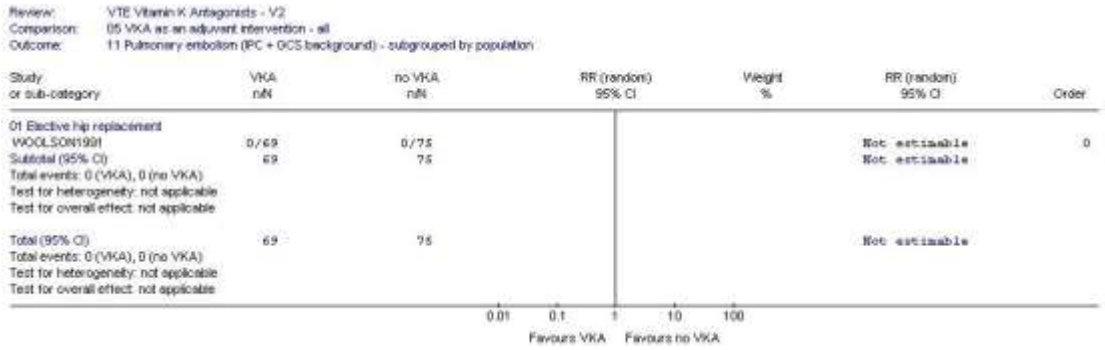


Forest Plot 156. VKA + GCS vs GCS – Major Bleeding



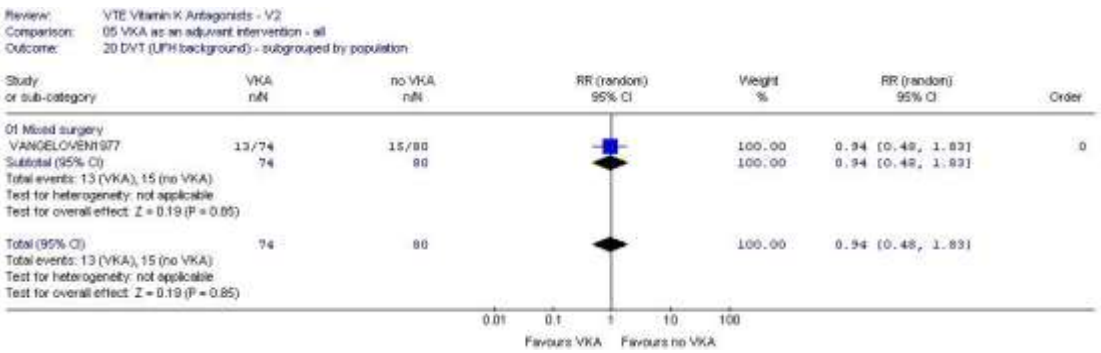
VKA + IPCD + GCS vs IPCD + GCS

Forest Plot 157. VKA +IPC + GCS vs +IPC + GCS – Pulmonary Embolism

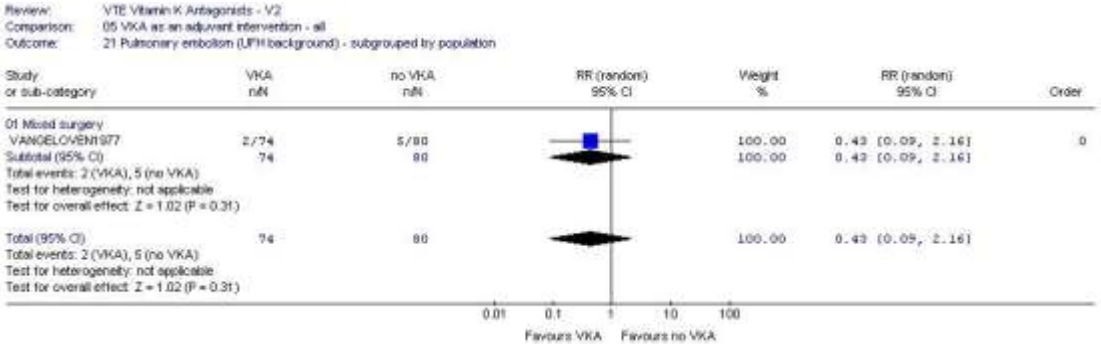


VKA + UFH vs UFH

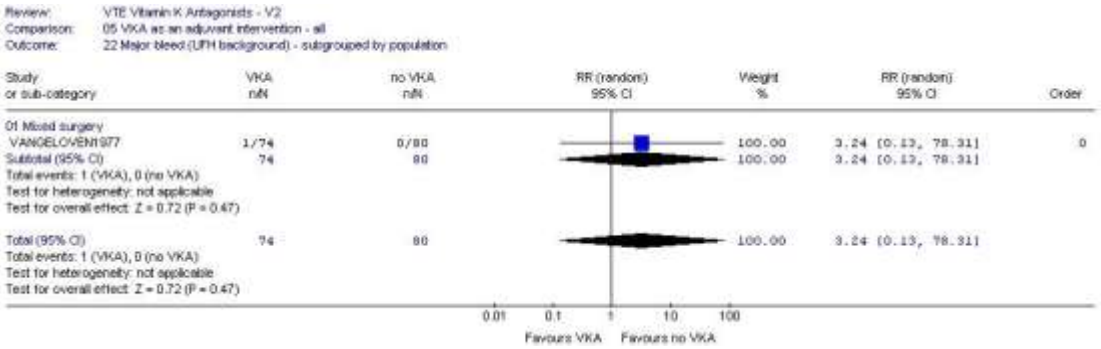
Forest Plot 158. VKA + UFH vs UFH – DVT



Forest Plot 159. VKA + UFH vs UFH – Pulmonary Embolism

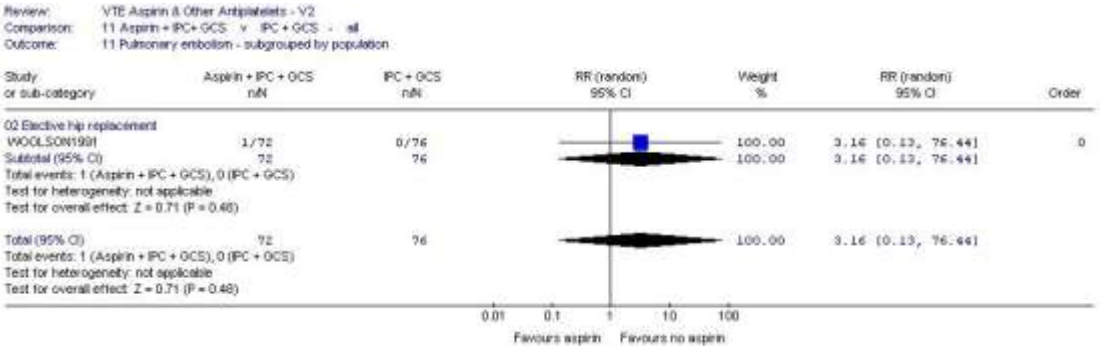


Forest Plot 160. VKA + UFH vs UFH – Major Bleeding



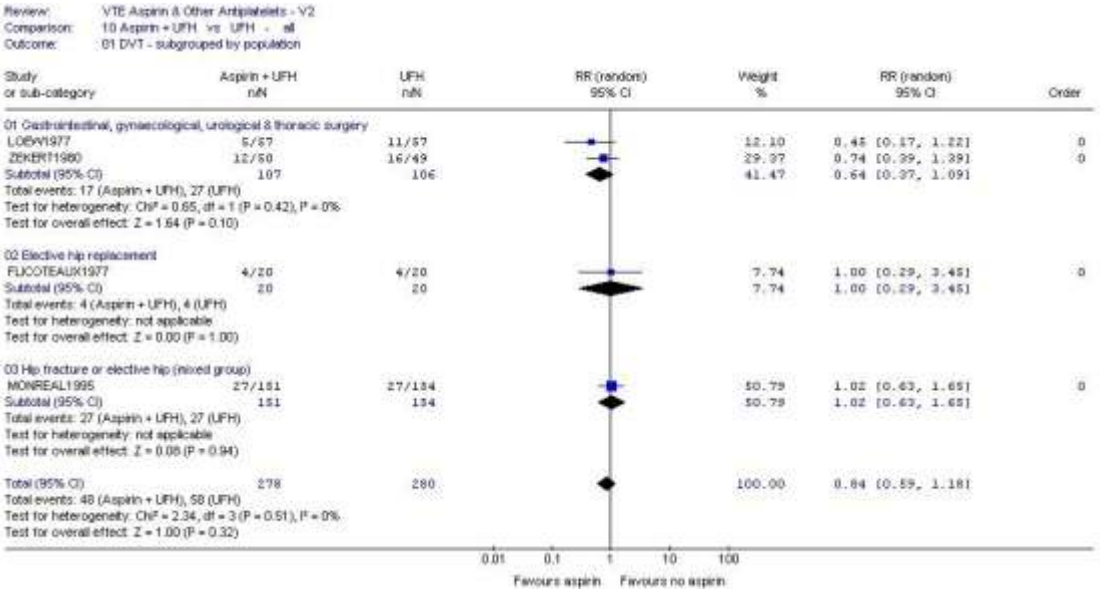
Aspirin + IPCD + GCS vs IPCD + GCS

Forest Plot 161. Aspirin + GCS vs GCS – Pulmonary Embolism

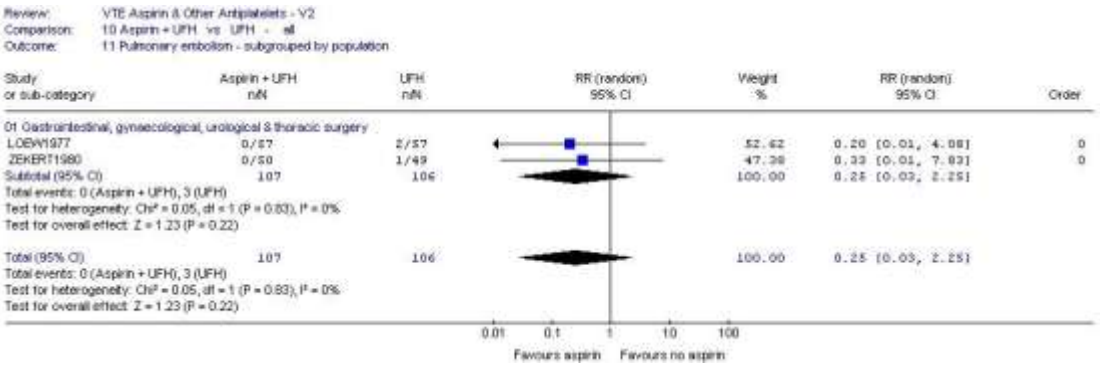


Aspirin + UFH vs UFH

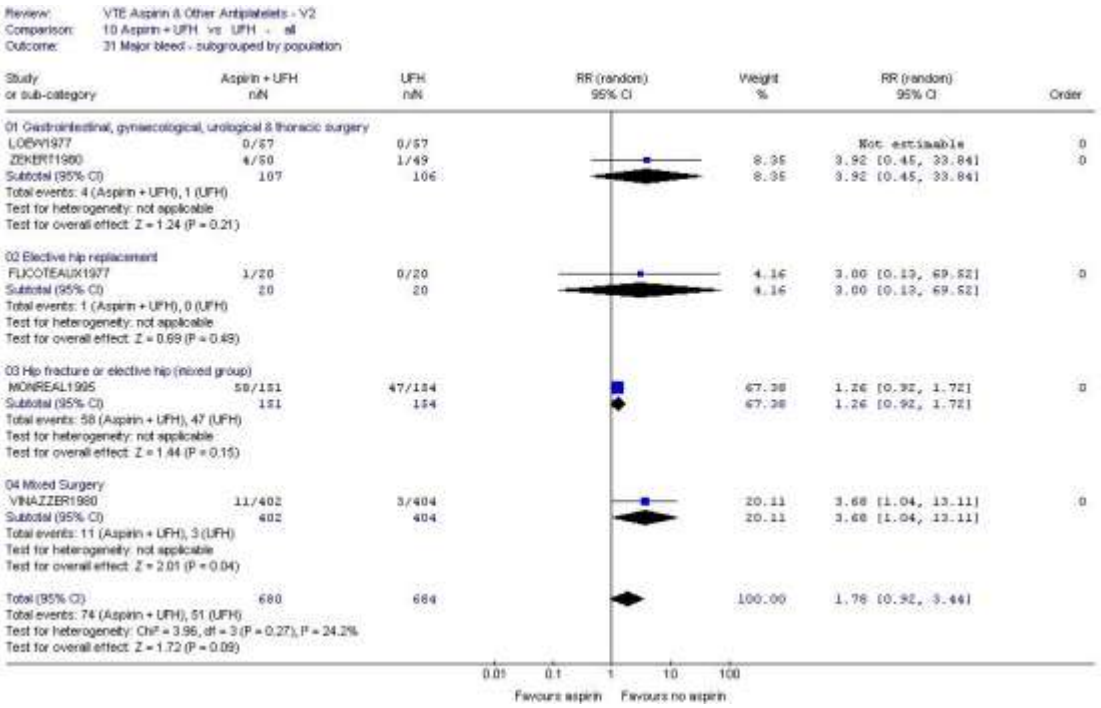
Forest Plot 162. Aspirin + UFH vs UFH - DVT



Forest Plot 163. Aspirin + UFH vs UFH – Pulmonary Embolism

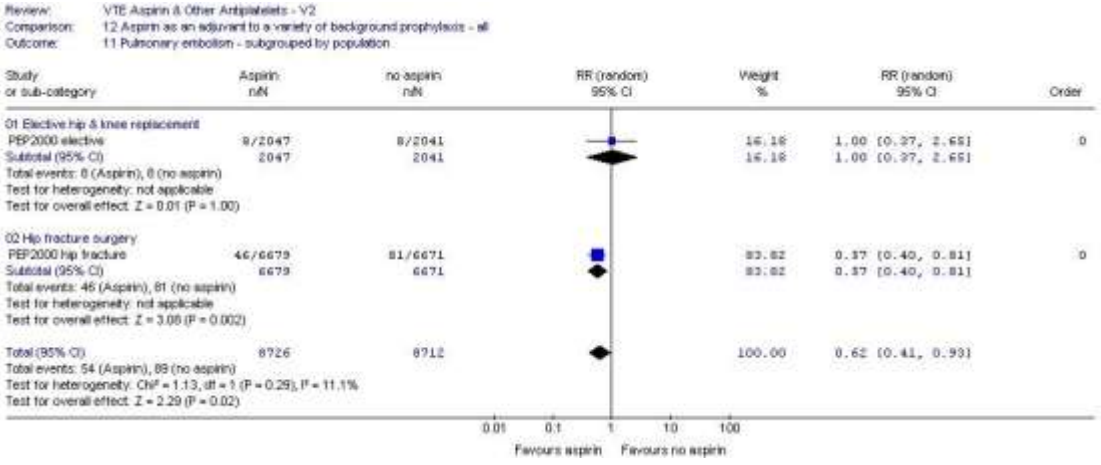


Forest Plot 164. Aspirin + UFH vs UFH – Major Bleeding

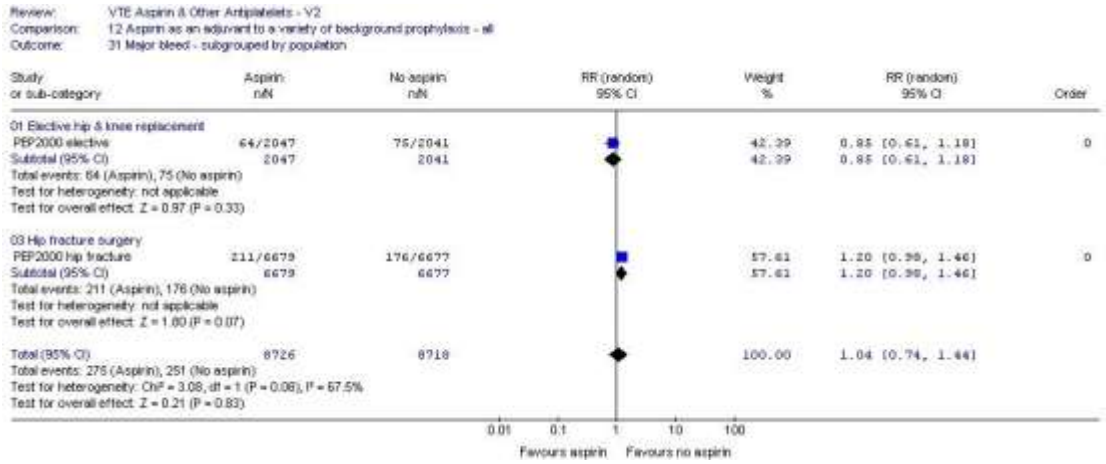


Aspirin As An Adjuvant To A Variety Of Background Prophylaxis

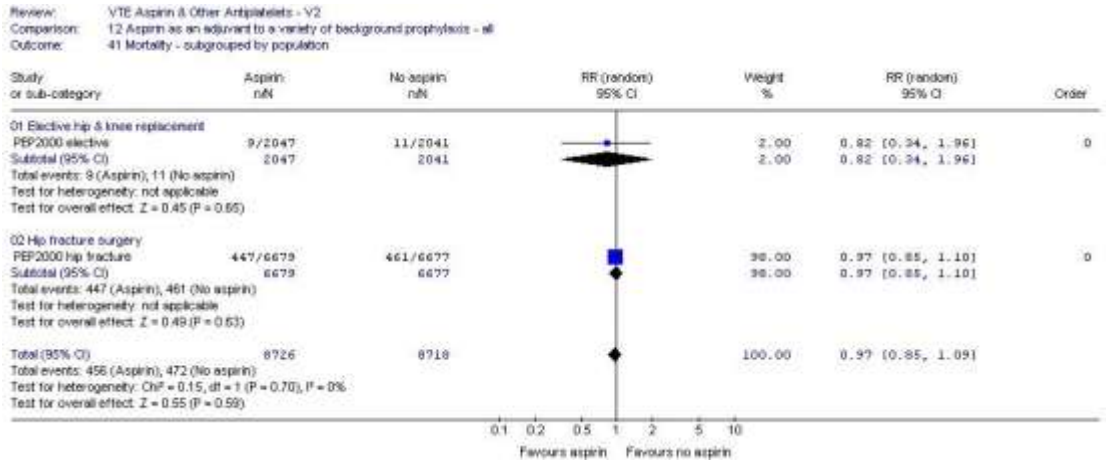
Forest Plot 165. Aspirin As An Adjuvant To A Variety Of Background Prophylaxis – Pulmonary Embolism



Forest Plot 166. Aspirin As An Adjuvant To A Variety Of Background Prophylaxis – Major Bleeding



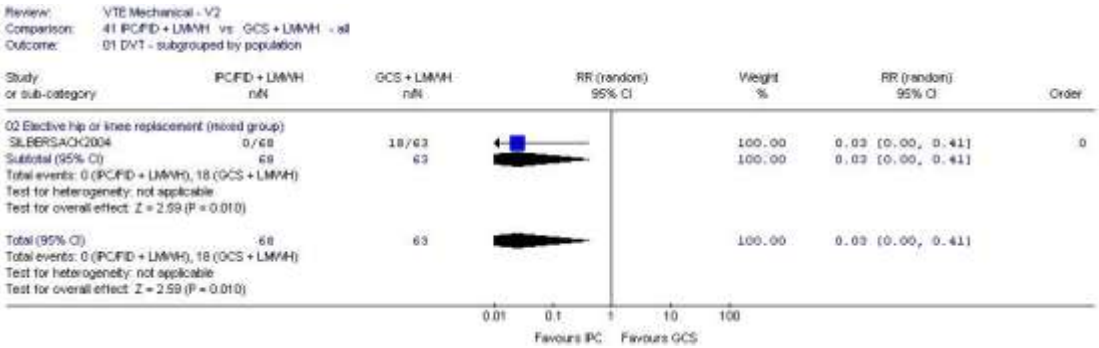
Forest Plot 167. Aspirin As An Adjuvant To A Variety Of Background Prophylaxis - Mortality



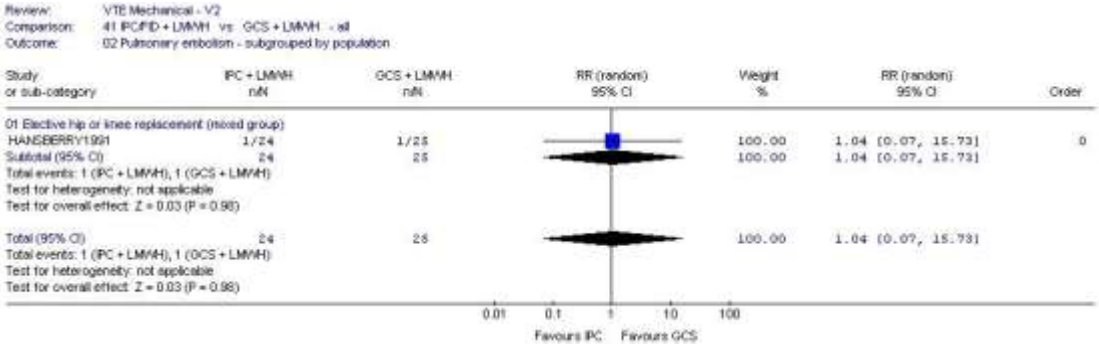
Two or More Prophylaxis vs Two or More Prophylaxis

IPCD/FID + LMWH vs GCS + LMWH

Forest Plot 168. IPCD/FID + LMWH vs GCS + LMWH – DVT

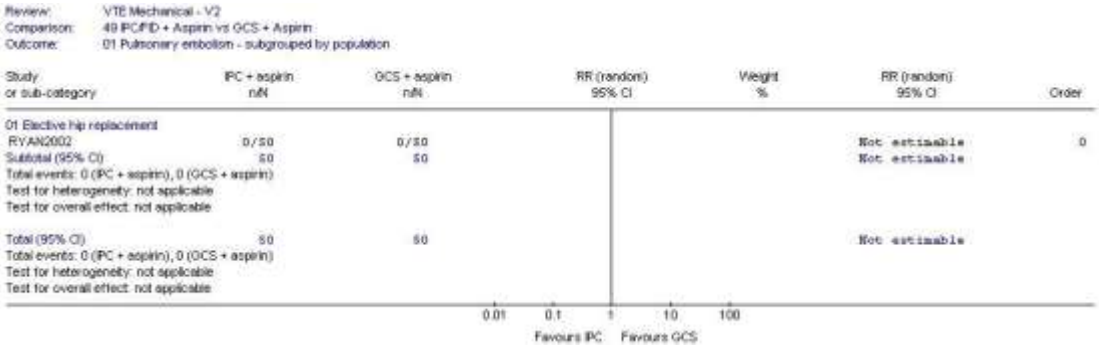


Forest Plot 169. IPCD/FID + LMWH vs GCS + LMWH – Pulmonary Embolism



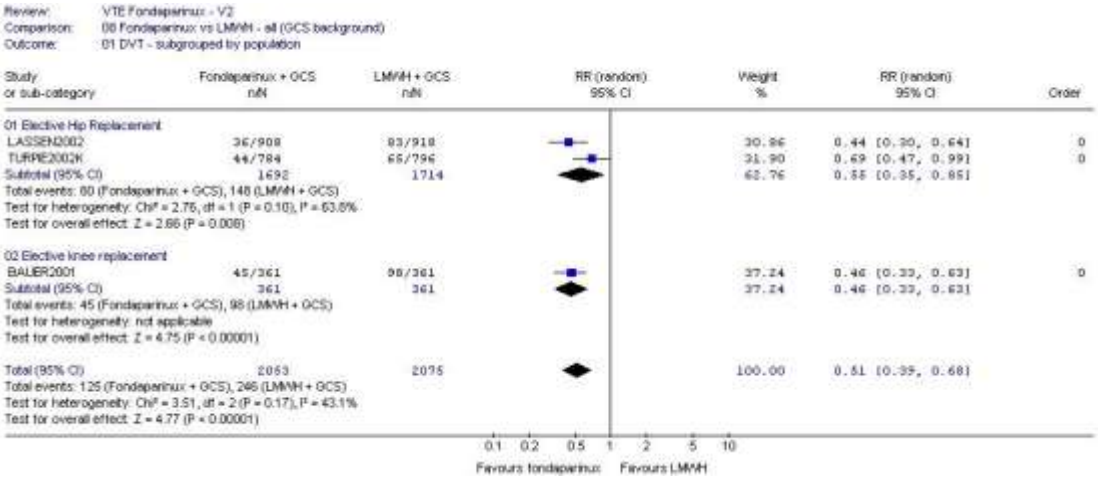
IPCD/FID + Aspirin vs GCS + Aspirin

Forest Plot 170. IPCD/FID + Aspirin vs GCS + Aspirin – Pulmonary Embolism

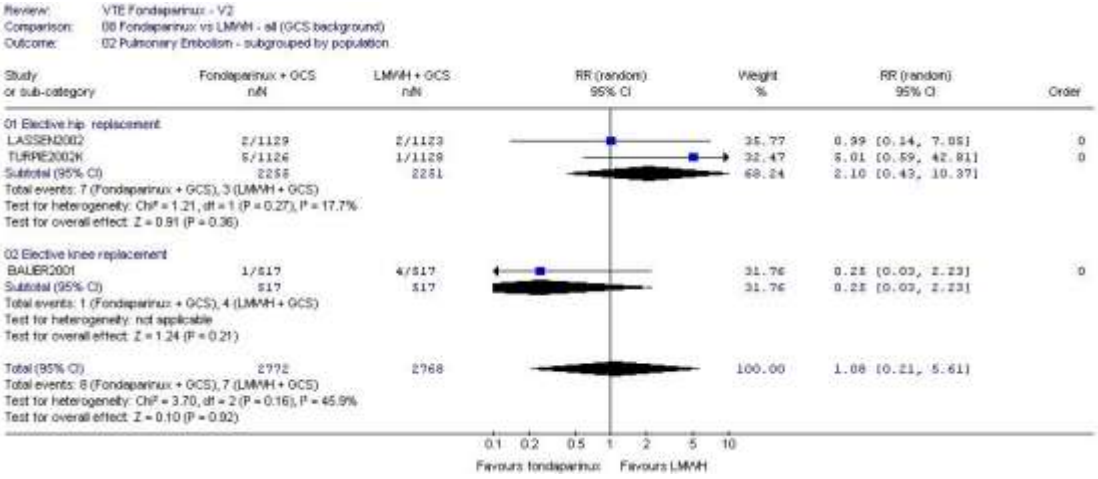


Fondaparinux + GCS vs LMWH + GCS

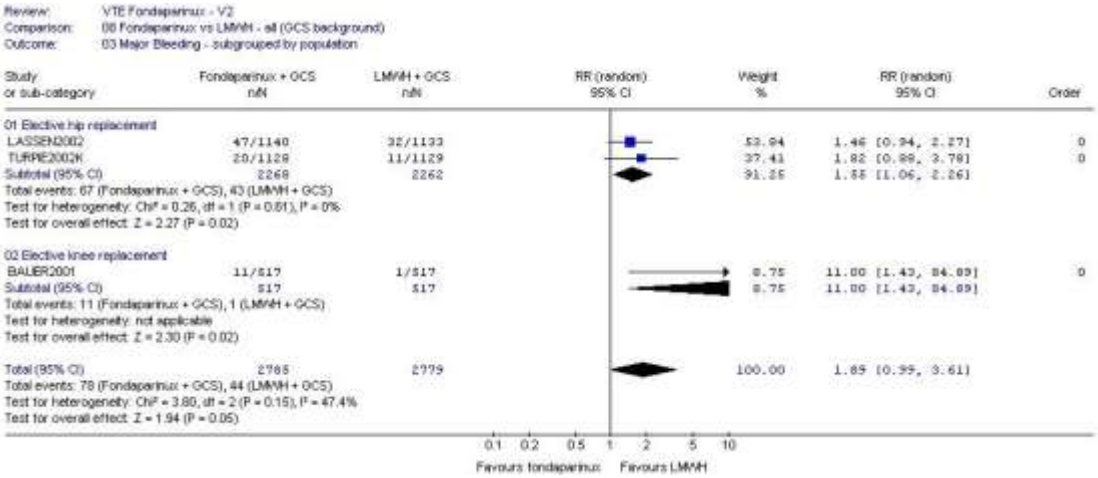
Forest Plot 171. Fondaparinux + GCS vs LMWH + GCS – DVT



