Appendix M: Network meta-analyses (NMAs)

M.1 Network meta-analysis for elective hip replacement surgery

M.1.1 Introduction

The results of conventional meta-analyses of direct evidence alone (as presented in the GRADE profiles in appendix K and forest plots in appendix L) does not help inform which intervention is most effective as VTE prophylaxis in patients undergoing elective hip replacement surgery. The challenge of interpretation has arisen for two reasons:

- In isolation, each pair-wise comparison does not inform the choice among the different treatments; in addition direct evidence is not available for some pair-wise comparisons in a randomised controlled trial.
- There are frequently multiple overlapping comparisons that could potentially give inconsistent estimates of effect.

To overcome these problems, a hierarchical Bayesian network meta-analysis (NMA) was performed. This type of analysis allows for the synthesis of data from direct and indirect comparisons without breaking randomisation and allows for the ranking of different interventions. In this case the outcomes were defined as:

- Deep vein thrombosis (DVT; symptomatic and asymptomatic)
- Pulmonary embolism (PE)
- Major bleeding

The analysis also provided estimates of effect (with 95% credible intervals) for each intervention compared to one another and compared to a single baseline risk (in this case the baseline treatment was no prophylaxis or in the case of the major bleeding outcome a combination of no prophylaxis and mechanical prophylaxis). These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on the best available evidence.

Conventional fixed effects meta-analysis assumes that the relative effect of one treatment compared to another is the same across an entire set of trials. In a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials.

Network meta-analysis requires an additional assumption over conventional meta-analysis. The additional assumption is that intervention A has the same effect on people in trials of intervention A compared to intervention B as it does for people in trials of intervention A versus intervention C, and so on. Thus, in a random effects network meta-analysis, the assumption is that intervention A has the same effect distribution across trials of A versus B, A versus C and so on.

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.

M.1.2 Methods

M.1.2.1 Study selection

To estimate the relative risks, we performed an NMA that simultaneously used all the relevant RCT evidence from the clinical evidence review. As with conventional meta-analyses, this type of analysis does not break the randomisation of the evidence, nor does it make any assumptions about adding the effects of different interventions. The effectiveness of a particular treatment strategy combination will be derived only from randomised controlled trials that had that particular combination in a trial arm.

M.1.2.2 Outcome measures

The NMA evidence reviews for interventions considered three clinical efficacy outcomes identified from the clinical evidence review; number of people with DVT, number of people with PE and number of people with major bleeding. Other outcomes were not considered for the NMA as they were infrequently reported across the studies. The guideline committee considered that these outcomes were the most critical clinical outcomes for testing effectiveness of VTE prophylaxis.

M.1.2.3 Comparability of interventions

The interventions compared in the model were those found in the randomised controlled trials and included in the clinical evidence review already presented in Chapter 26 of the full guideline and in appendix H. If an intervention was evaluated in a study that met the inclusion criteria for the network (that is if it reported at least one of the outcomes of interest and matched the inclusion criteria for the meta-analysis) then it was included in the network meta-analysis, otherwise it was excluded.

The treatments included in each network are shown in **Table 237**.

Table 237: Treatments included in network meta-analysis

Network 1: Number of people with DVT	Network 2: Number of people with PE	Network 3: Number of people with major bleeding
No prophylaxis	No prophylaxis	No prophylaxis/mechanical
LMWH (standard dose; standard duration)	LMWH (standard dose; standard duration)	UFH (standard duration)
UFH (standard duration)	LMWH (standard dose) + AES	LMWH (high dose; standard duration)
LMWH (standard dose) + AES	IPCD (length unspecified)	LMWH (standard dose; standard duration)
LMWH (high dose; standard duration)	UFH (standard duration)	Fondaparinux
IPCD	Rivaroxaban	LMWH (low dose; post-op)
LMWH (standard dose; extended duration)	LMWH (standard dose; extended duration)	VKA (standard duration)
Dabigatran	LMWH (high dose; standard duration)	Dabigatran
Foot pump	Dabigatran	Apixaban
Apixaban	Foot pump	Rivaroxaban
Rivaroxaban	Apixaban	LMWH (standard dose; extended duration)

Network 1: Number of people with DVT	Network 2: Number of people with PE	Network 3: Number of people with major bleeding
VKA (standard duration)	AES (length unspecified)	LMWH (low dose; pre-op)
UFH (extended duration)	LMWH (low dose) + AES	VKA (extended duration)
Aspirin	Fondaparinux + AES	LMWH (standard dose; standard duration) followed by aspirin (extended duration)
LMWH (low dose) + AES	LMWH (standard dose; extended duration) + AES	LMWH (high dose; extended duration)
LMWH (extended duration) + AES	Aspirin (standard duration)	-
Fondaparinux + AES	LMWH (standard dose; standard duration) followed by aspirin (extended duration)	-
AES (length unspecified)	VKA (standard duration)	-
LMWH (low dose; pre-op)	UFH + AES	-
LMWH (low dose; post-op)	AES (above-knee)	-
VKA (extended duration)	LMWH (high dose) + AES	-
AES (above-knee)	VKA (extended duration)	-
LMWH (high dose) + AES	LMWH (high dose; extended duration)	
UFH + AES	-	-
Foot pump + AES	-	-
LMWH (high dose; extended duration)	-	