Forest Plot 172. Fondaparinux + GCS vs LMWH + GCS – Pulmonary Embolism

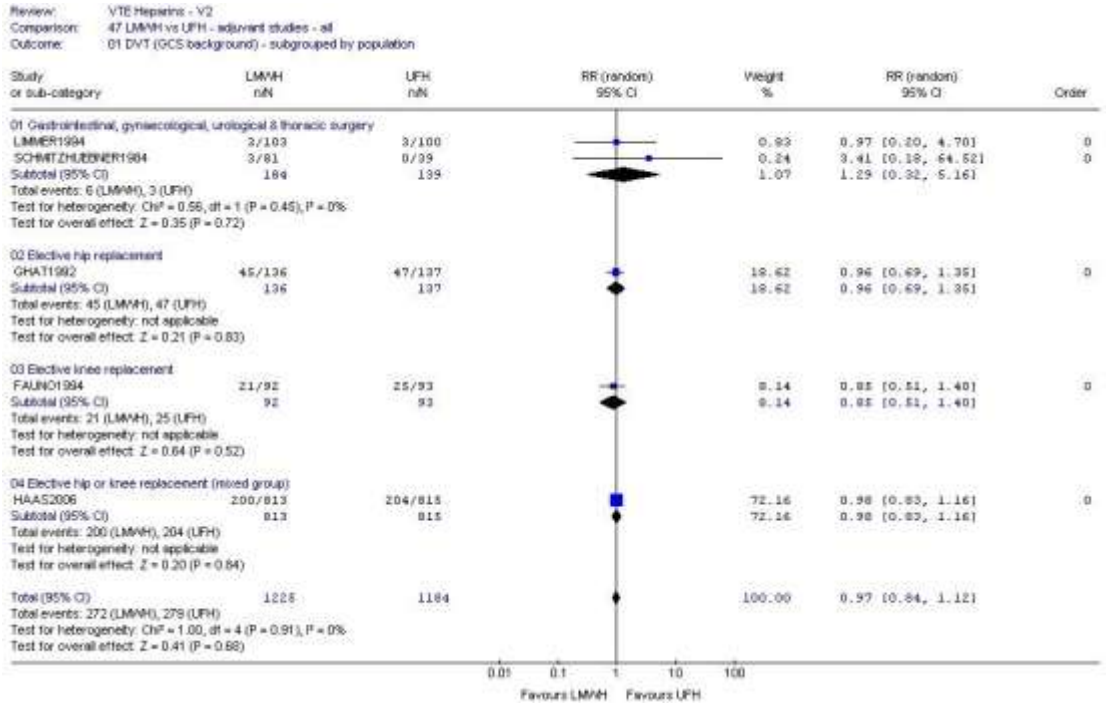


Forest Plot 173. Fondaparinux + GCS vs LMWH + GCS – Major Bleeding

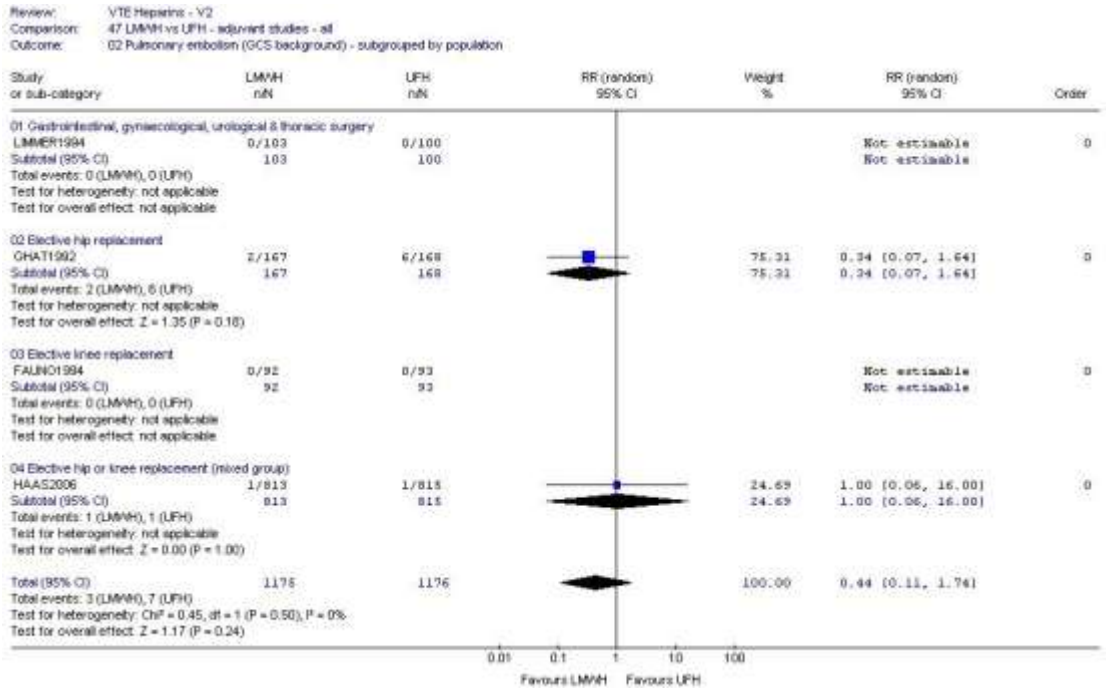


LMWH + GCS vs UFH + GCS

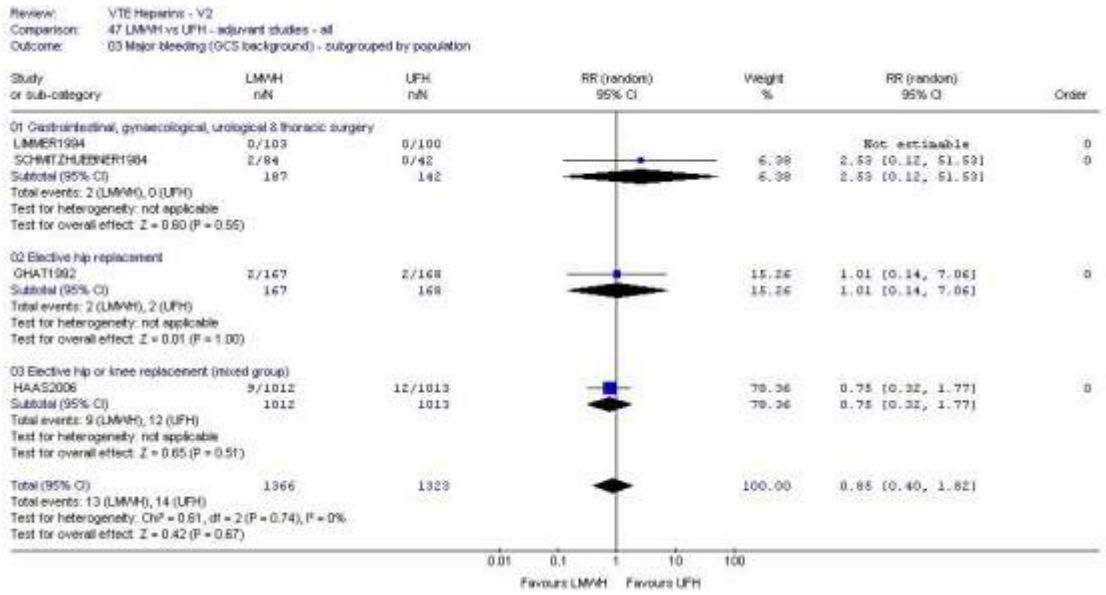
Forest Plot 174. LMWH + GCS vs UFH + GCS – DVT



Forest Plot 175. LMWH + GCS vs UFH + GCS – Pulmonary Embolism

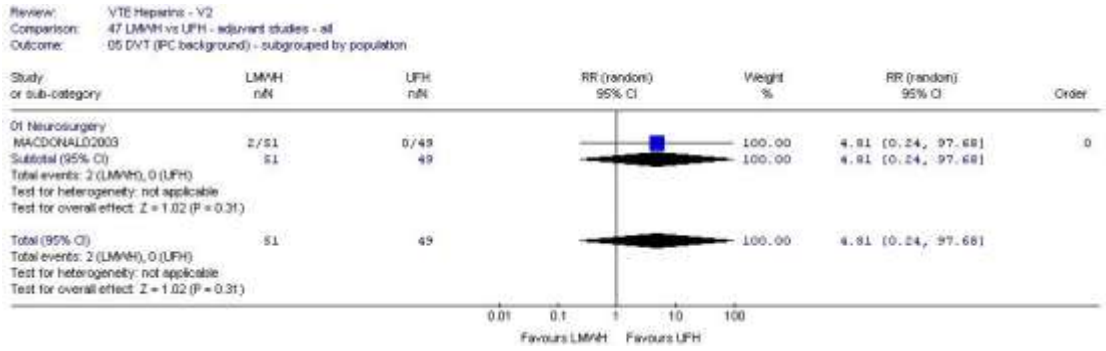


Forest Plot 176. LMWH + GCS vs UFH + GCS – Major Bleeding

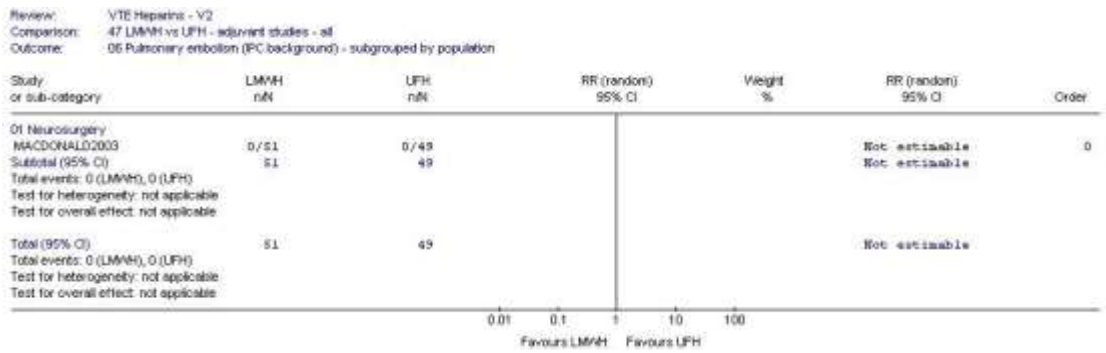


LMWH + IPCD vs UFH + IPCD

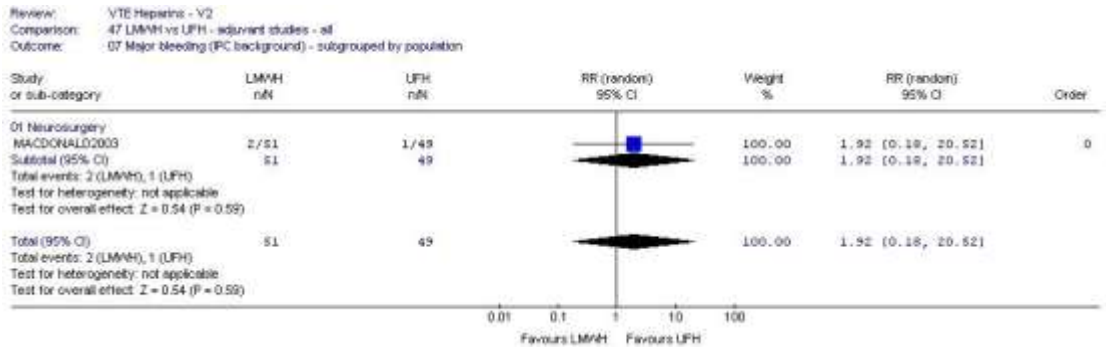
Forest Plot 177. LMWH + IPCD vs UFH + IPCD – DVT



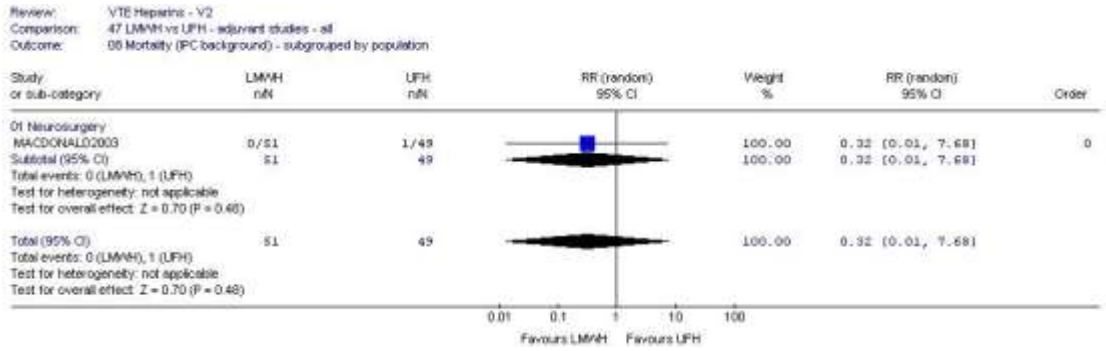
Forest Plot 178. LMWH + IPCD vs UFH + IPCD – Pulmonary Embolism



Forest Plot 179. LMWH + IPCD vs UFH + IPCD – Major Bleeding

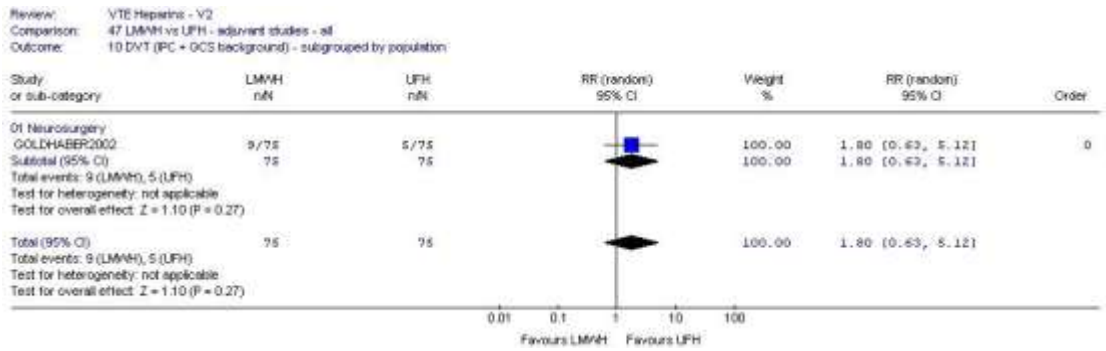


Forest Plot 180. LMWH + IPCD vs UFH + IPCD – Mortality

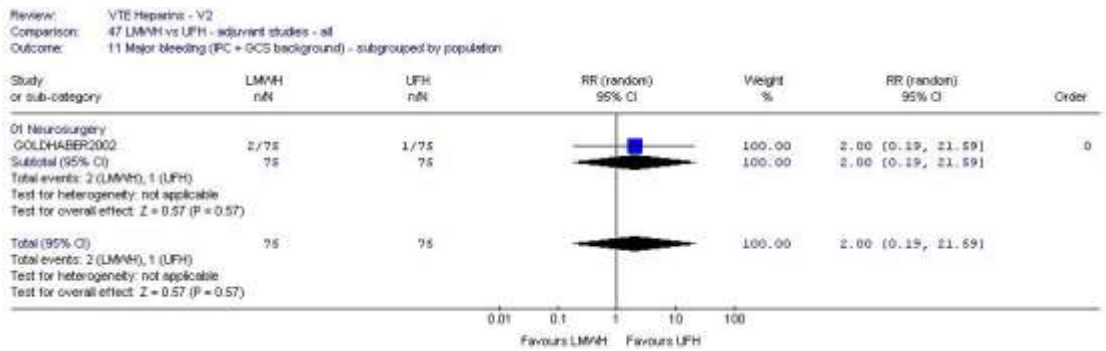


LMWH + IPCD + GCS vs UFH + IPCD + GCS

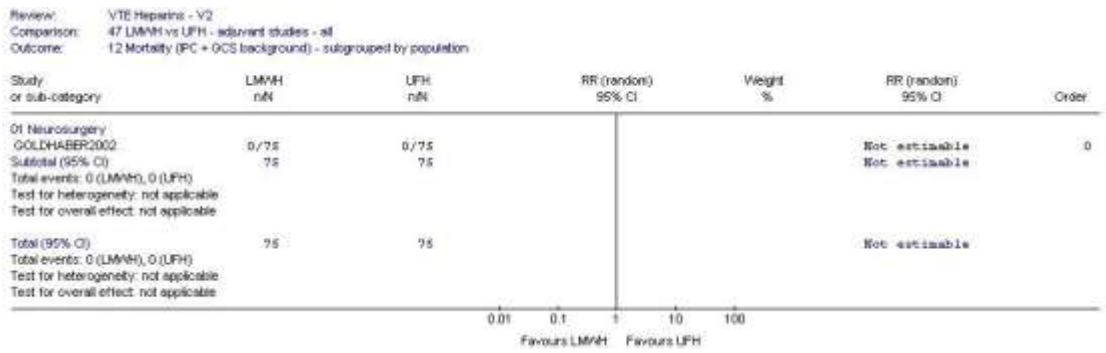
Forest Plot 181. LMWH + IPCD + GCS vs UFH + IPCD + GCS – DVT



Forest Plot 182. LMWH + IPCD + GCS vs UFH + IPCD + GCS – Major Bleeding

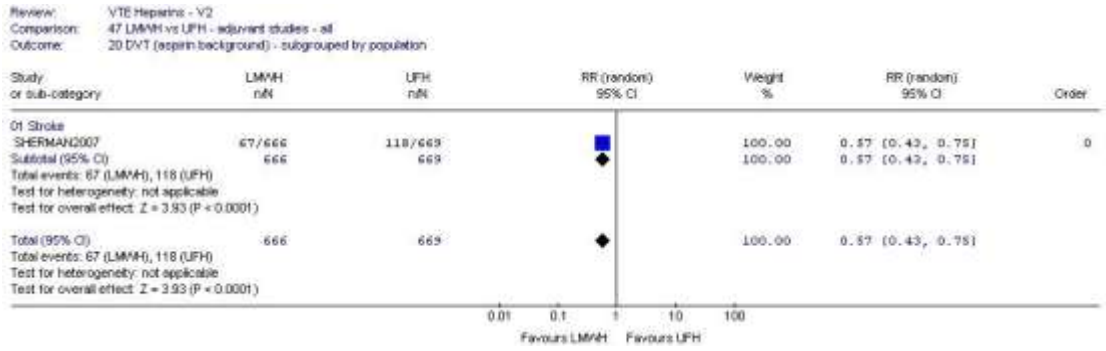


Forest Plot 183. LMWH + IPCD + GCS vs UFH + IPCD + GCS – Mortality

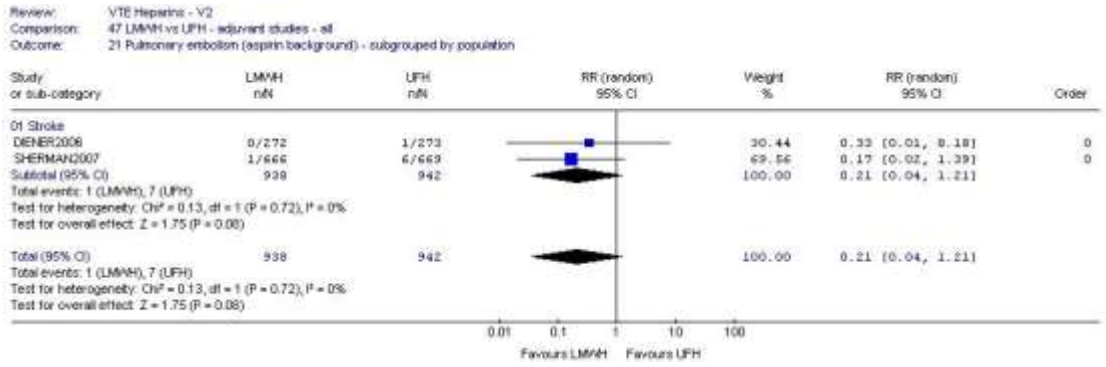


LMWH + Aspirin vs UFH + Aspirin

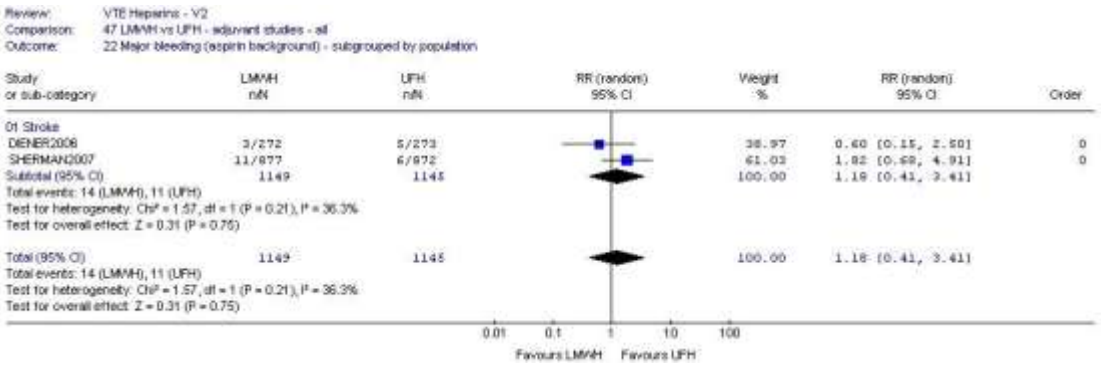
Forest Plot 184. LMWH + Aspirin vs UFH + Aspirin – DVT



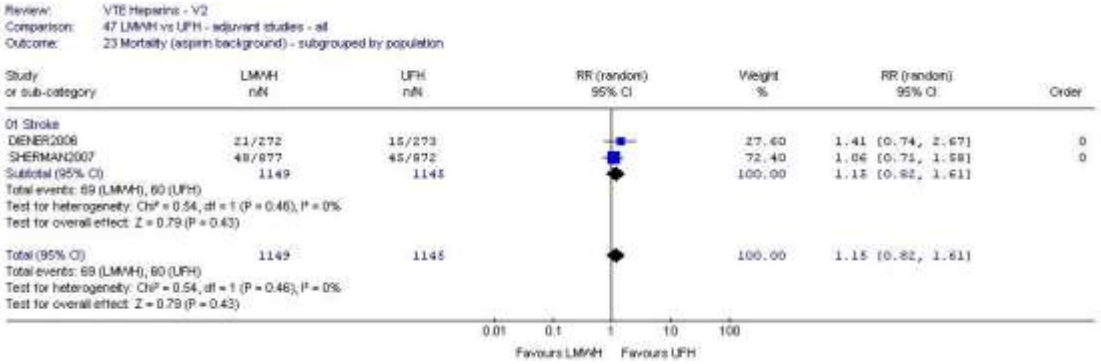
Forest Plot 185. LMWH + Aspirin vs UFH + Aspirin – Pulmonary Embolism



Forest Plot 186. LMWH + Aspirin vs UFH + Aspirin – Major Bleeding

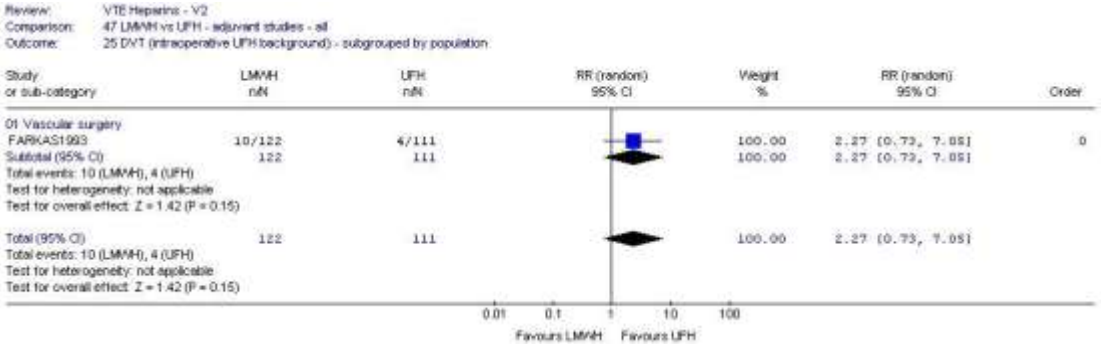


Forest Plot 187. LMWH + Aspirin vs UFH + Aspirin – Mortality

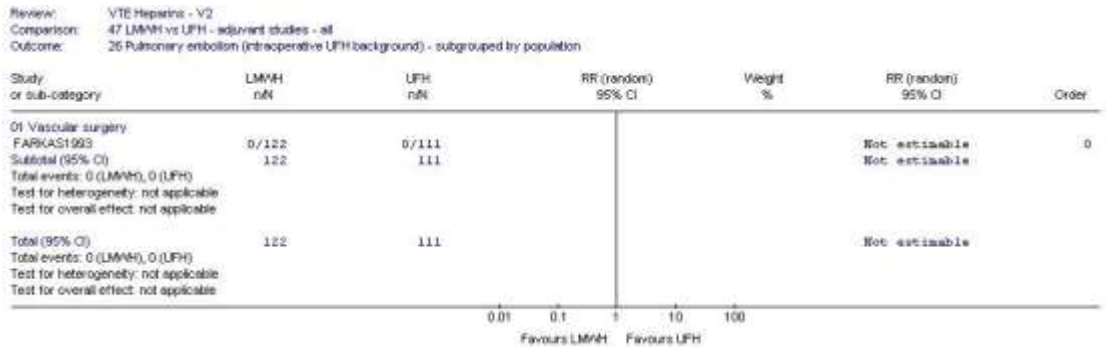


LMWH + Intraoperative UFH vs UFH + Intraoperative UFH

Forest Plot 188. LMWH + Intraoperative UFH vs UFH + Intraoperative UFH – DVT

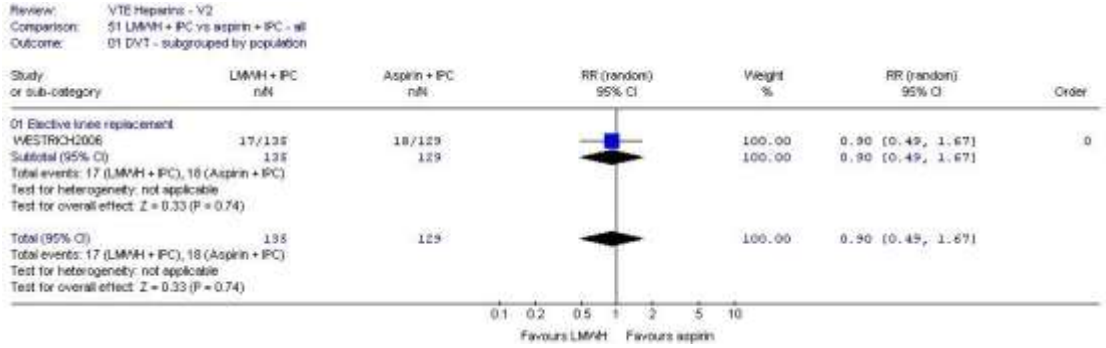


Forest Plot 189. LMWH + Intraoperative UFH vs UFH + Intraoperative UFH – Pulmonary Embolism

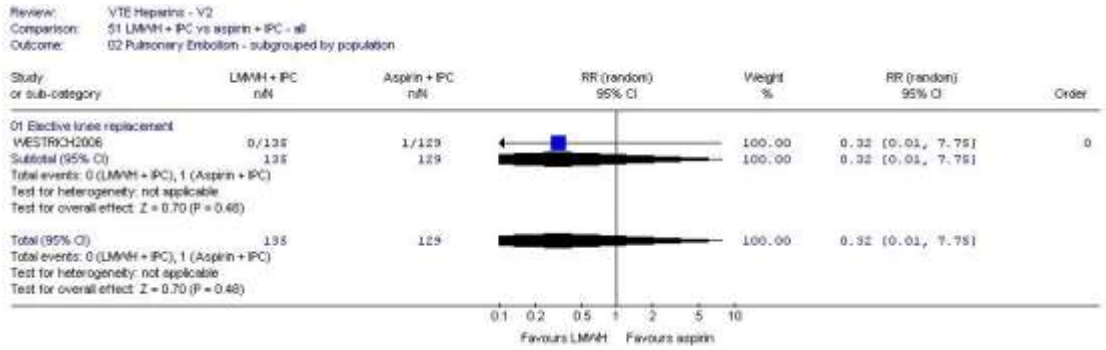


LMWH + IPCD vs Aspirin + IPCD

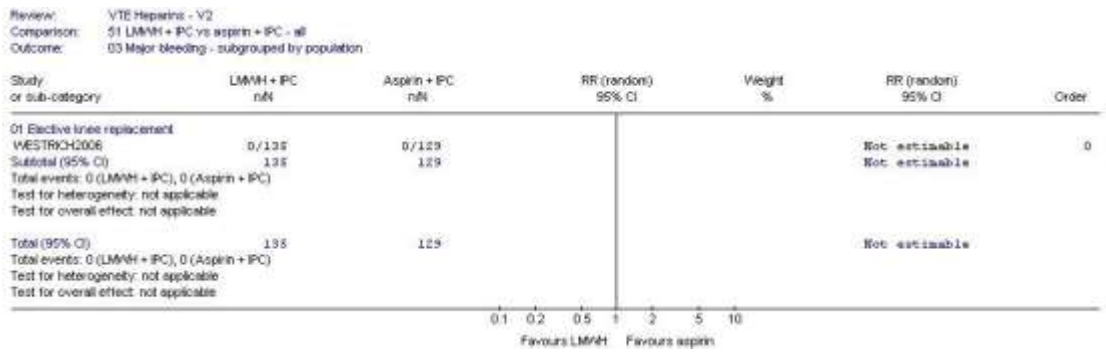
Forest Plot 190. LMWH + IPCD vs Aspirin + IPCD – DVT



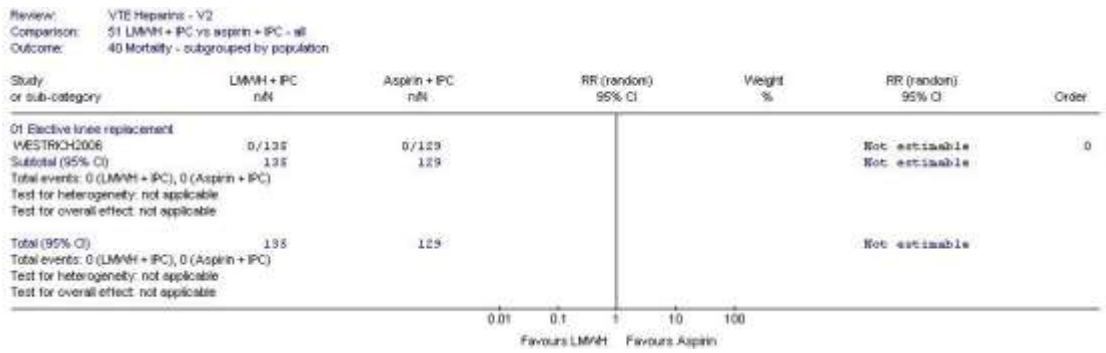
Forest Plot 191. LMWH + IPCD vs Aspirin + IPCD – Pulmonary Embolism



Forest Plot 192. LMWH + IPCD vs Aspirin + IPCD – Major Bleeding

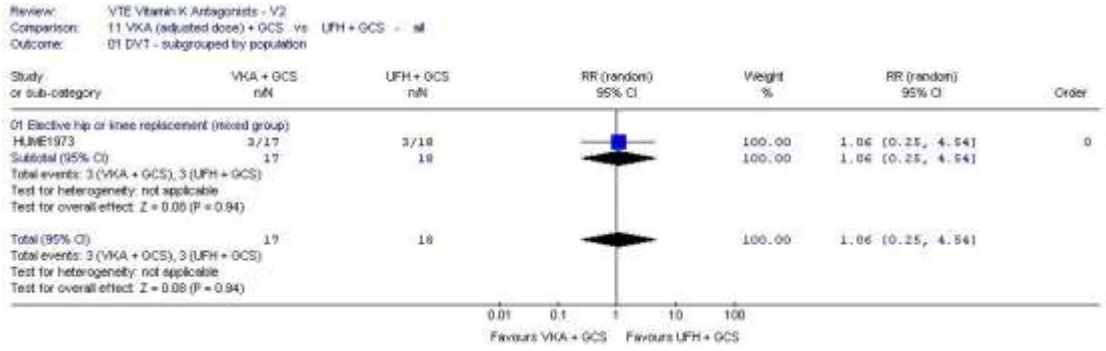


Forest Plot 193. LMWH + IPCD vs Aspirin + IPCD – Mortality

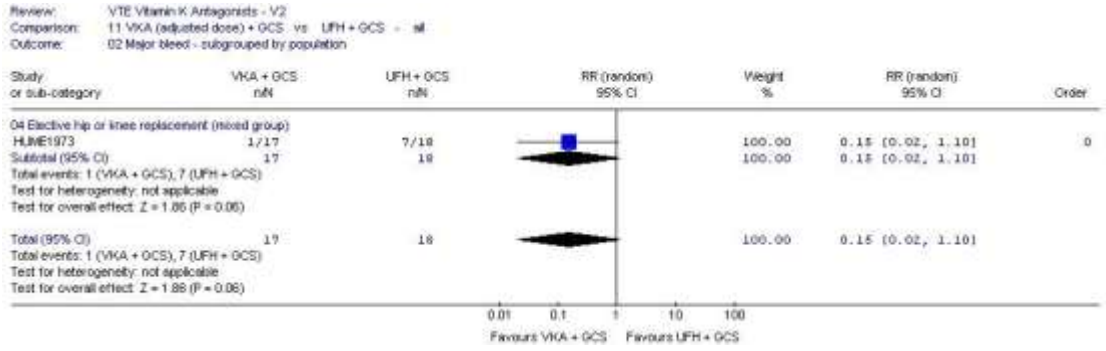


VKA + GCS vs UFH + GCS

Forest Plot 194. VKA + GCS vs UFH + GCS - DVT

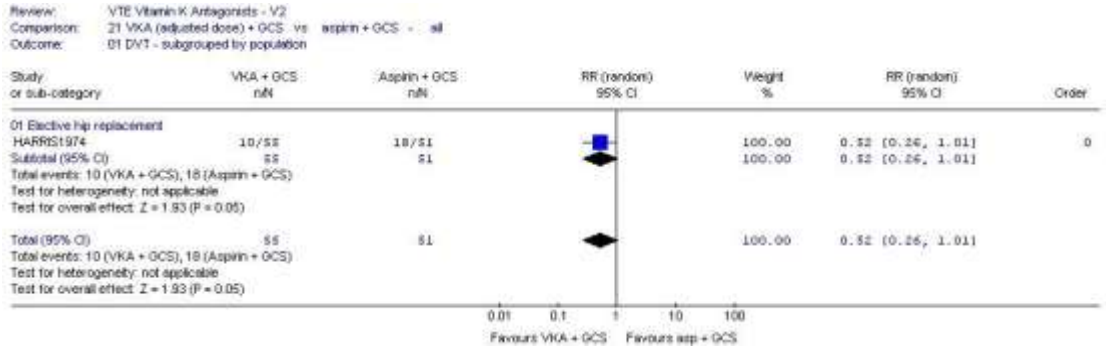


Forest Plot 195. VKA + GCS vs UFH + GCS – Major Bleeding

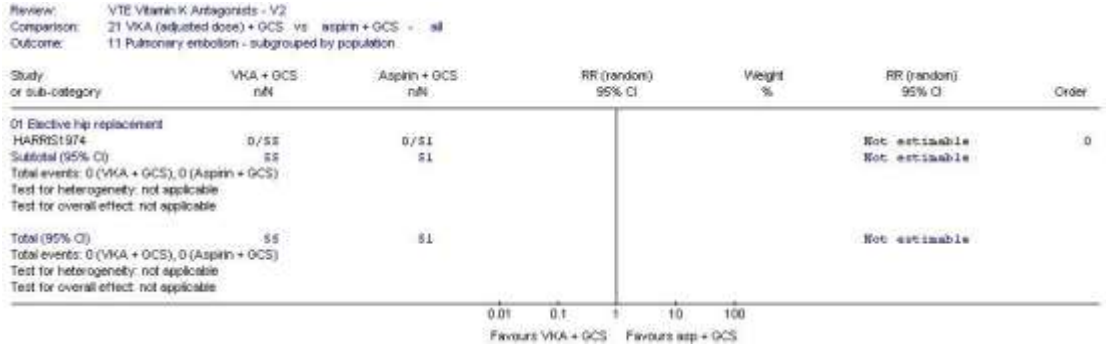


VKA + GCS vs Aspirin + GCS

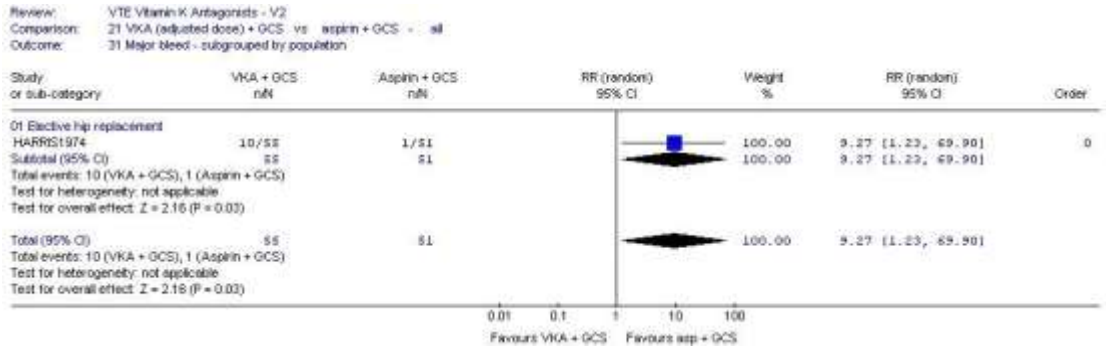
Forest Plot 196. VKA + GCS vs Aspirin + GCS - DVT



Forest Plot 197. VKA + GCS vs Aspirin + GCS – Pulmonary Embolism

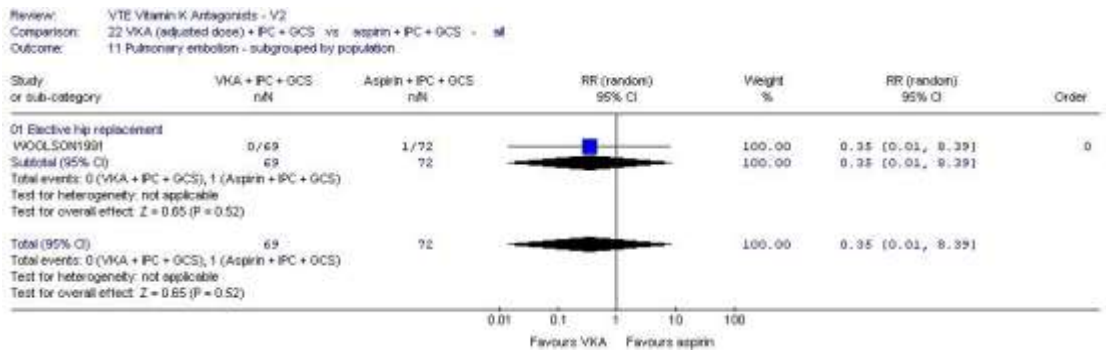


Forest Plot 198. VKA + GCS vs Aspirin + GCS – Major Bleeding



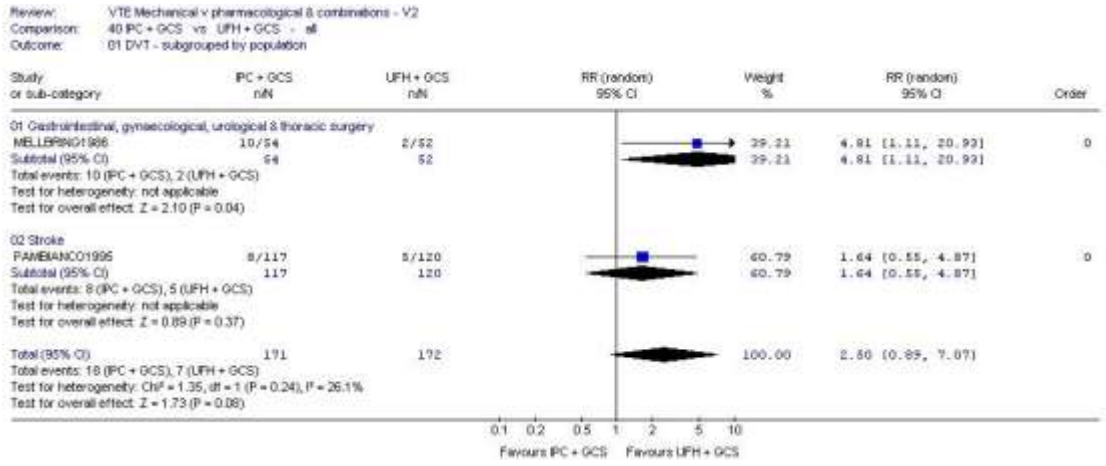
VKA + IPCD + GCS vs Aspirin + IPCD + GCS

Forest Plot 199. VKA + IPCD + GCS vs Aspirin + IPCD + GCS – Pulmonary Embolism

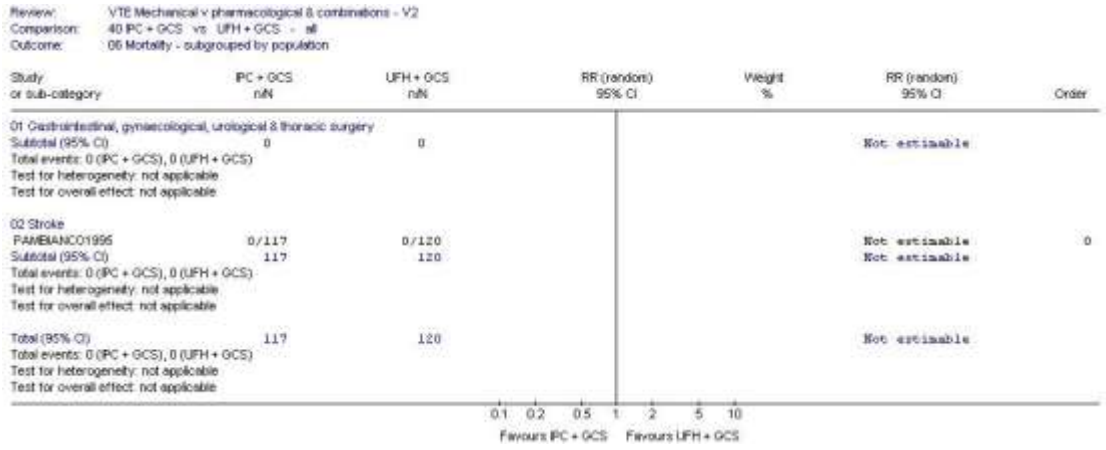


IPCD + GCS vs UFH+ GCS

Forest Plot 200. IPCD + GCS vs UFH + GCS – DVT

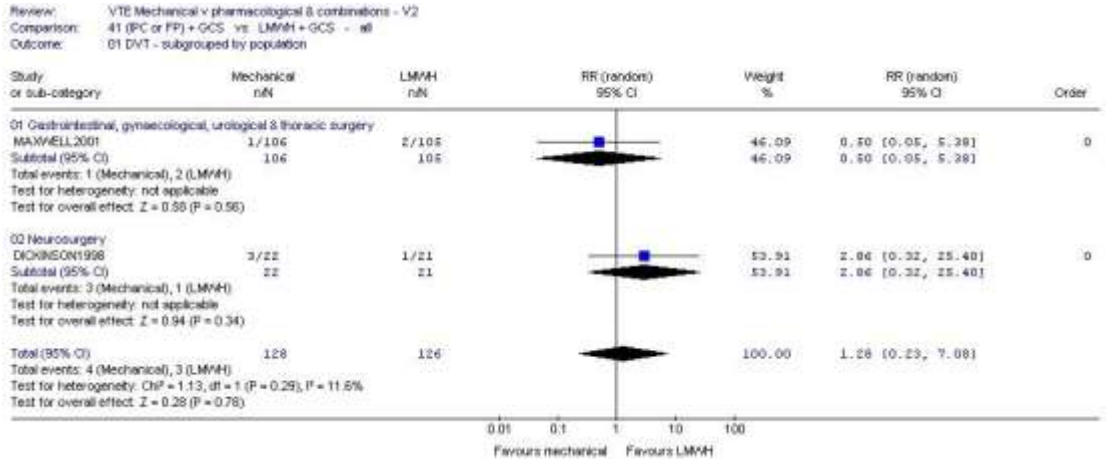


Forest Plot 201. IPCD + GCS vs UFH + GCS – Mortality

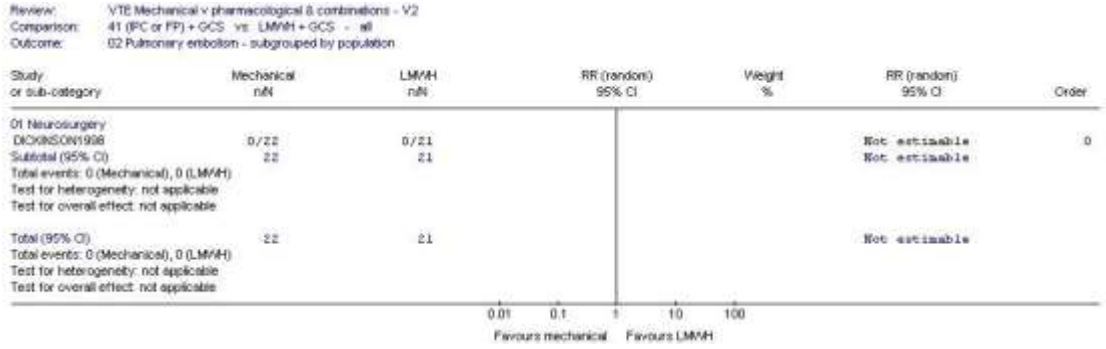


IPCD/FID + GCS vs LMWH + GCS

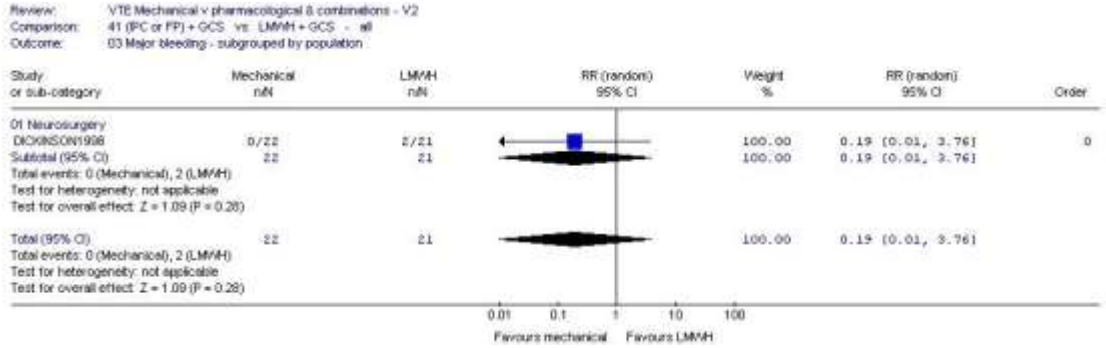
Forest Plot 202. IPCD + GCS vs LMWH + GCS – DVT



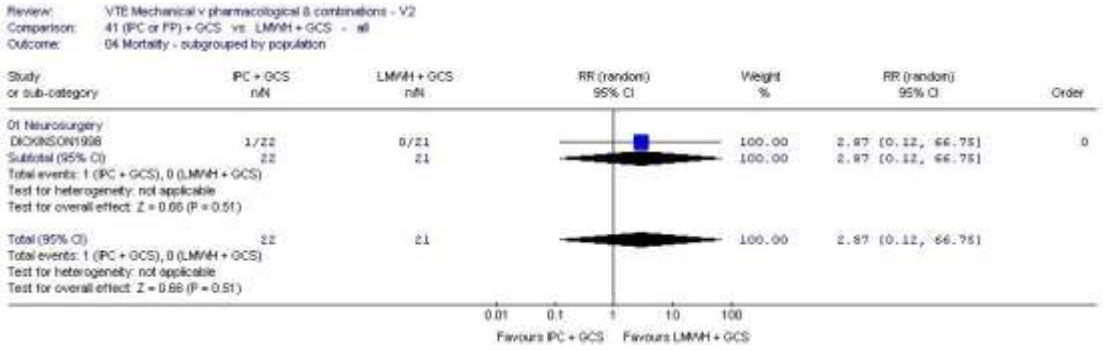
Forest Plot 203. IPCD + GCS vs LMWH + GCS – Pulmonary Embolism



Forest Plot 204. IPCD + GCS vs LMWH + GCS – Major Bleeding

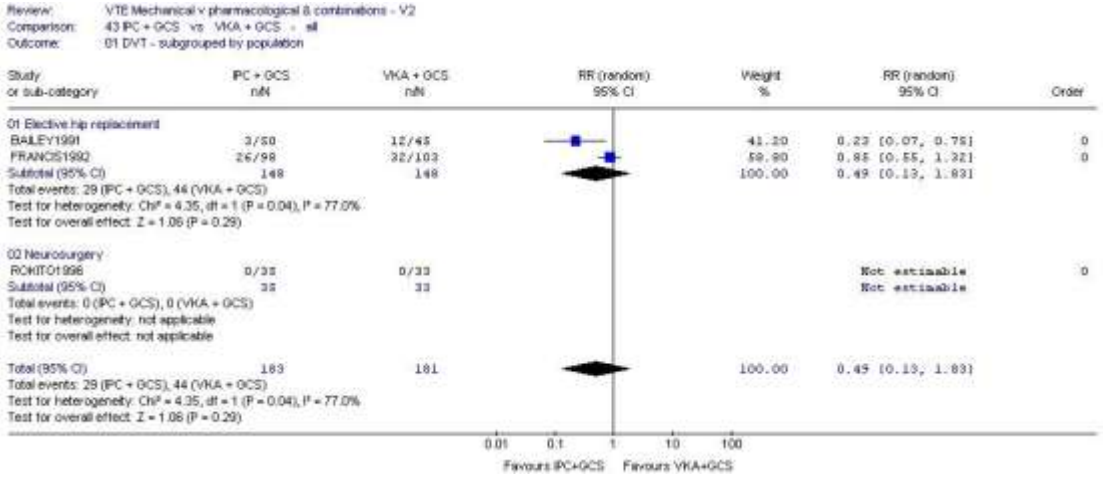


Forest Plot 205. IPCD + GCS vs LMWH + GCS – Mortality

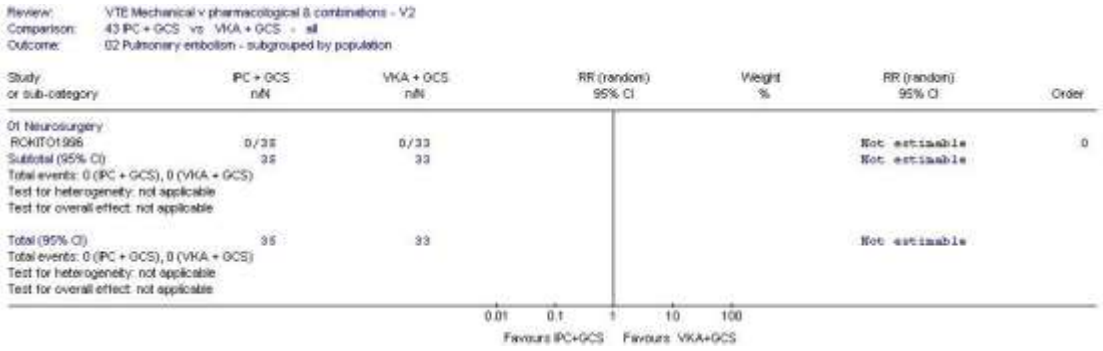


IPCD + GCS vs VKA + GCS

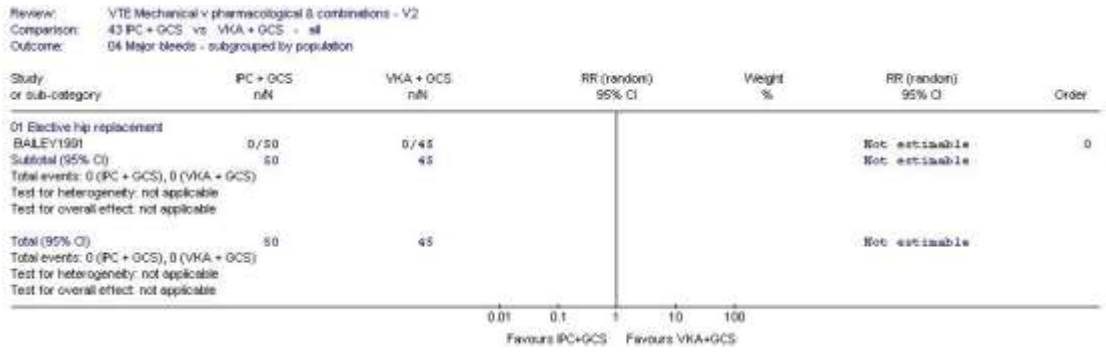
Forest Plot 206. IPCD + GCS vs VKA + GCS – DVT



Forest Plot 207. IPCD + GCS vs VKA + GCS – Pulmonary Embolism

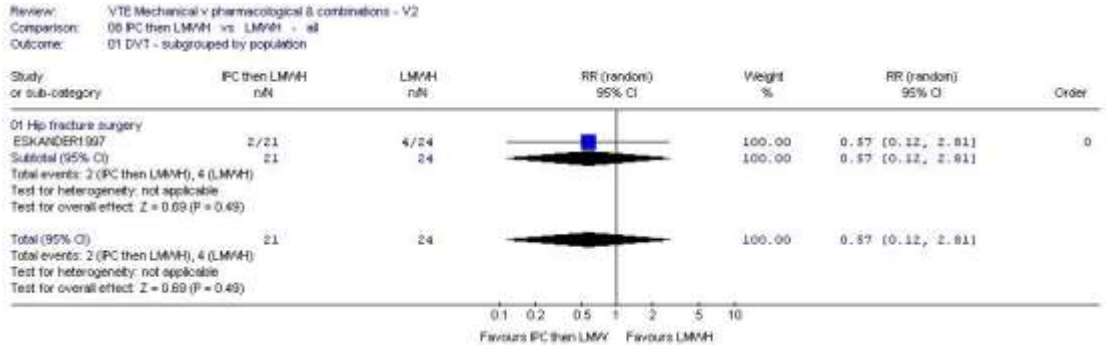


Forest Plot 208. IPCD + GCS vs VKA + GCS – Major Bleeding

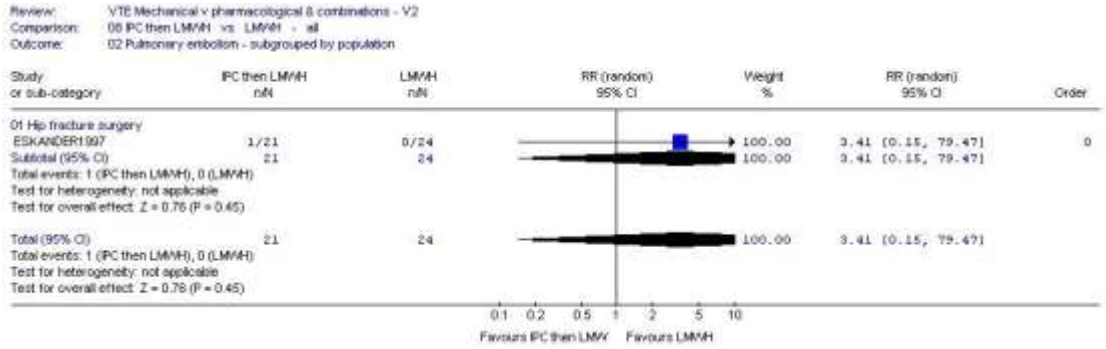


IPCD then LMWH vs LMWH

Forest Plot 209. IPCD then LMWH vs LMWH – DVT

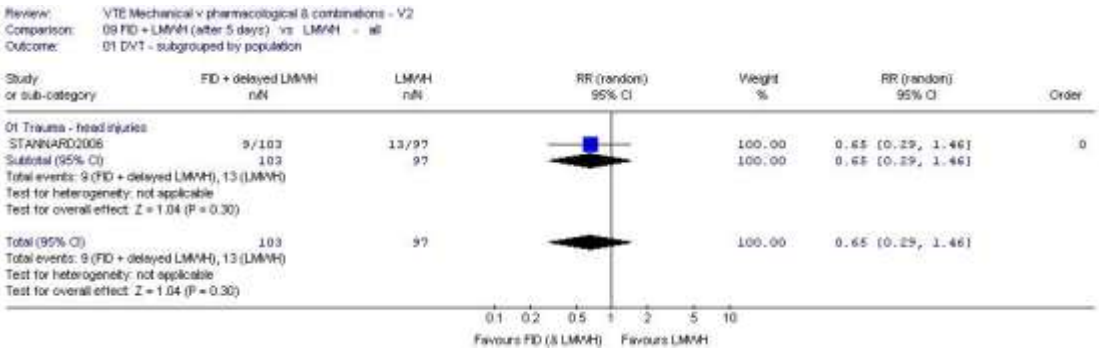


Forest Plot 210. IPCD then LMWH vs LMWH – pulmonary embolism

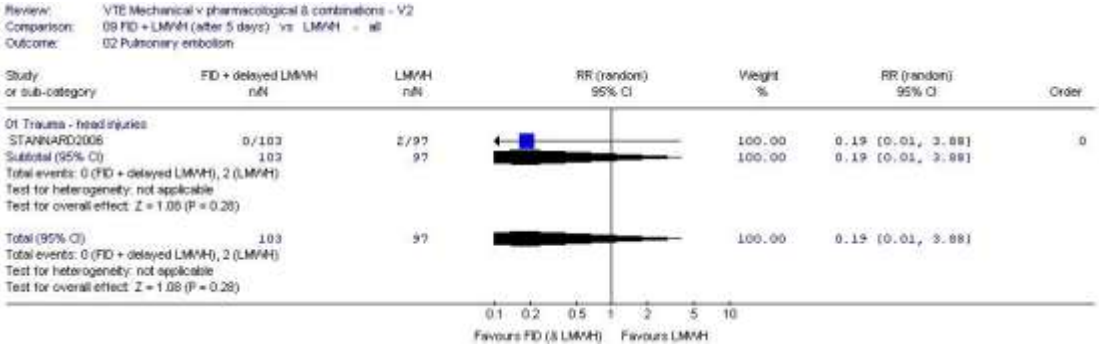


FID + LMWH after 5 days vs LMWH

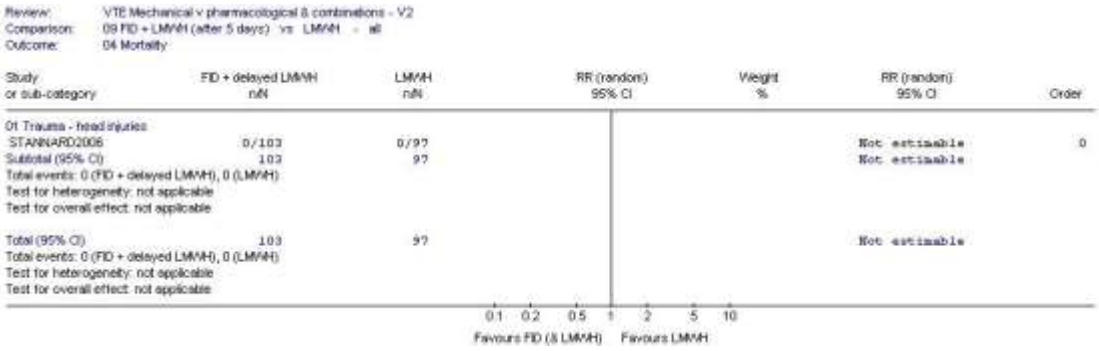
Forest Plot 211. FID + LMWH after 5 days vs LMWH – DVT



Forest Plot 212. FID + LMWH after 5 days vs LMWH – pulmonary embolism

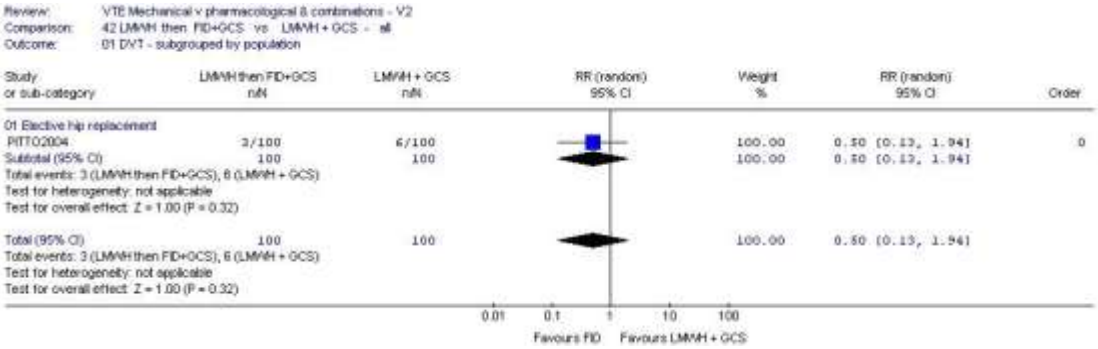


Forest Plot 213. FID + LMWH after 5 days vs LMWH – mortality

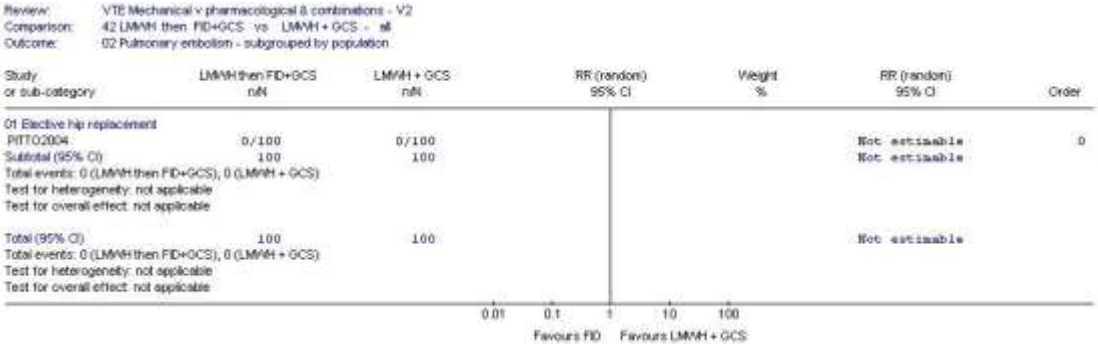


LMWH then FID + GCS vs LMWH + GCS

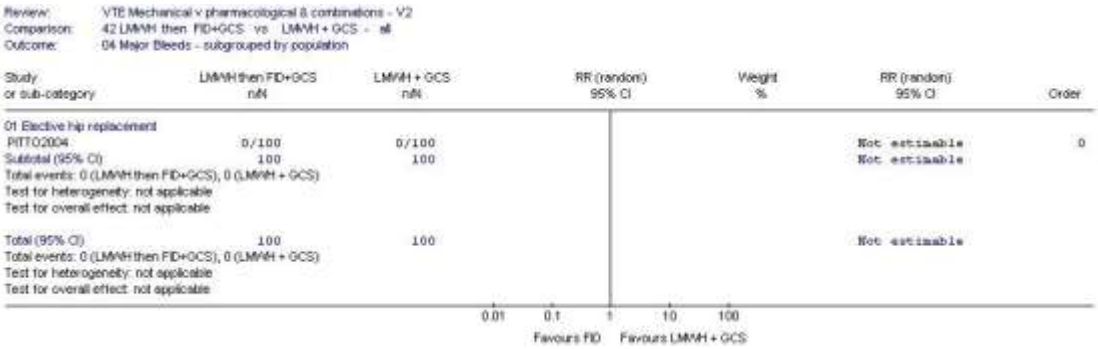
Forest Plot 214. LMWH then FID + GCS vs LMWH vs GCS – DVT



Forest Plot 215. LMWH then FID + GCS vs LMWH vs GCS – pulmonary embolism

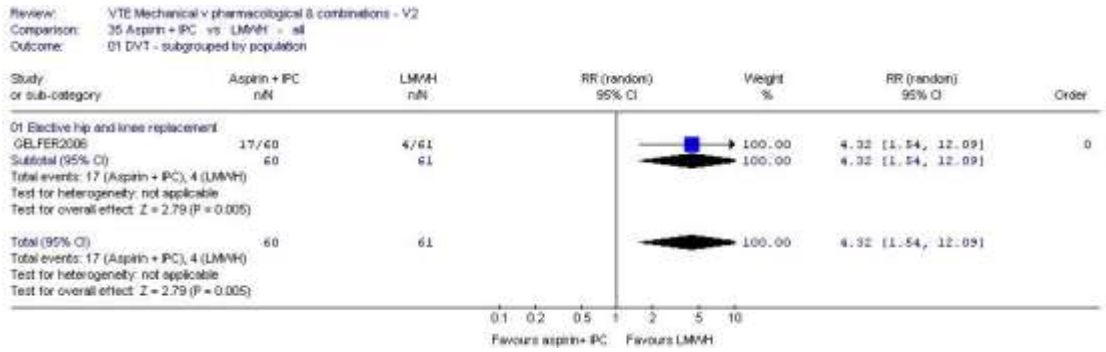


Forest Plot 216. LMWH then FID + GCS vs LMWH vs GCS – major bleeding

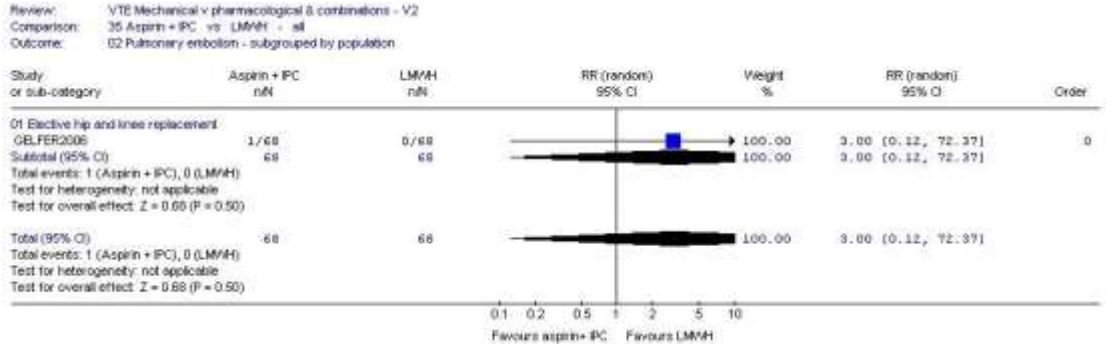


Aspirin + IPCD vs LMWH

Forest Plot 217. Aspirin + IPCD vs LMWH – DVT

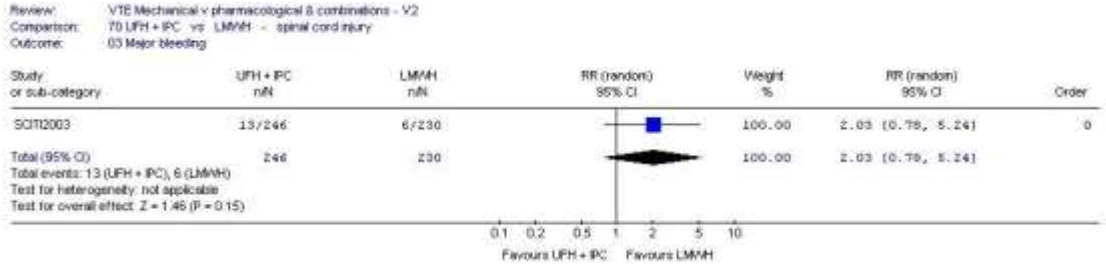


Forest Plot 218. Aspirin + IPCD vs LMWH – pulmonary embolism

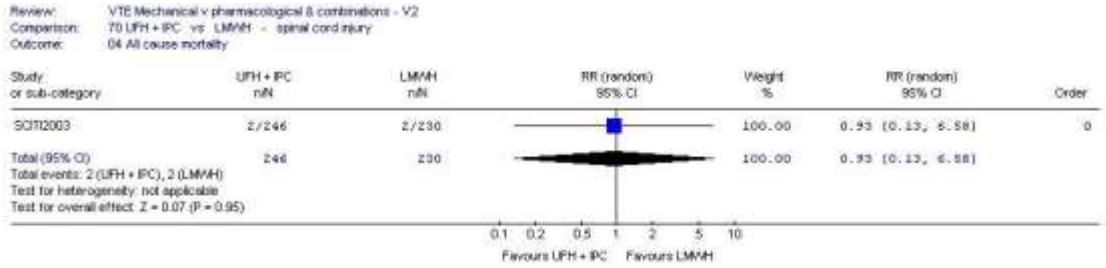


UFH + IPCD vs LMWH

Forest Plot 219. UFH + IPCD vs LMWH – major bleeding



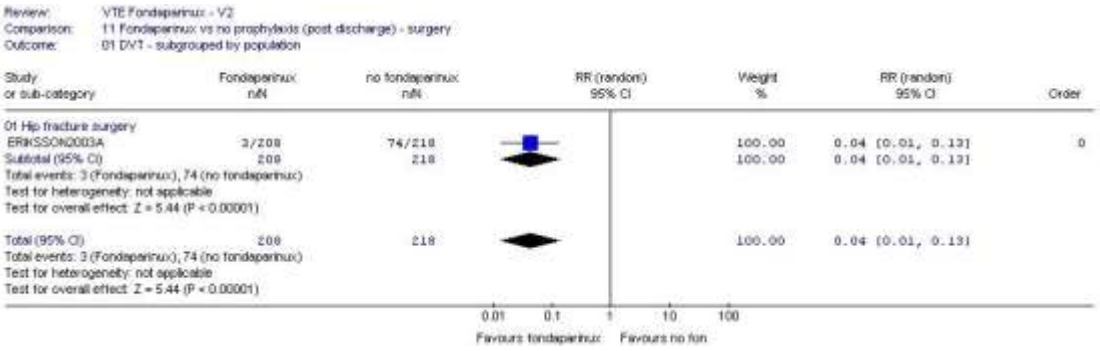
Forest Plot 220. UFH + IPCD vs LMWH – mortality



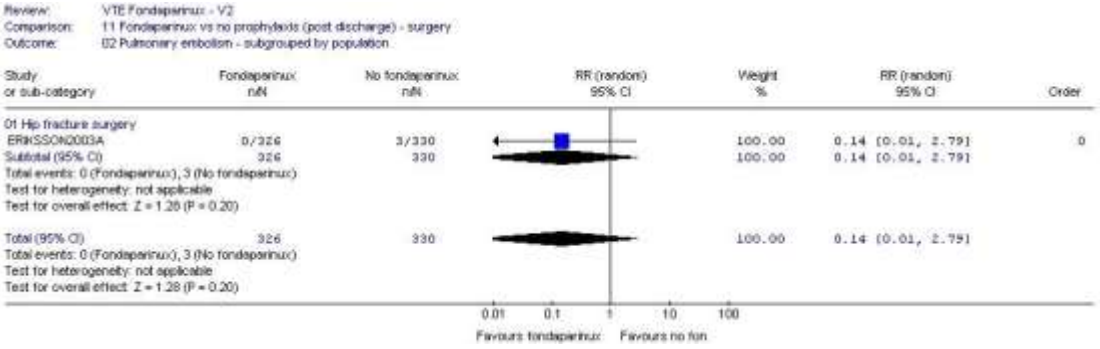
Post Discharge Prophylaxis vs No Post Discharge Prophylaxis

Fondaparinux Post Discharge

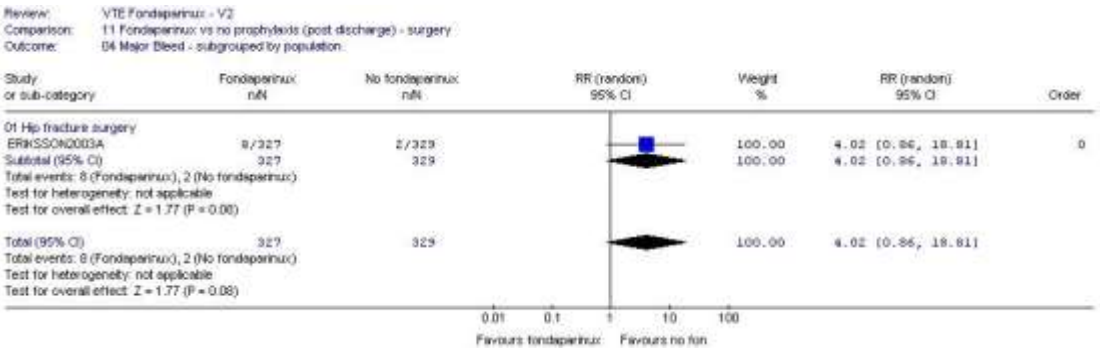
Forest Plot 221. Fondaparinux Post Discharge – DVT



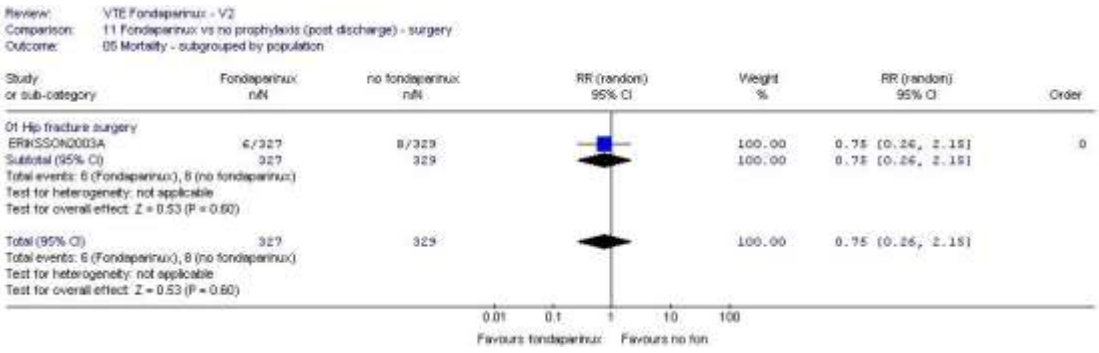
Forest Plot 222. Fondaparinux Post Discharge – Pulmonary Embolism



Forest Plot 223. Fondaparinux Post Discharge – Major Bleeding

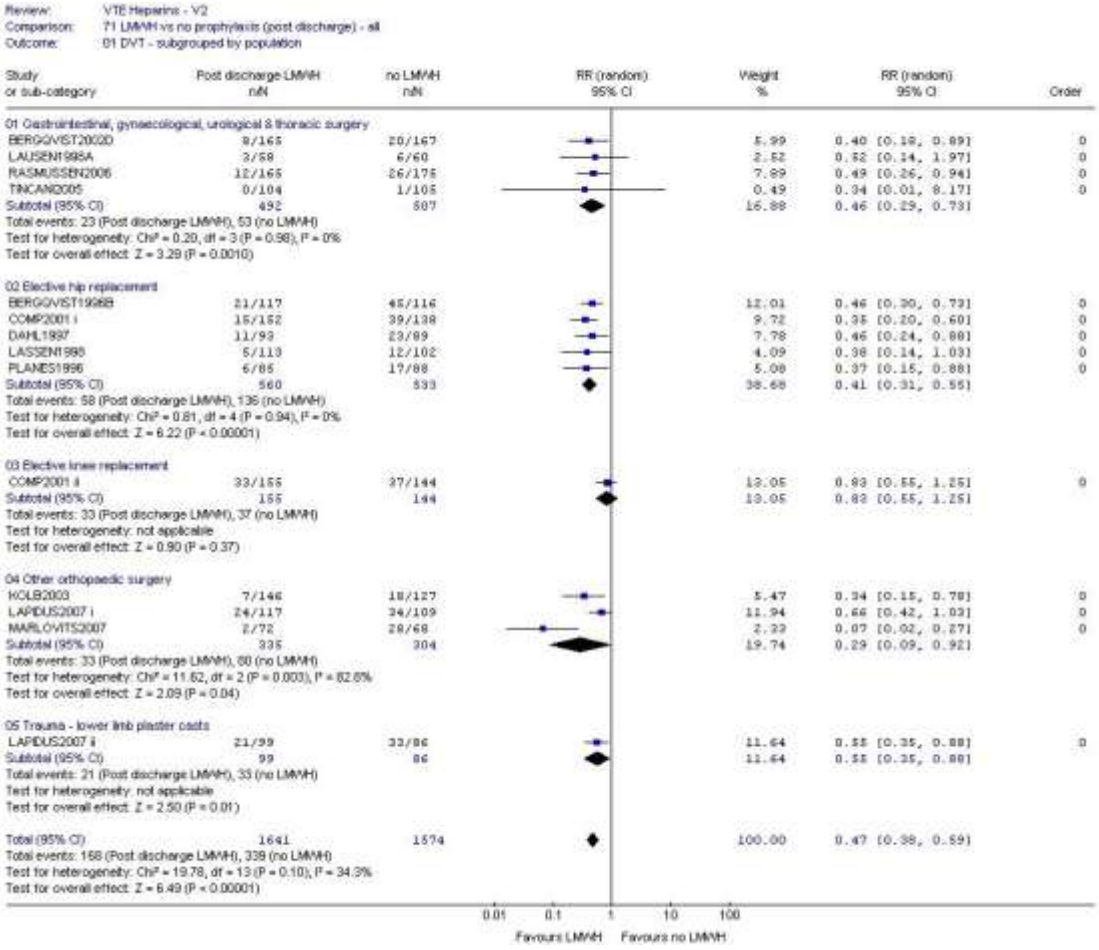


Forest Plot 224. Fondaparinux Post Discharge – Mortality

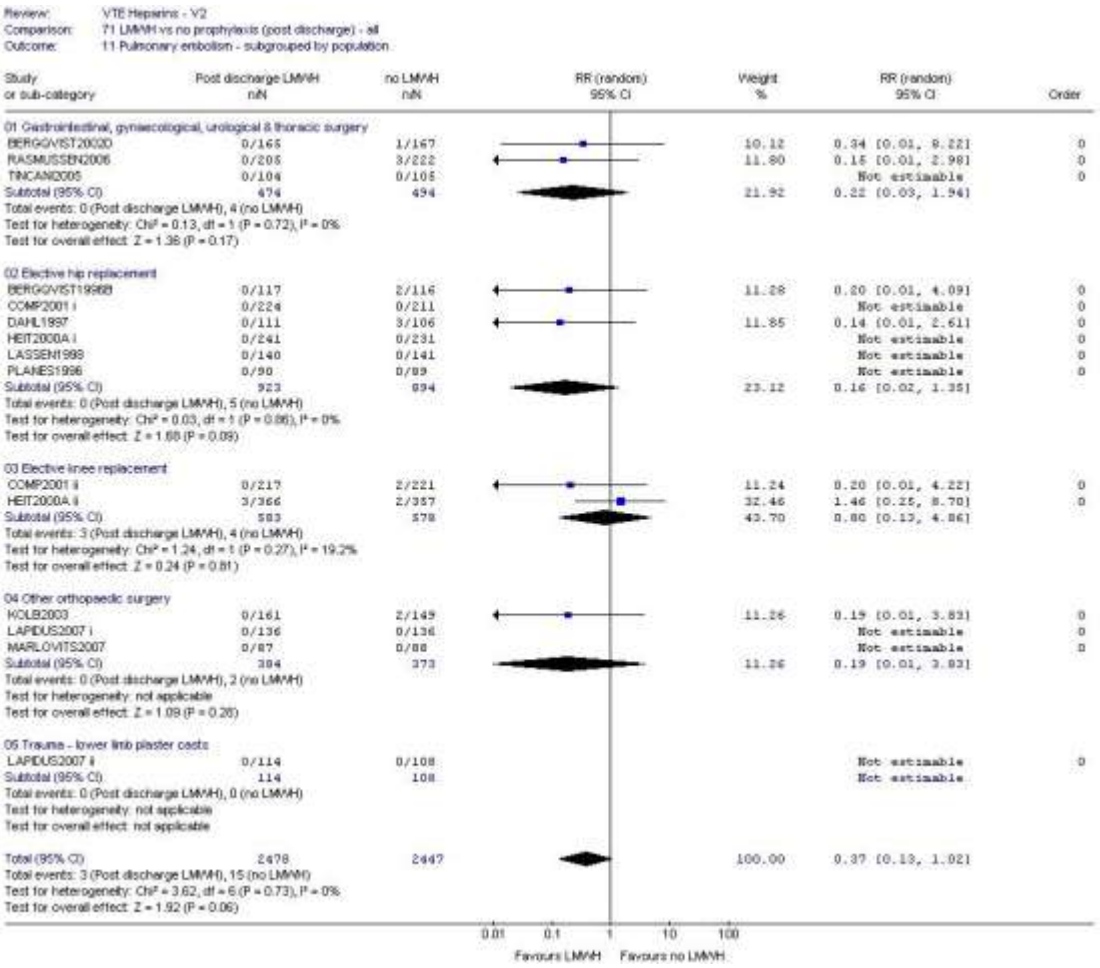


LMWH Post Discharge – Surgery Patients

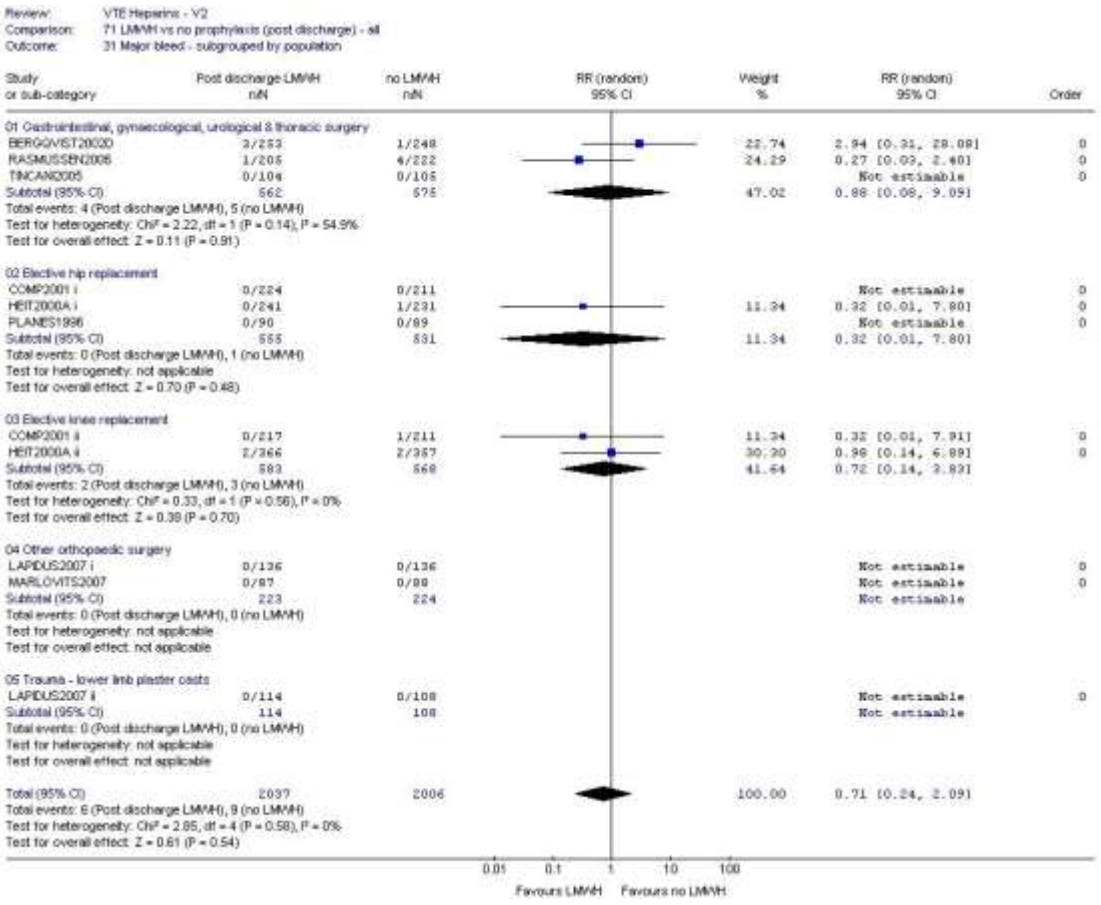
Forest Plot 225. LMWH Post Discharge – Surgery Patients – DVT



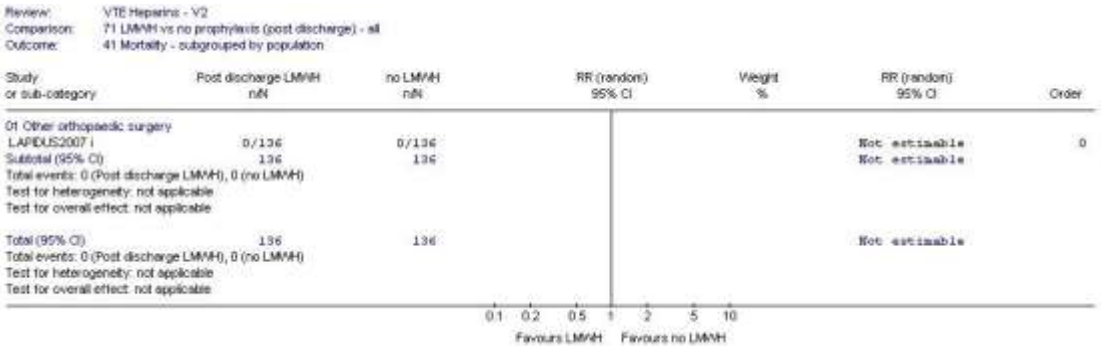
Forest Plot 226. LMWH Post Discharge – Surgery Patients – Pulmonary Embolism



Forest Plot 227. LMWH Post Discharge – Surgery Patients – Major Bleeding

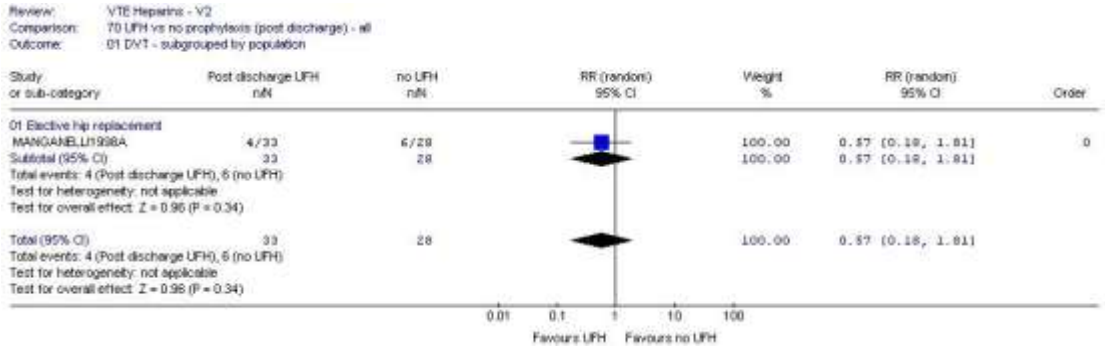


Forest Plot 228. LMWH Post Discharge – Surgery Patients – Mortality

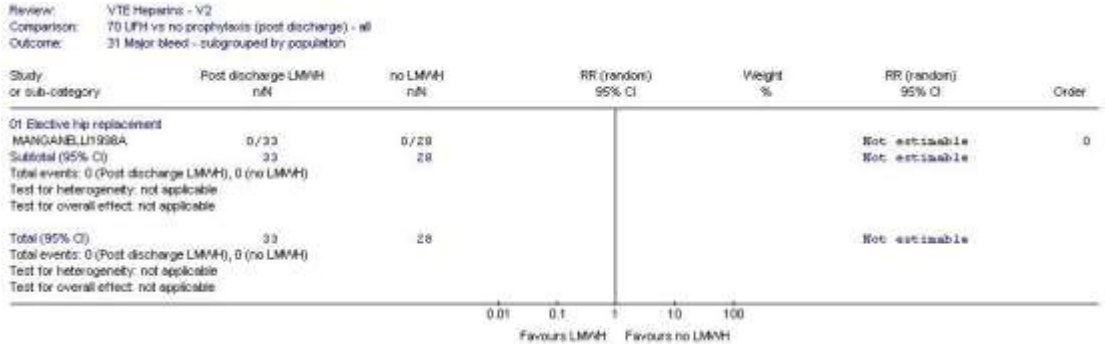


UFH Post Discharge

Forest Plot 229. UFH Post Discharge – DVT

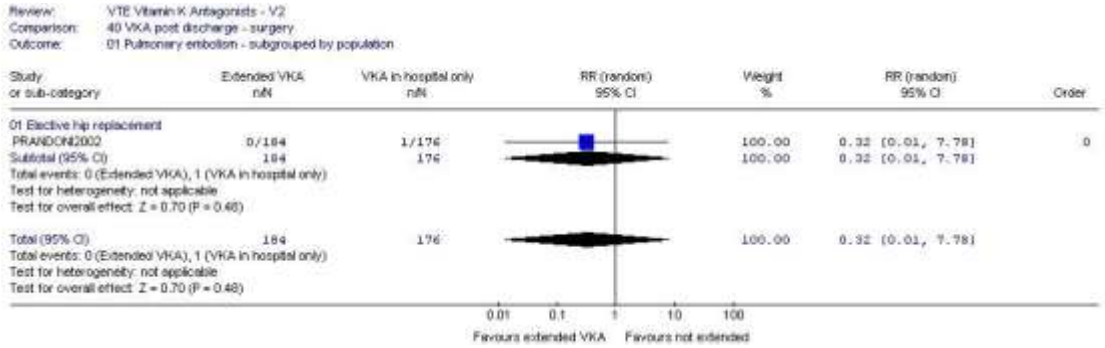


Forest Plot 230. UFH Post Discharge – Major Bleeding

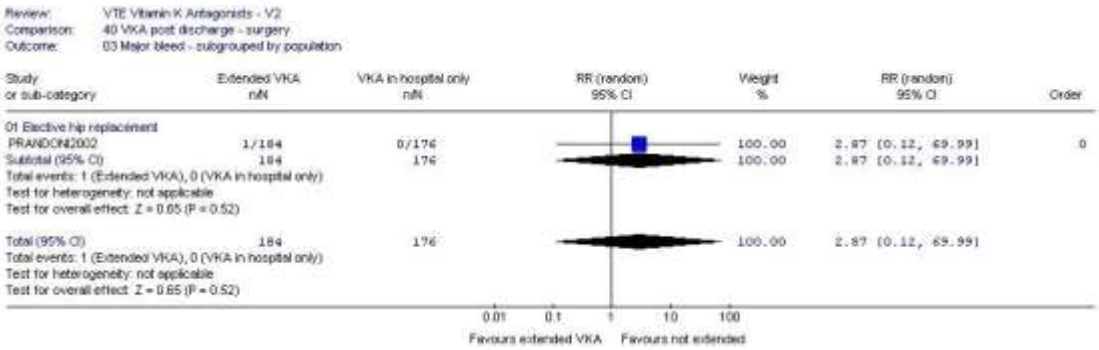


VKA Post Discharge – Surgery Patients

Forest Plot 231. VKA Post Discharge – Surgery Patients – pulmonary embolism

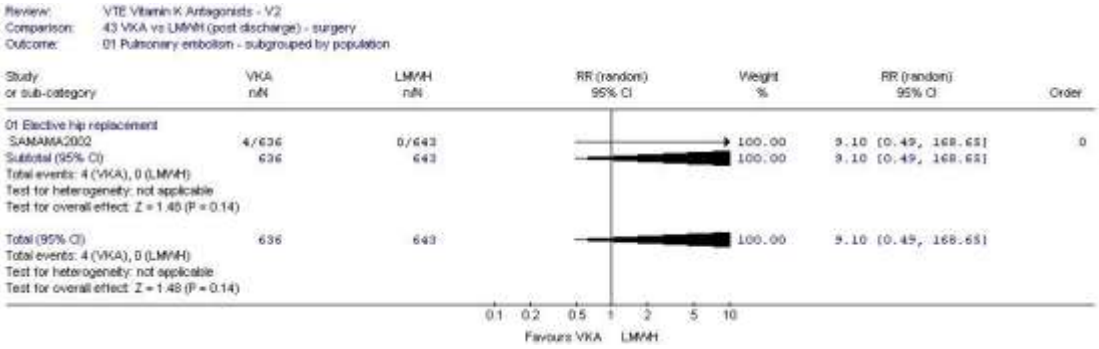


Forest Plot 232. VKA Post Discharge – Surgery Patients – major bleeding

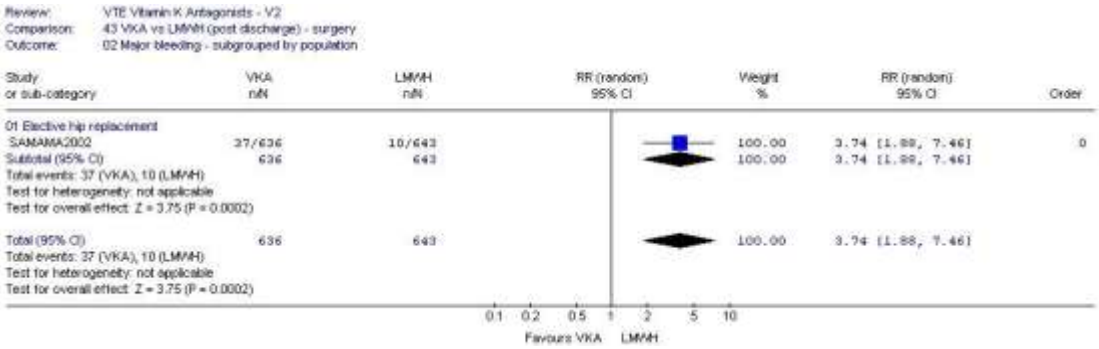


VKA vs LMWH Post Discharge – Surgery Patients

Forest Plot 233. VKA vs LMWH Post Discharge – Surgery Patients – pulmonary embolism



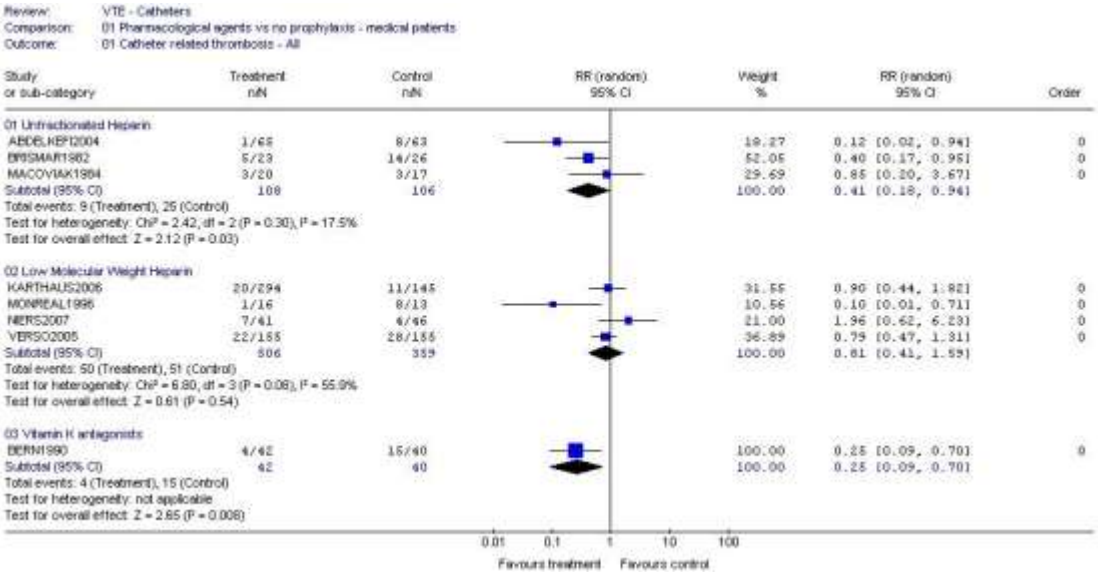
Forest Plot 234. VKA vs LMWH Post Discharge – Surgery Patients – major bleeding



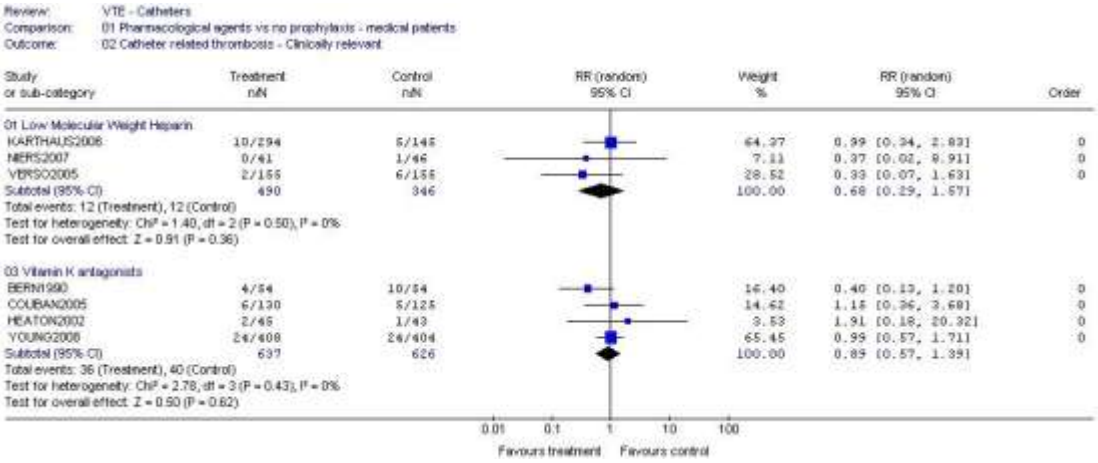
Central Venous Catheters

CVC - Pharmacological Agents vs No Prophylaxis – Subgrouped by Agent

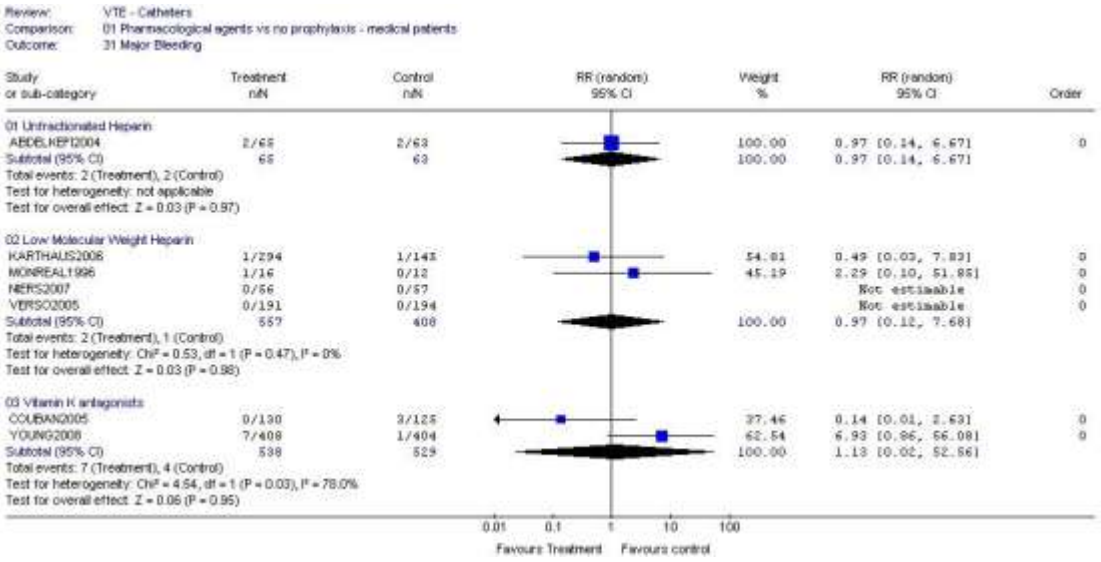
Forest Plot 235. CVC - Pharmacological Agents vs No Prophylaxis – Subgrouped By Agent – Catheter Related Thrombosis (Asymptomatic And Symptomatic)



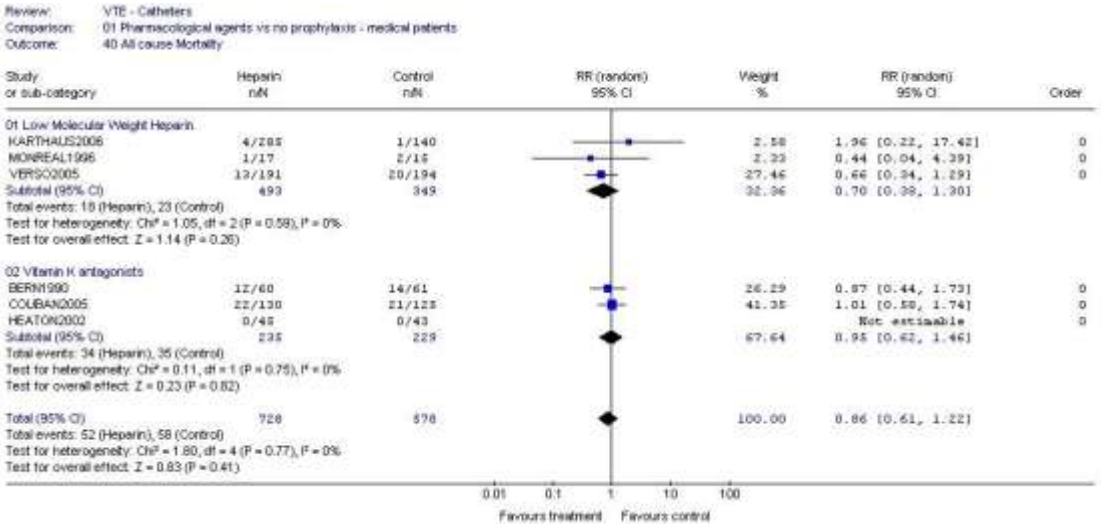
Forest Plot 236. CVC - Pharmacological Agents vs No Prophylaxis – Subgrouped by Agent – Clinically Relevant (Symptomatic) Catheter Related Thrombosis



Forest Plot 237. CVC - Pharmacological Agents vs No Prophylaxis – Subgrouped by Agent – Major Bleeding

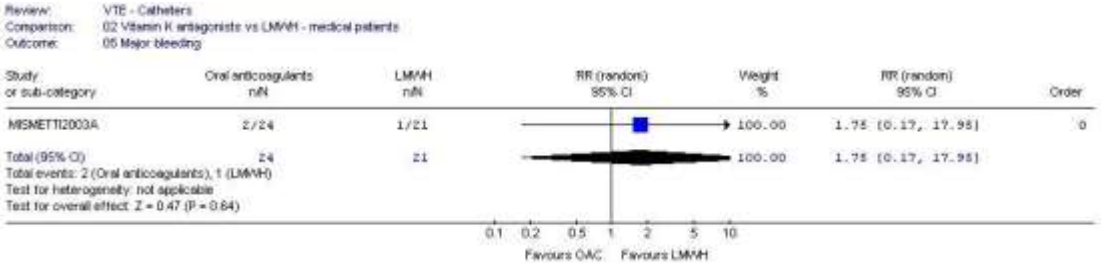


Forest Plot 238. Central Venous Catheters - Pharmacological Agents vs No Prophylaxis – Subgrouped By Agent – Mortality

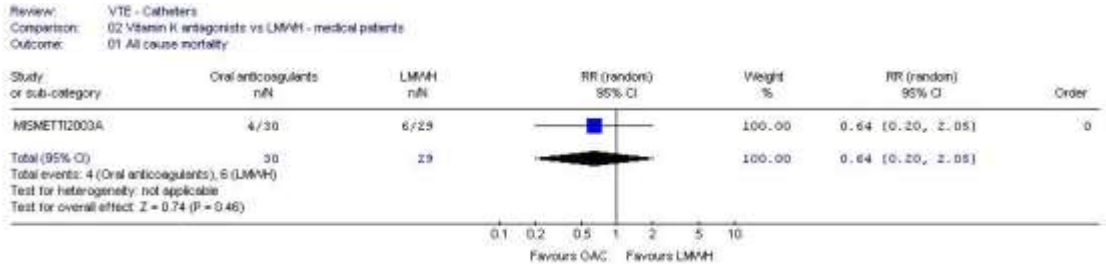


Central Venous Catheters - VKA vs LMWH

Forest Plot 239. CVC - VKA vs LMWH – Major Bleeding

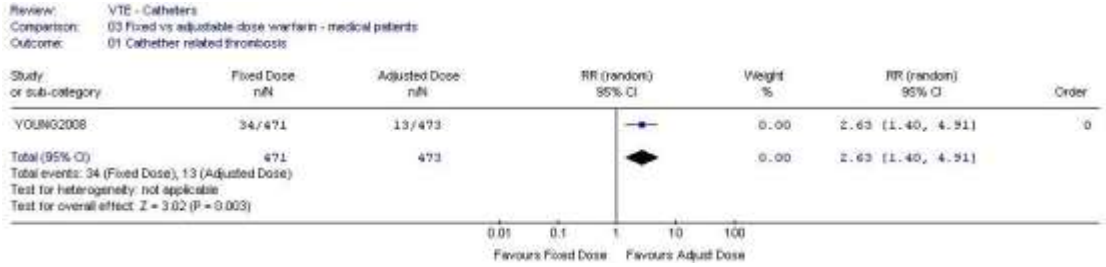


Forest Plot 240. Central Venous Catheters - VKA vs LMWH – Mortality

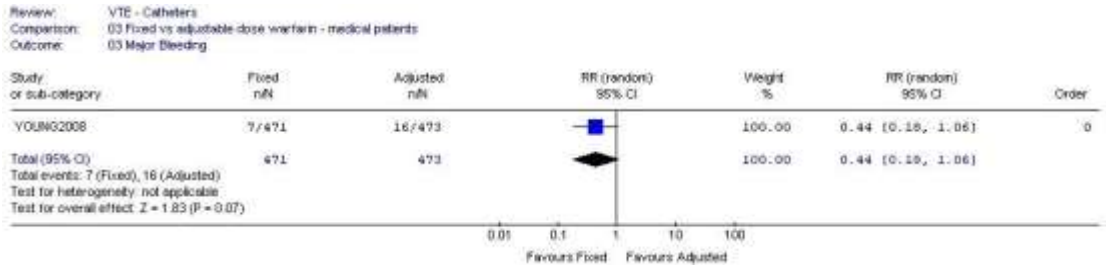


Central Venous Catheters - VKA (Fixed vs Adjusted Dose)

Forest Plot 241. CVC - VKA (Fixed vs Adjusted Dose) – Clinically Relevant (Symptomatic) Catheter Related Thrombosis



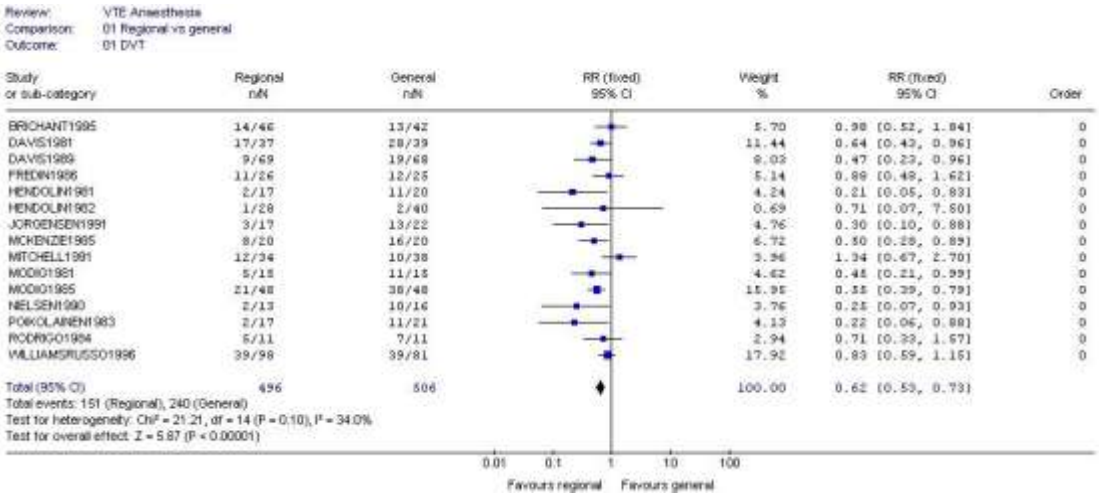
Forest Plot 242. CVC - VKA (Fixed vs Adjusted Dose) – Subgrouped By Agent – Major Bleeding



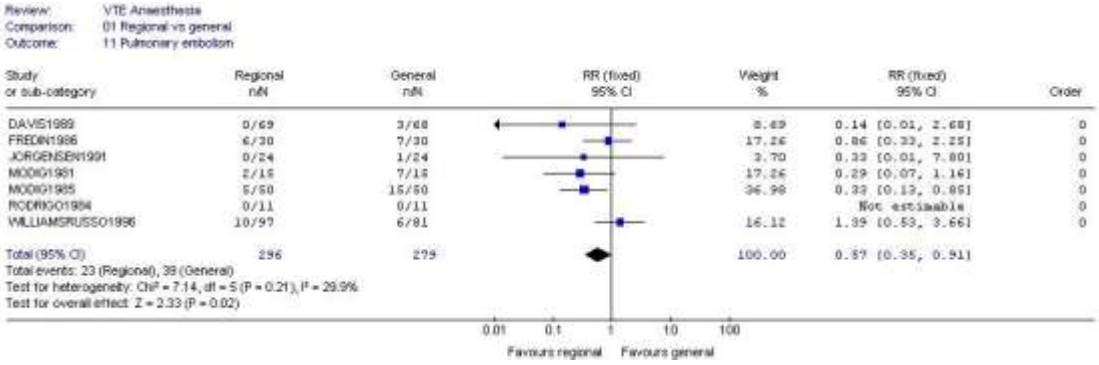
Anaesthesia

Regional vs General Anaesthesia

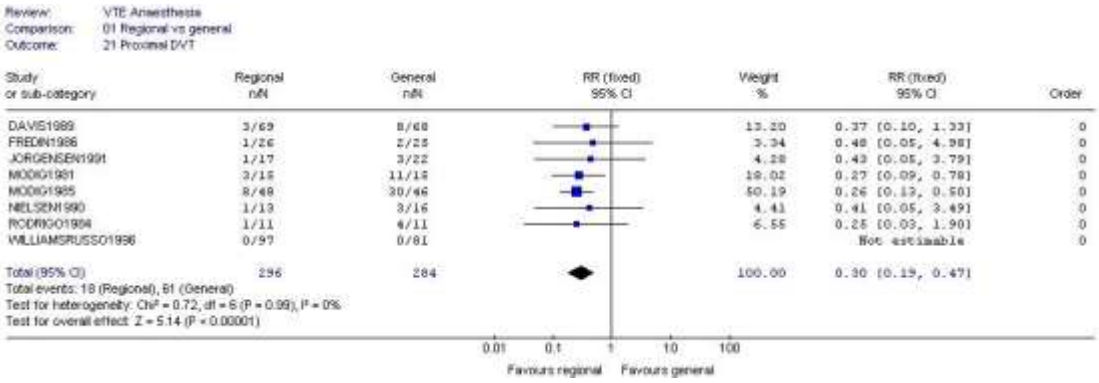
Forest Plot 243. Regional vs General Anaesthesia - DVT



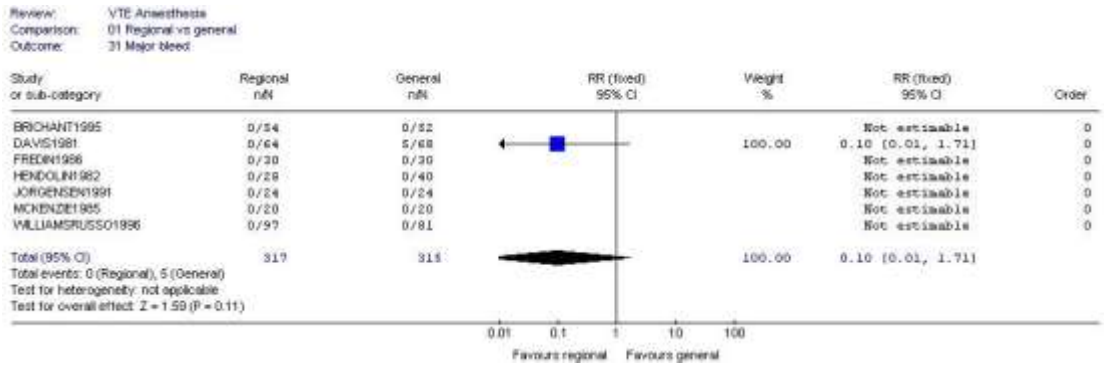
Forest Plot 244. Regional vs General Anaesthesia – Pulmonary Embolism



Forest Plot 245. Regional vs General Anaesthesia – Proximal DVT

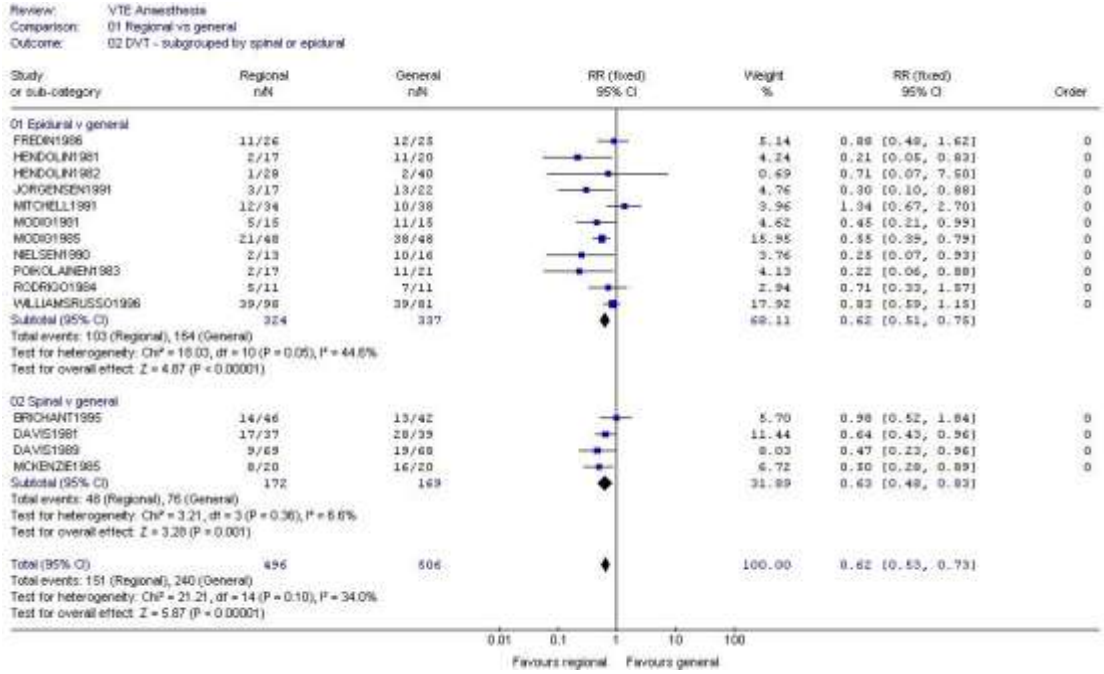


Forest Plot 246. Regional vs General Anaesthesia – Major Bleeding

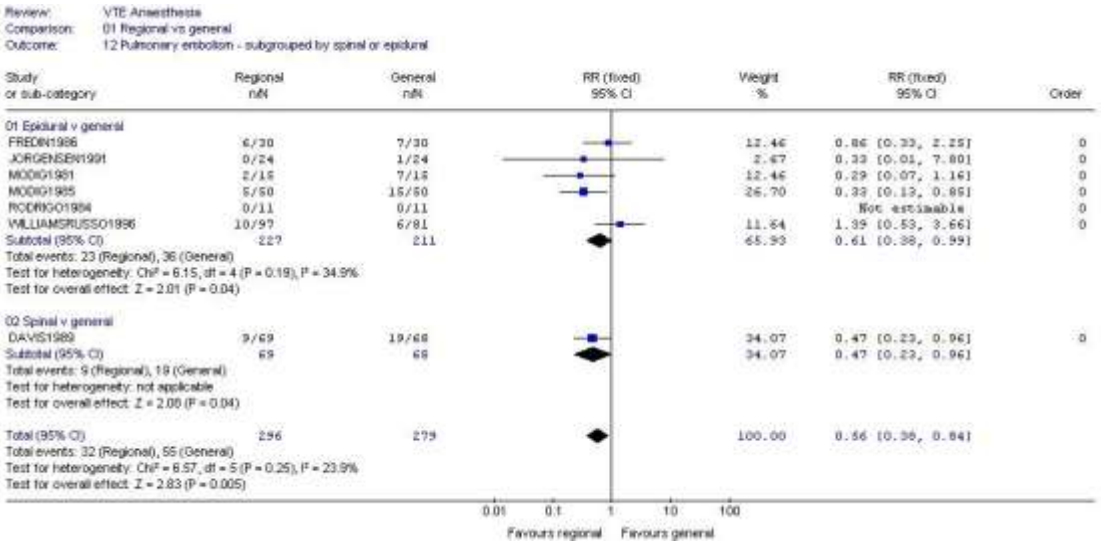


Regional vs General Anaesthesia Subgrouped By Spinal And Epidural

Forest Plot 247. Regional vs General Anaesthesia Subgrouped By Spinal And Epidural –DVT

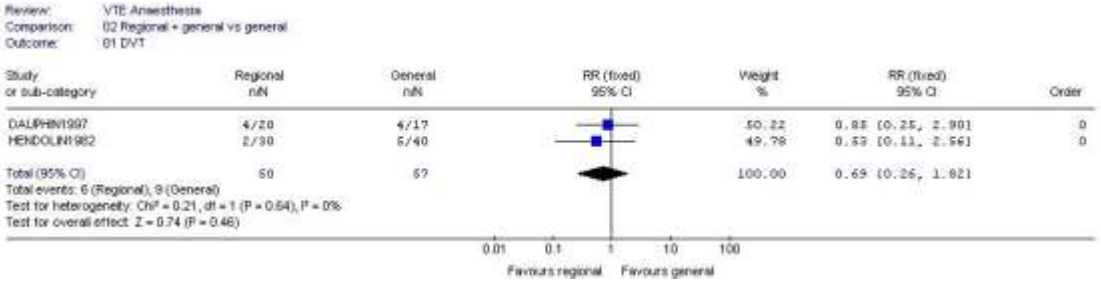


Forest Plot 248. Regional vs General Anaesthesia Subgrouped By Spinal And Epidural – Pulmonary Embolism



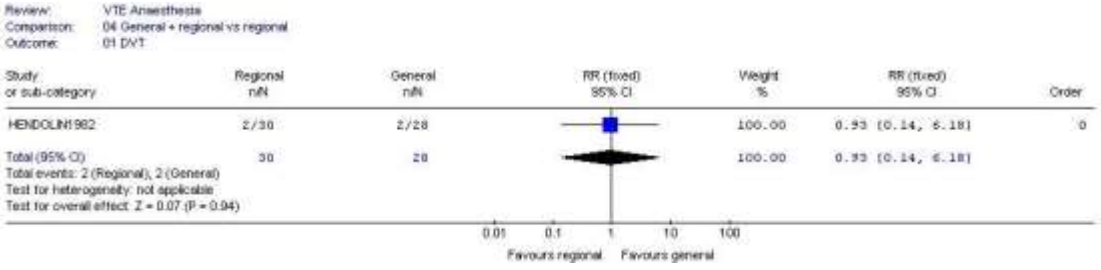
Regional + General vs General Anaesthesia

Forest Plot 249. Regional + General vs General Anaesthesia - DVT



General + Regional vs Regional Anaesthesia

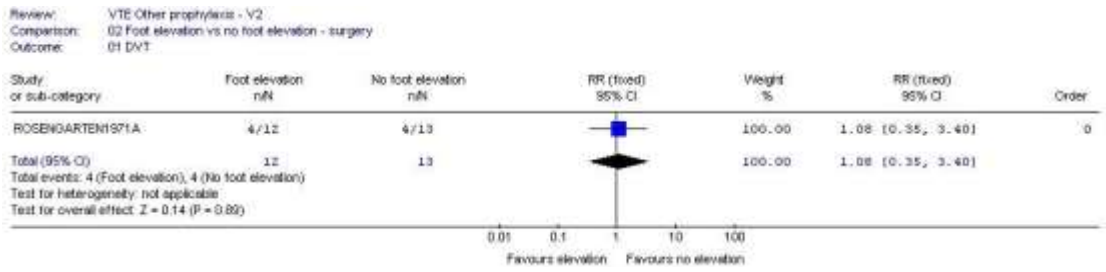
Forest Plot 250. General + Regional vs Regional Anaesthesia - DVT



Other Prophylaxis

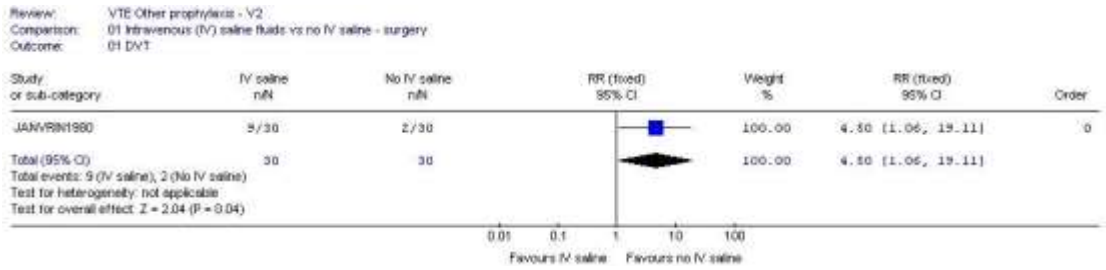
Foot Elevation

Forest Plot 251. Foot Elevation vs No Foot Elevation - DVT



Hydration

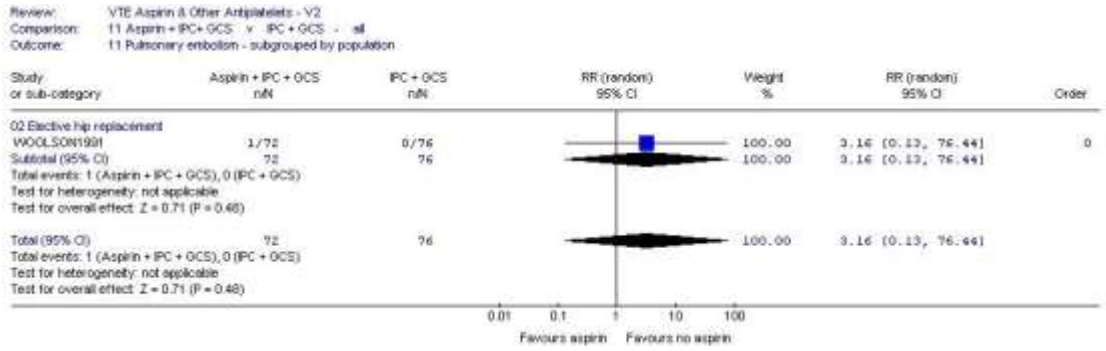
Forest Plot 252. IV Saline vs No IV Saline - DVT



Extra forest plots

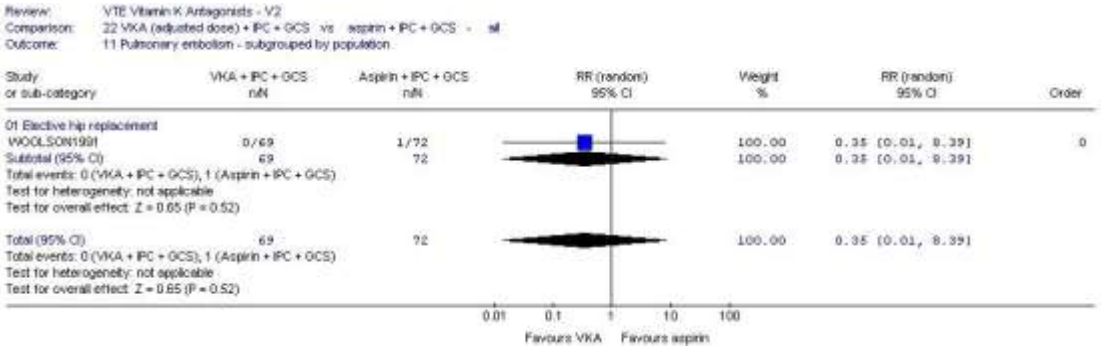
Aspirin + IPCD + GCS vs IPCD + GCS

Forest Plot 253. Aspirin + IPCD + GCS vs IPCD + GCS – pulmonary embolism



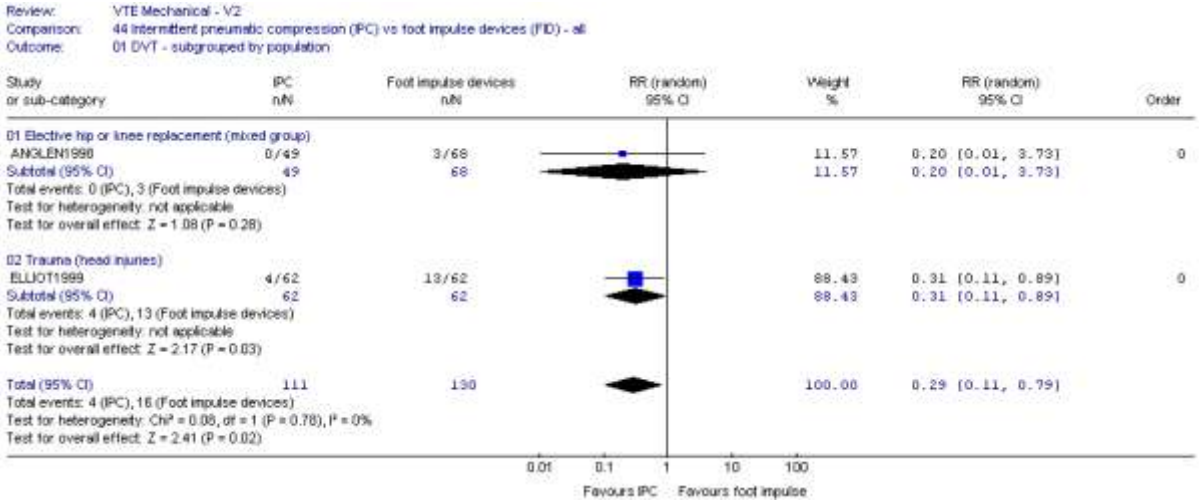
VKA + IPCD + GCS vs IPCD + GCS

Forest Plot 254. VKA + IPCD + GCS vs IPCD + GCS – pulmonary embolism

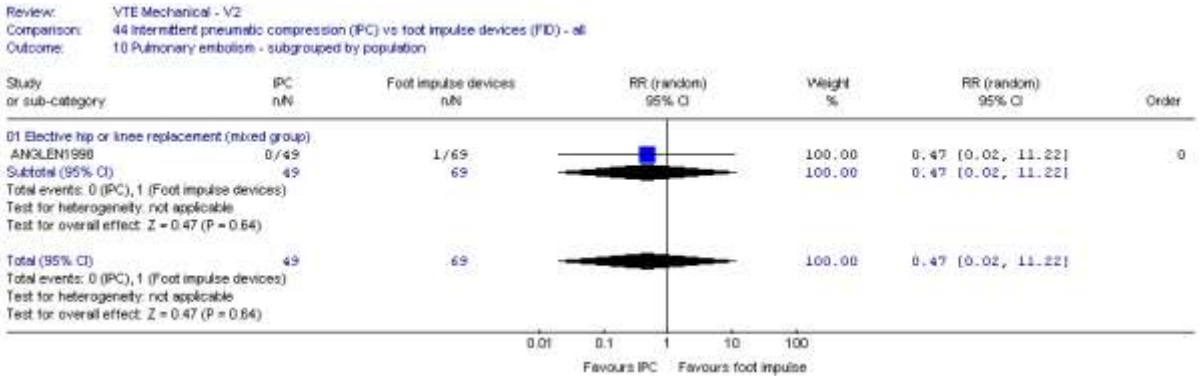


IPCD vs FID

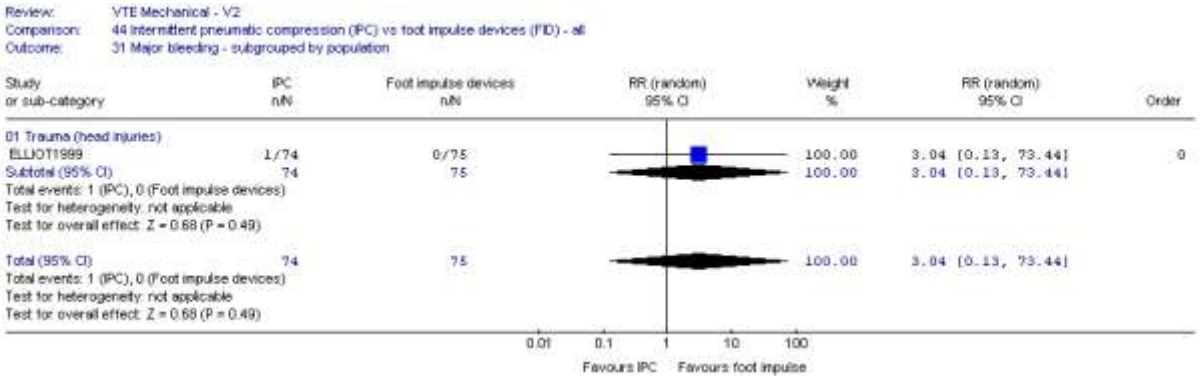
Forest Plot 255. IPCD vs FID - DVT



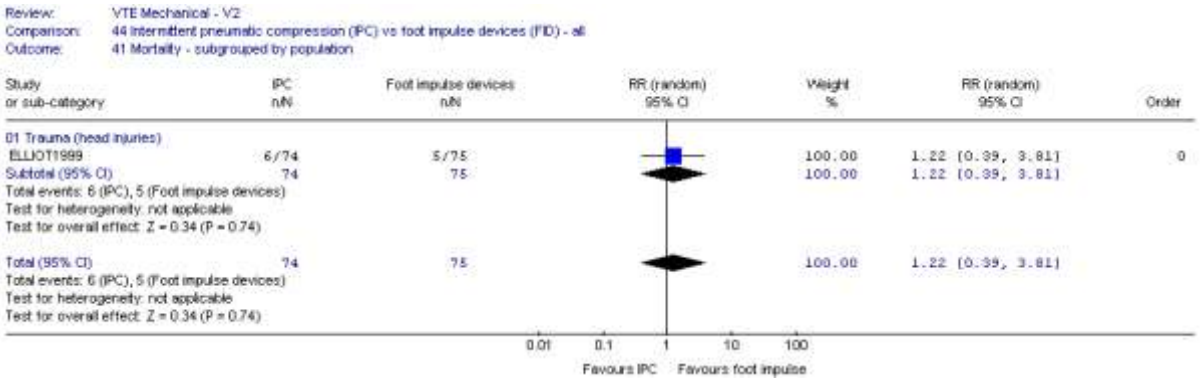
Forest Plot 256. IPCD vs FID – pulmonary embolism



Forest Plot 257. IPCD vs FID – major bleeding

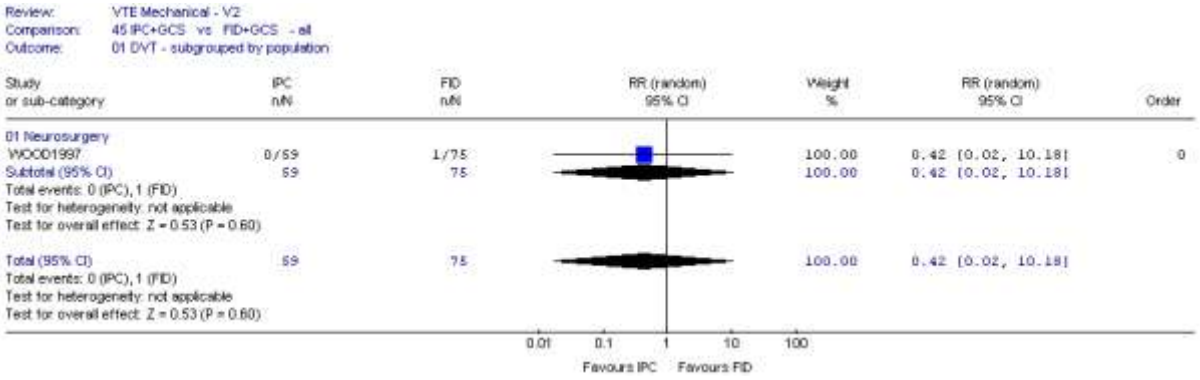


Forest Plot 258. IPCD vs FID - mortality

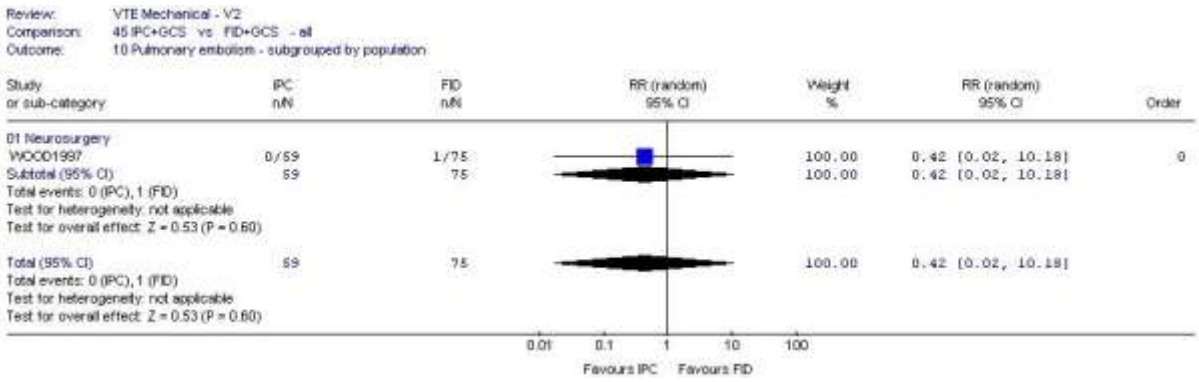


IPCD + GCS vs FID + GCS

Forest Plot 259. IPCD + GCS vs FID + GCS - DVT



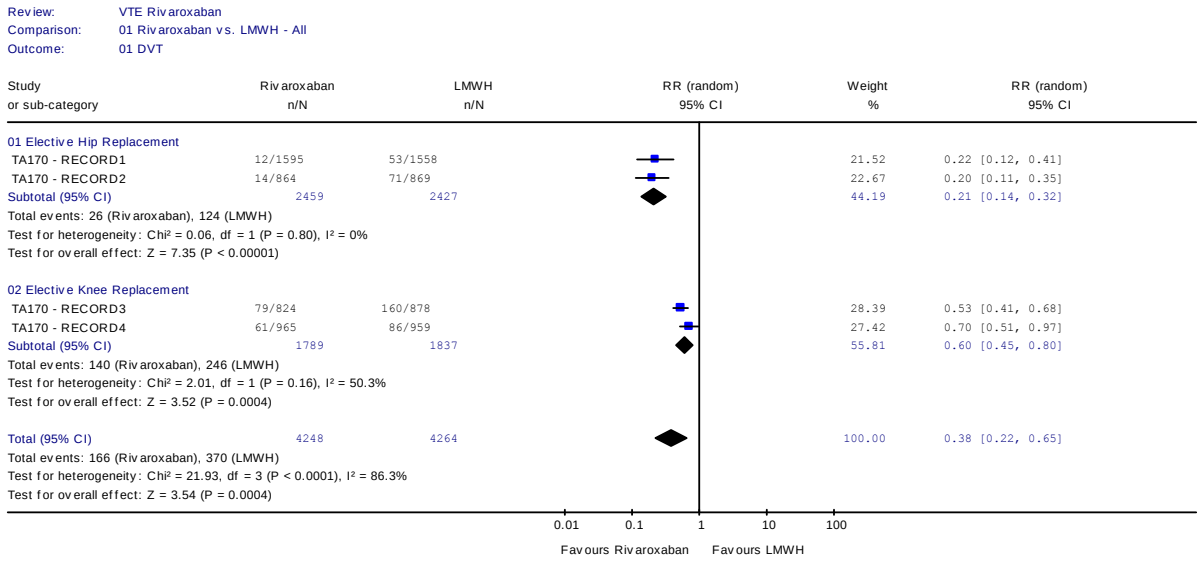
Forest Plot 260. IPCD + GCS vs FID + GCS – pulmonary embolism



Forest plots added after Consultation

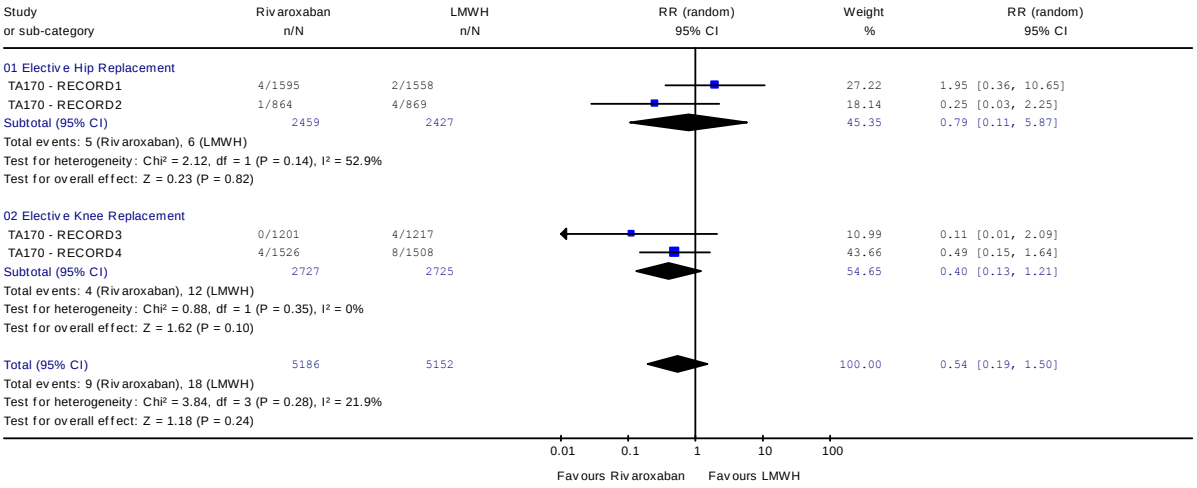
Rivaroxaban vs LMWH

Forest Plot 261. Rivaroxaban vs LMWH - DVT



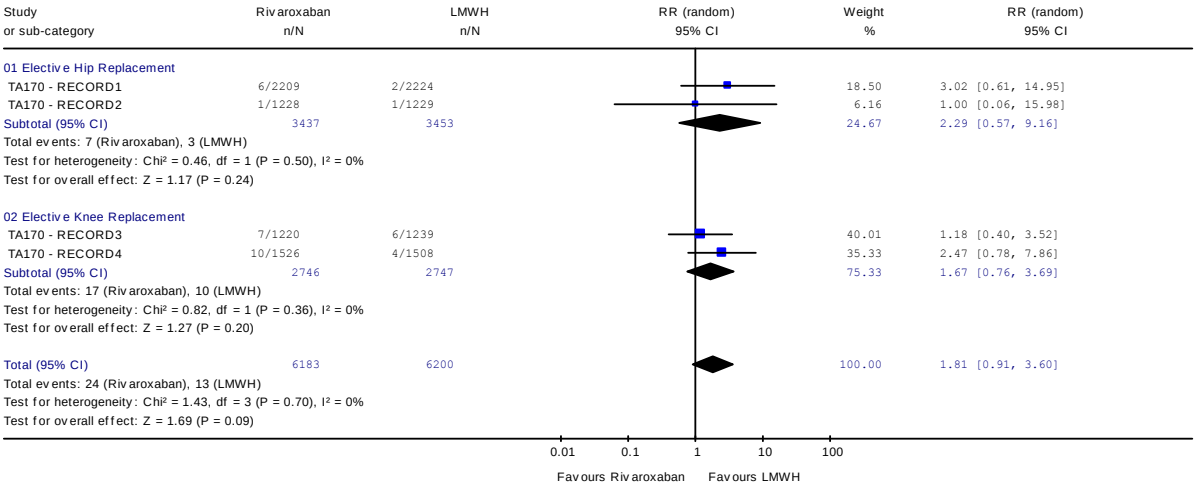
Forest Plot 262. Rivaroxaban vs LMWH – Pulmonary Embolism

Review: VTE Rivaroxaban
Comparison: 01 Rivaroxaban vs. LMWH - All
Outcome: 10 Pulmonary Embolism



Forest Plot 263. Rivaroxaban vs LMWH – Major Bleeding

Review: VTE Rivaroxaban
Comparison: 01 Rivaroxaban vs. LMWH - All
Outcome: 30 Major Bleeding



Appendix F

1 Recommendations for Research

1.1 Research recommendation for identifying risk factors for VTE

PICO question	What is the absolute risk for VTE among different groups of hospitalised patients and can the risk be reliably estimated on admission to hospital to ensure appropriate patients are offered prophylaxis? *Population:* Patients admitted to hospital *Exposure:* Admission to hospital. Factors collected should include: baseline patient related factors, procedures and duration of stay, complications, prophylactic therapies and concomitant drug use. *Outcome:* Development of VTE (symptomatic DVT or symptomatic pulmonary embolism)
Importance to patients or the population	If clinicians could estimate with confidence the absolute risks of VTE and bleeding in individuals it should be possible to spare patients at very low risk of VTE from the risk of bleeding associated with all pharmacological methods while ensuring that those at substantial risk of VTE are appropriately targeted.
Relevance to NICE	This question is central to the overall guideline: it is the entry point to every recommendation and every clinical decision to be made.
Relevance to the NHS	The impact would be on rationalising resources and optimising patient care. At present the level of concern from the Parliamentary Committee and the Chief Medical Officer is such that very wide groups of patients are considered. If we knew with confidence which groups are at such low risk that prophylaxis is not cost effective, or even has net negative effects, there would be saving in drug, device and staff costs. Conversely we could treat with confidence those where it is cost effective and thus reduce health costs caused by avoidable VTE
National priorities	Because this affects every patient admitted to hospital it might well merit a national service framework in its own right.
Current evidence base	The present evidence base is a combination of analyses of data bases, usually set up for other purposes, and some retrospective studies (evidence tables 1-2, appendix D). Most of the studies did not record the prophylaxis strategy and had

	different ascertainment which mainly captured only events occurring in hospital. These factors made it difficult to compare and evaluate across studies. The information found on patient risk factors comes from systematic reviews of cohorts and case control studies (evidence tables 3-22, appendix D). Most of the studies were set up to investigate only one of the risk factors and the differences in methods across studies made the results difficult to interpret. The latest literature search was conducted in December 2008.
Study design	New prospective cohort study, record linkage study using Hospital Episode Statistics (HES) and General Practice Research Database (GPRD) (or some combination) The data should be divided into test and validation sets. Futher validation studies should then be carried out in particular patient groups. The outcome should be the development of a clinically useful tool for estimating absolute risk for VTE in hopsitalised patients coupled to recommentdations on targeting of therapies.
Feasibility	There are groups with great expertise in cohort analysis and record linkage work using databases of routinely collected clinical data. Feasibility would depend on expert advice but included should be a study of randomly selected cases to verify the quality of the data and quantify the level of error in the data set being used. No ethical issues but considerable technical issues are anticipated. Record linkage between HES and GPRD has been established using the NHS number as a unique identifier.
Other comments	This merits NHS funding in our view. We do not think that this has been previously attempted at the population level we are suggesting.
Importance	HIGH

1.2 Research recommendation for identifying the incidence of post thrombotic syndrome after DVT

PICO question	What is the incidence, loss of quality of life and the cost associated with post thrombotic syndrome (PTS) after potentially preventable deep vein thrombosis? *Population:* Patients (medical or surgery) admitted to hospital. *Exposure:* Objectively identified DVT (asymptomatic) or no DVT *Outcome:* Post thrombotic syndrome identified using a standard, validated definition
Importance to patients or the population	Post thrombotic syndrome is an irreversible condition which has a high burden of symptoms and disability. Chronic leg ulceration which is one of the consequences has high treatment costs.
Relevance to NICE	The costs of management of patients with post thrombotic syndrome (PTS) is known to be high but how many of these follow a preventable episode of deep vein thrombosis associated with hospitalisation? Economic models developed and run for this guideline are sensitive to the inclusion of PTS but without better evidence of cost effectiveness of VTE prophylaxis in reducing PTS, economic estimations will continue to contain a large element of uncertainty.
Relevance to the NHS	The potential reduction in NHS costs is considerable if post thrombotic syndrome could be prevented by a VTE prophylactic strategy.
National priorities	This is not a national priority in term in terms of national service framework or white paper.
Current evidence base	There are no trials identified that used post-thrombotic syndrome as an outcome and followed patients up. Two systematic reviews of cohort studies were identified that followed up patients after asymptomatic or symptomatic DVT. The problem is that it is impossible to ascertain the proportion of hospital acquired episodes of deep vein thrombosis (symptomatic and asymptomatic) that go on to cause post thrombotic syndrome. In addition, it was unclear from these studies whether patients were provided with VTE prophylaxis and if this had any impact on the incidence of post-thrombotic syndrome.
Study design	This would entail long term follow up (minimum of three years) of all cases of hospital acquired VTE along with a control group. This is essential because PTS can follow undiagnosed DVT.
Feasibility	The feasibility will require expert evaluation and costing. On initial review the GDG did not think that there should be

	ethical or technical issues with the research.
Other comments	We are not aware of any prospective study which addresses the question.
Importance	HIGH

1.3 Research recommendation for reducing the risk of VTE in medical patients

PICO question	What is the clinical and cost effectiveness of pharmacological prophylaxis, mechanical prophylaxis and combined pharmacological and mechanical prophylaxis for the prevention of VTE in medical patients? *Population:* Medical patients admitted to hospital. *Intervention:* Pharmacological prophylaxis as recommended by the NICE guideline (low molecular weight heparin, fondaparinux or unfractionated heparin). Newer oral anticoagulants (e.g. dabigatran and rivaroxaban) do not have a license for this population *Comparison:* Three arm trial with either mechanical prophylaxis (such as anti-embolism stockings, foot impulse or intermittent pneumatic compression devices). *Outcome:* All cause mortality, DVT events (all patient screened to identify asymptomatic events), symptomatic PE and major bleeding.
Importance to patients or the population	VTE in hospitalised patients is believed to constitute a very large total of preventable death and morbidity.
Relevance to NICE	Guidance at present is mainly based on extrapolation from the effect of strategies in surgical patients. More direct evidence would enable the NICE guideline to target guidance for this group.
Relevance to the NHS	Extra bed days, readmissions and intensive care stay attributable to preventable VTE might be high and is believed to be so by some. In addition, if we knew with confidence which groups are at such low risk that a higher level prophylaxis (e.g. pharmacological prophylaxis) is not cost effective, or even has net negative effects, there would be saving in drug, device and staff costs.
National priorities	This research should be a national priority.
Current evidence base	There was a lack of evidence in medical patients compared with surgical patients. The only studies identified included a wide range of medical patients and many did not attempt any stratification to determine if there were any characteristics which identified particular groups at particular risk. There were only two small studies investigating mechanical prophylaxis in medical patients (conducted in patients with stroke and acute coronary syndromes). Information about mechanical only prophylaxis and combination prophylaxis (both mechanical and pharmacological methods) is lacking in this population. There is no evidence for extending prophylaxis outside the initial

	hospital period in these groups. The latest literature search was conducted in December 2008.
Study design	An RCT with a wide entry and clinical outcome measures including length of stay, readmission for VTE, ITU admission and one year survival.
Feasibility	This trial would clearly be a large and expensive exercise but feasible. This is the sort of trial which would merit strong central direction and imperatives.
Other comments	The newer oral anticoagulants (such as dabigatran and rivaroxaban) provide an opportunity to update the evidence and to obtain industry funding.
Importance	HIGH

1.4 Research recommendation for reducing the risk of VTE in patients after stroke

PICO question	What is the overall risk/benefit on both stroke outcome and VTE, for LMWH and/or fondaparinux in patients with acute stroke? *Population:* Patients with new onset stroke admitted to hospital. *Intervention:* Pharmacological prophylaxis as recommended by the NICE guideline (low molecular weight heparin or fondaparinux) in addition to the standard treatments for stroke as recommended by the NICE stroke guideline. *Comparison:* Standard treatments for stroke as recommended by the NICE stroke guideline. *Outcome:* All cause mortality, VTE events, stroke outcomes (such as level of disability at 6 months), major bleeding including intracranial bleeding.
Importance to patients or the population	Stroke is the commonest cause of disability and a common cause of death. There is a drive towards active treatments to improve outcomes for this group of patients who may have a lot to gain from active evidence based strategies.
Relevance to NICE	At present there is a potential conflict for NICE guidance. Doctors concerned with stroke outcome fear the potential additional neurological damage from bleeding. At the same time we are aware of the risk of VTE in these immobilised patients. Where does the balance lie?
Relevance to the NHS	The potential for adding harm and thus adding costs by anticoagulation should be a major concern to the NHS. This needs to be balanced against the cost of treating VTE events and the long term cost of the consequences of VTE.
National priorities	Yes. Stroke is already the subject of a national service framework.
Current evidence base	During the preparation of the VTE guideline we had discussions with our opposite numbers in the Stroke GDG. It was clear that we both lacked evidence on which to base confident advice. There are two RCTs in patients with ischaemic stroke which investigate the VTE outcomes after combining unfractionated heparin or low molecular weight heparin with aspirin. These studies identified a reduction in risk of all DVT events without a significant increase in major bleeding. The effects of this treatment relating specifically to stroke outcomes were not well recorded in the trials. The latest date of the literature search was December 2008.
Study design	RCT

Feasibility	Although the set-up and running of RCTs is costly, it is clearly feasible through the two recent trials which have been run. The GDG did not consider there would be any ethical or technical issues relating to this research.
Other comments	None
Importance	HIGH

1.5 Research recommendation for reducing the risk of VTE in patients with lower limb plaster casts

PICO question	What is the clinical and cost effectiveness of pharmacological prophylaxis for the prevention of VTE in patients with lower limb plaster casts? *Population:* Patients with lower limb plaster casts after conservative fracture management, operative fracture fixation, and elective surgery. *Intervention:* Pharmacological prophylaxis until plaster cast removal. *Control:* No prophylaxis *Outcome:* all cause mortality, confirmed VTE, subsequent hospital admission for VTE and features of post thrombotic syndrome. Adverse events of prophylaxis should also be reported.
Importance to patients or the population	Death from pulmonary embolism, although very rare, is a tragic consequence of a completely recoverable lower limb fracture. This might occur in a very young person and represent a great loss in life years. The incidence of post thrombotic syndrome (PTS) in this context is not known. PTS is associated with a high level of symptoms and disability.
Relevance to NICE	This is a large patient group for whom the evidence is not clear and the recommendation is tentative. Further information in this area would allow more specific recommendations for which patients should receive thromboprophylaxis to be created.
Relevance to the NHS	A very large number of patients have a lower limb (ankle or ankle and knee) immobilised in a plaster cast. This is designed to prevent movement to alleviate pain and allow healing of the injury. At the same time this prevents the normal pumping mechanisms which assist venous blood flow. There would be a substantial cost to the NHS of providing thromboprophylaxis to all patients with a lower limb plast cast, particularly if patients use prophylaxis until cast removal which may be a number of weeks.
National priorities	Although the GDG thought this was important research it is probably not a national priority in terms of national service framework or white paper.
Current evidence base	There were 5 studies of the use of low molecular weight heparin with lower limb plaster casts identified in the systematic review for this guideline. These studies indicate that there is a significant reduction in asymptomatic DVT events with low molecular weight heparin. However, within the studies the incidence of DVT in the arms of the studies not receiving prophylaxis vary from 4% to 40%, and the incidence of

	symptomatic pulmonary embolism was low. The GDG felt that more work to ensure that more evidence to identify the factors that increased the risk in this population warranted attention. The latest date of the literature search was December 2008.
Study design	A randomised controlled trial using an oral agent with three year follow up with clinical outcome measures including death, confirmed VTE, subsequent hospital admission for VTE and features of post thrombotic syndrome. The population (in the first row above) would either have to be a selected subset of the groups listed above or a stratified design.
Feasibility	A randomised controlled trial for patients is clearly feasible and able to be completed in a feasible timescale, although it is likely to be costly. Members of the orthopaedic subgroup did not foresee any ethical or technical issues with the research.
Other comments	This is a potential use of the new oral anticoagulants. Joint NHS and industry funding might be considered.
Importance	HIGH

Appendix G

Additional Results from Cost-effectiveness Analysis

Table 1: Event rates per 1000 patients: General medical - in-hospital

	All DVT	Sympto-matic DVT		Fatal PE	Sympto-matic PE non-fatal		PTS	CTEPH		All major bleed	Fatal bleed	Intra-cranial bleed
Nil	134.0	8.3		4.0	5.0		22.2	0.04		3.8	0.55	0.11
Fon	98.7	6.1		2.9	3.6		16.3	0.03		11.5	1.64	0.34
LMWH	58.0	3.6		1.7	2.1		9.6	0.02		6.1	0.87	0.18
UFH	85.9	5.3		2.6	3.2		14.2	0.02		7.0	0.99	0.21

Table 2: Event rates per 1000 patients: Hip fracture surgery - in-hospital

	All DVT	Sympto-matic DVT		Fatal PE	Sympto-matic PE non-fatal		PTS	CTEPH		All major bleed	Fatal bleed	Intra-cranial bleed	Reope ration
Nil	398.0	83.6		24.5	54.5		81.7	0.41		32.0	0.26	0.96	4.2
AspHD	315.5	66.2		19.4	43.2		64.7	0.32		32.0	0.26	0.96	4.2
Fon	50.7	10.6		3.1	6.9		10.4	0.05		74.2	0.59	2.23	9.65
LMWH	117.1	24.6		7.2	16.0		24.0	0.12		40.8	0.33	1.23	5.31
UFH	163.8	34.4		10.1	22.4		33.6	0.17		46.4	0.37	1.39	6.03
Warf	133.5	28.0		8.2	18.3		27.4	0.14		40.5	0.32	1.22	5.27
IPC/FID	247.4	52.0		15.2	33.9		50.8	0.25		32.0	0.26	0.96	4.16

Table 3: Event rates per 1000 patients: Total hip replacement - in-hospital

	All DVT	Sympto-matic DVT		Fatal PE	Sympto-matic PE non-fatal		PTS	CTEPH		All major bleed	Fatal bleed	Intra-cranial bleed	Reope ration
Nil	450.0	94.5		2.0	32.0		84.9	0.24		16.0	0.13	0.48	2.08
AspHD	297.9	62.6		1.4	21.2		56.2	0.16		16.0	0.13	0.48	2.08
AspLD	215.9	45.3		1.0	15.3		40.8	0.12		16.0	0.13	0.48	2.08
GCS	209.7	44.0		1.0	14.9		39.6	0.11		16.0	0.13	0.48	2.08
LMWH	161.1	33.8		0.7	11.4		30.4	0.09		30.0	0.240	0.900	3.90
UFH	226.7	47.6		1.0	16.1		42.8	0.12		34.1	0.273	1.022	4.43
Warf	291.2	61.1		1.3	20.7		55.0	0.16		29.7	0.24	0.89	3.86
IPC/FID	246.5	51.8		1.1	17.5		46.5	0.13		16.0	0.13	0.48	2.08
UFH+GCS	92.9	19.5		0.4	6.6		17.5	0.0		34.1	0.27	1.02	4.43
UFH+AspHD	255.6	53.7		1.2	18.2		48.2	0.1		72.4	0.58	2.17	9.42
UFH+IPC/FID	143.8	30.2		0.7	10.2		27.1	0.1		34.1	0.27	1.02	4.43
LMWH+GCS	105.3	22.1		0.5	7.5		19.9	0.1		30.0	0.24	0.90	3.90
AspHD+GCS	357.8	75.1		1.6	25.4		67.5	0.2		16.0	0.13	0.48	2.08
Fon+GCS	61.1	12.8		0.3	4.3		11.5	0.0		55.1	0.44	1.65	7.16
Warf+GCS	204.4	42.9		0.9	14.5		38.6	0.1		29.7	0.24	0.89	3.86

Table 4: Event rates per 1000 patients: Total knee replacement - in-hospital

	All DVT	Sympto-matic DVT		Fatal PE	Sympto-matic PE non-fatal		PTS	CTEPH		All major bleed	Fatal bleed	Intra-cranial bleed	Reope ration
Nil	600.0	30.0		0.6	9.4		95.4	0.07		19.00	0.15	0.57	2.47
AspHD	57.1	2.9		0.1	0.9		9.1	0.01		43.9	0.351	1.32	5.70
Fon	57.1	2.9		0.1	0.9		9.1	0.01		43.9	0.351	1.32	5.70
LMWH	128.2	6.4		0.1	2.0		20.4	0.02		23.7	0.190	0.71	3.09
UFH	215.9	10.8		0.2	3.4		34.3	0.03		27.0	0.216	0.81	3.51
Warf	222.9	11.1		0.2	3.5		35.4	0.03		23.5	0.188	0.71	3.06
IPC/FID	193.0	9.7		0.2	3.0		30.7	0.02		19.0	0.152	0.57	2.47
LMWH+I PC/FID	137.6	6.9		0.1	2.2		21.9	0.0		23.7	0.19	0.71	3.09
AspHD+ IPC/FID	143.6	7.2		0.1	2.3		22.8	0.0		19.0	0.15	0.57	2.47
Dabig	143.5	7.2		0.1	2.2		22.8	0.0		19.0	0.15	0.57	2.47
Rivaroxa ban	79.1	4.0		0.1	1.2		12.6	0.0		47.0	0	1	6

Table 5: Event rates per 1000 patients: General surgery - in-hospital

	All DVT	Sympto-matic DVT		Fatal PE	Sympto-matic PE non-fatal		PTS	CTEPH		All major bleed	Fatal bleed	Intra-cranial bleed	Reope ration
Nil	209.0	13.0		0.8	12.6		35.8	0.09		13.65	0.11	0.41	2.87
AspHD	126.8	7.9		0.5	7.6		21.7	0.06		13.65	0.11	0.41	2.87
Fon	48.3	3.0		0.2	2.9		8.3	0.02		59.1	0.473	1.77	12.40
GCS	75.7	4.7		0.3	4.5		13.0	0.03		13.6	0.109	0.41	2.87
LMWH	58.7	3.6		0.2	3.5		10.0	0.03		32.3	0.258	0.97	6.77
UFH	70.7	4.4		0.3	4.2		12.1	0.03		36.7	0.293	1.10	7.70
Warf	65.0	4.0		0.2	3.9		11.1	0.03		32.0	0.256	0.96	6.72
IPC/FID	77.6	4.8		0.3	4.7		13.3	0.03		13.6	0.109	0.41	2.87
UFH+GCS	19.6	1.2		0.1	1.2		3.4	0.0		36.7	0.29	1.10	7.70
UFH+AspHD	40.7	2.5		0.2	2.4		7.0	0.0		77.4	0.62	2.32	16.26
LMWH+GCS	50.4	3.1		0.2	3.0		8.6	0.0		32.3	0.26	0.97	6.77
Fon+IPC/FID	29.1	1.8		0.1	1.7		5.0	0.0		59.1	0.47	1.77	12.40

Table 6: Event rates per 1000 patients: Hip fracture surgery - post-discharge

	All DVT	Sympto-matic DVT		Fatal PE	Sympto-matic PE non-fatal		PTS	CTEPH		All major bleed	Fatal bleed	Intra-cranial bleed	Reope ration
Nil	339.0	71.2		2.8	6.2		59.5	0.05		6.00	0.05	0.18	0.78
Fon	13.6	2.8		0.1	0.2		2.4	0.00		24.1	0.193	0.72	3.14

Table 7: Event rates per 1000 patients: General surgery - post-discharge

	All DVT	Sympto-matic DVT		Fatal PE	Sympto-matic PE non-fatal		PTS	CTEPH		All major bleed	Fatal bleed	Intra-cranial bleed	Reope ration
Nil	105.0	6.5		0.5	7.5		18.3	0.06		9.00	0.07	0.27	1.89
LMWH	48.3	3.0		0.2	3.5		8.4	0.03		9.0	0.072	0.27	1.89

Table 8: Event rates per 1000 patients: Total hip replacement - post-discharge

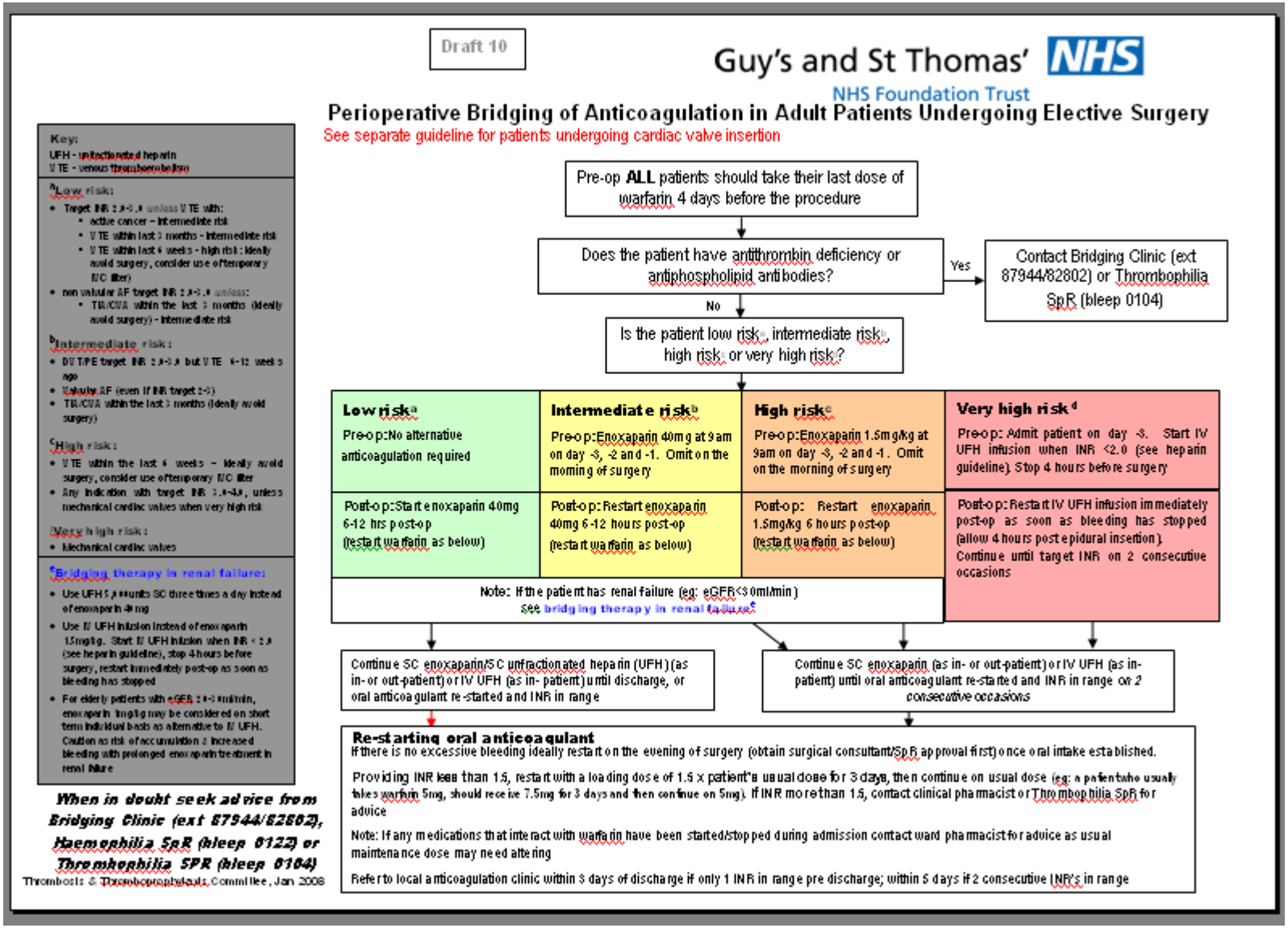
	All DVT	Sympto-matic DVT		Fatal PE	Sympto-matic PE non-fatal		PTS	CTEPH		All major bleed	Fatal bleed	Intra-cranial bleed	Reope ration
Nil	255.0	53.6		0.4	5.6		45.0	0.04		2.00	0.02	0.06	0.26
LMWH	104.6	22.0		0.1	2.3		18.5	0.02		2.0	0.016	0.06	0.26

Table 9: Event rates per 1000 patients: Total hip replacement - extended prophylaxis

	All DVT	Sympto-matic DVT		Fatal PE	Sympto-matic PE non-fatal		PTS	CTEPH		All major bleed	Fatal bleed	Intra-cranial bleed	Reope ration
LMWH	44.0	9.2		0.1	1.9		8.0	0.01		4.00	0.03	0.12	0.52
Dabig	46.2	9.7		0.1	2.0		8.4	0.0		4.2	0.03	0.13	0.55
Rivaroxa ban	9.7	2.0		0.0	0.4		1.8	0.0		12.1	0	0	2

Appendix H

Warfarin Bridging Algorithm (example)



Draft 10

Guy's and St Thomas' NHS
NHS Foundation Trust

Perioperative Bridging of Anticoagulation in Adult Patients Undergoing Elective Surgery

See separate guideline for patients undergoing cardiac valve insertion

Key:
UFH - unfractionated heparin
VTE - venous thromboembolism

[a] Low risk:
- Target INR 2.0-3.0 unless VTE with:
  - active cancer – intermediate risk
  - VTE within last 3 months - intermediate risk
  - VTE within last 6 weeks - high risk: ideally avoid surgery, consider use of temporary IVC filter)
- non valvular AF target INR 2.0-3.0 unless:
  - TIA/CVA within the last 3 months (ideally avoid surgery) - intermediate risk

[b] Intermediate risk:
- DVT/PE target INR 2.0-3.0 but VTE 6-12 weeks ago
- Valvular AF (even if INR target 2-3)
- TIA/CVA within the last 3 months (ideally avoid surgery)

[c] High risk:
- VTE within the last 6 weeks – ideally avoid surgery, consider use of temporary IVC filter
- Any indication with target INR 3.0-4.0, unless mechanical cardiac valves when very high risk

[d] Very high risk:
- Mechanical cardiac valves

[e] Bridging therapy in renal failure:
- Use UFH 5,000 units SC three times a day instead of enoxaparin 40 mg
- Use IV UFH infusion instead of enoxaparin 1.5mg/kg. Start IV UFH infusion when INR < 2.0 (see heparin guideline), stop 4 hours before surgery, restart immediately post-op as soon as bleeding has stopped
- For elderly patients with eGFR 10-30 ml/min, enoxaparin 1mg/kg may be considered on short term individual basis as alternative to IV UFH. Caution as risk of accumulation & increased bleeding with prolonged enoxaparin treatment in renal failure

When in doubt seek advice from Bridging Clinic (ext 87944/82802), Haemophilia SpR (bleep 0122) or Thrombophilia SPR (bleep 0104)

Thrombosis & Thromboprophylaxis Committee, Jan 2008

Pre-op **ALL** patients should take their last dose of warfarin 4 days before the procedure

Does the patient have antithrombin deficiency or antiphospholipid antibodies?

Yes → Contact Bridging Clinic (ext 87944/82802) or Thrombophilia SpR (bleep 0104)

No

Is the patient low risk[a], intermediate risk[b], high risk[c] or very high risk[d]?

Low risk[a]	Intermediate risk[b]	High risk[c]	Very high risk[d]
Pre-op: No alternative anticoagulation required	Pre-op: Enoxaparin 40mg at 9am on day -3, -2 and -1. Omit on the morning of surgery	Pre-op: Enoxaparin 1.5mg/kg at 9am on day -3, -2 and -1. Omit on the morning of surgery	Pre-op: Admit patient on day -3. Start IV UFH infusion when INR <2.0 (see heparin guideline). Stop 4 hours before surgery
Post-op: Start enoxaparin 40mg 6-12 hrs post-op (restart warfarin as below)	Post-op: Restart enoxaparin 40mg 6-12 hours post-op (restart warfarin as below)	Post-op: Restart enoxaparin 1.5mg/kg 6 hours post-op (restart warfarin as below)	Post-op: Restart IV UFH infusion immediately post-op as soon as bleeding has stopped (allow 4 hours post epidural insertion). Continue until target INR on 2 consecutive occasions

Note: If the patient has renal failure (eg: eGFR<30ml/min) see bridging therapy in renal failure[e]

Continue SC enoxaparin/SC unfractionated heparin (UFH) (as in- or out-patient) or IV UFH (as in- patient) until discharge, or oral anticoagulant re-started and INR in range

Continue SC enoxaparin (as in- or out-patient) or IV UFH (as in-patient) until oral anticoagulant re-started and INR in range on *2 consecutive occasions*

Re-starting oral anticoagulant

If there is no excessive bleeding ideally restart on the evening of surgery (obtain surgical consultant/SpR approval first) once oral intake established.

Providing INR less than 1.5, restart with a loading dose of 1.5 x patient's usual dose for 3 days, then continue on usual dose (eg: a patient who usually takes warfarin 5mg, should receive 7.5mg for 3 days and then continue on 5mg). If INR more than 1.5, contact clinical pharmacist or Thrombophilia SpR for advice

Note: If any medications that interact with warfarin have been started/stopped during admission contact ward pharmacist for advice as usual maintenance dose may need altering

Refer to local anticoagulation clinic within 3 days of discharge if only 1 INR in range pre discharge; within 5 days if 2 consecutive INR's in range

Appendix I

1 Winbugs code for Network Meta-Analysis

Random effect model template: includes correlation structure for 3-arm trials

Adapted from code to be found here:

https://www.bris.ac.uk/cobm/research/mpes/mixed-treatment-comparisons.html

Yellow highlighted sections need to be edited for each analysis.

Substitute these for the numerical values:

N = number of data points (total number of trial arms)

NS = number of studies

NT = number of treatment strategies

BR = baseline risk = event rate in arm 1

```
model{
sw[1] <- 0
for(i in 1:N)  {
logit(p[i])<-mu[s[i]]+ delta[i]  * (1-equals(t[i],b[i]))      #  model
      r[i]~dbin(p[i],n[i])                                    #  binomial likelihood
       delta[i] ~ dnorm(md[i],taud[i])I(-5,5)                 # trial-specific LOR distributions
       taud[i] <- tau * (1 + equals(m[i],3) /3)               # precisions of LOR distributions
      md[i] <- d[t[i]] - d[b[i]]  +  equals(m[i],3) * sw[i]          # means of LOR distributions
```

#Deviance residuals for data i

```
      rhat[i] <- p[i] * n[i]
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-rhat[i])))
     }

sumdev <- sum(dev[ ])                                  # Calculate residual deviance


for (i in 2:N)
{   sw[i] <- (delta[i-1] -  d[t[i-1]] + d[b[i-1]])/2}        # adjustment for 3-arm trials

for(j in 1:NS){ mu[j]~dnorm(0,.0001) }                  # vague priors for trial baselines

d[1]<-0
for (k in 2:NT)  {d[k] ~ dnorm(0,.0001) }        # vague priors for basic parameters

sd~dunif(0,2)                    #  vague prior for random effects standard deviation
tau<-1/pow(sd,2)

rr[1]<-1
for (k in 2:NT)  {logit(v[k])<-logit(BR)+d[k]
rr[k]<-v[k]/BR  }                                       # calculate relative risk

# Pairwise ORs
for (c in 1:(NT-1))
        {  for (k in (c+1):NT)
              {  lor[c,k] <- d[k] - d[c]
                 log(or[c,k]) <- lor[c,k]
              }
```

```
        }
}
```

Data from trials

s[ ] t[ ] r[ ] n[ ] b[ ] m[ ]

Insert data here (one row for each trial arm) e.g.

1 1 79 702 1 1

1 2 80 699 1 2

END

s[ ]=Study number

t[ ]=Treatment number

r[ ]=Number of patients experiencing the event

n[ ]=Number of patients in the trial arm

b[ ]=Baseline arm (i.e. lowest treatment number within the trial)

m[ ]=Arm number in the trial

#initial values

```
list(
d=c(NA,-0.5,-1,-0.2),            # ensure there is one initial value for each treatment (NT)
sd=1.2,
mu=c(-2.2,-2.3,-2.4,-2.5,-2.6,  -2.2,-2.3,-2.4,-2.5,-2.6,  -2.2,-2.3,-2.4,-2.5,-2.6,  -
2.2,-2.3,-2.4,-2.5,-2.6,  -2.2,-2.3,-2.4,-2.5,-2.6),
                                 # ensure there is one initial value for each trial (NS)
delta=c(0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-
0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-0.8,
0,-0.2,-0.4,-0.6,-0.8)
                                 # ensure there is one initial value for each data point (N)
)
```

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