M.1.2.4 Baseline risks

The baseline risk is defined as the risk of achieving the outcome of interest in the baseline treatment arm of the included trials. This figure is useful because it allows us to convert the results of the NMA from odds ratios to relative risks. However, the majority of the trials were old studies that reported very high risk of DVT and PE in the no prophylaxis arm that the orthopaedic subgroup considered to be not reflective of the baseline risk in the UK. Hence, for the purpose of calculating the relative risks of these events for presentation in this appendix, the baseline risk values were obtained from a large observational study that used data from the UK National Joint Registry (NJR).[451] For full details please refer to HE write-up (appendix P, section P.1.3.3).

M.1.2.5 Statistical analysis

A hierarchical Bayesian network meta-analysis (NMA) was performed using the software WinBUGS. We adapted a three-arm random effects model template for the networks, from the University of Bristol website (https://www.bris.ac.uk/cobm/research/mpes/mtc.html). This model accounts for the correlation between study level effects induced by multi-arm trials.

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 outcome subgroup, a diagram of the evidence network is presented in section M.1.3.

The model used was a random effects logistic regression model, with parameters estimated by Markov chain Monte Carlo simulation. As it was a Bayesian analysis, for each parameter the evidence distribution is weighted by a distribution of prior beliefs. Due to the sparse nature of the networks

(few studies per direct treatment comparison), the between-study heterogeneity parameter is imprecisely estimated in a random effects model. Therefore it is beneficial to apply informative priors in order to restrict the prior distribution for heterogeneity to avoid unreasonably wide credible intervals. Turner et al (2015)[946] derived a novel set of predictive distributions for the degree of heterogeneity across 80 different settings. Appropriate predictive distributions for heterogeneity were chosen from Turner et al (2015)[946] and used directly as informative priors. The log normal (μ, σ^2) predictive distributions obtained for the between-study heterogeneity in a future meta-analysis presented in Table IV[946] were selected according to the outcome and treatment comparison. For the DVT and PE NMAs the distributions defined by the outcome of "general physical health indicators" and by the intervention/comparison type "non-pharmacological vs. pharmacological" were chosen (LN[-1.26, 1.25^2]). For the major bleeding NMA the distributions defined by the outcome of "adverse events" and by the intervention/comparison type "non-pharmacological vs. pharmacological" were chosen (LN[-0.84, 1.24^2]). These distributions were chosen as they represented outcomes measured by an assessor, whose method of measurement as well as judgement may influence the outcome (as studies provided slightly variable ways of defining these critical outcomes), and the interaction aspect encompassed both the pharmacological and mechanical prophylaxis options covered in our review protocol.

For the analyses, a series of 60,000 burn-in simulations were run to allow convergence and then a further 60,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots.

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.

The results, in terms of relative risk, of pair-wise meta-analyses are presented in the clinical evidence review (Chapter 26, and appendix H).

The aim of the NMA was to calculate treatment specific log odds ratios and relative risks for response to be consistent with the comparative effectiveness results presented elsewhere in the clinical evidence review and for ease of interpretation. Let BO, $\tilde{\theta}$, $\widetilde{\mathrm{OR}}$ and p denote the baseline odds, treatment specific odds, treatment specific log odds ratio and treatment specific absolute probability respectively. Then:

$$\widetilde{\boldsymbol{\theta}} = \boldsymbol{Ln}\left(\widetilde{\boldsymbol{OR}}\right) + \boldsymbol{Ln}(\boldsymbol{BO})$$

And:

$$\boldsymbol{p} = \frac{\boldsymbol{e}^{\tilde{\boldsymbol{\theta}}}}{\mathbf{1} + \boldsymbol{e}^{\tilde{\boldsymbol{\theta}}}}$$

Once the treatment specific probabilities for response are calculated, we divide them by the baseline probability ($\boldsymbol{p_b}$) to get treatment specific relative risks ($\boldsymbol{rr_b}$):

$$\boldsymbol{p_b} = \frac{\boldsymbol{e}^{\boldsymbol{BO}}}{\mathbf{1} + \boldsymbol{e}^{\boldsymbol{BO}}}$$

$$\boldsymbol{rr_b} = \frac{\boldsymbol{p}}{\boldsymbol{p_b}}$$

This approach has the advantage that baseline and relative effects are both modelled on the same log odds scale, and also ensures that the uncertainty in the estimation of both baseline and relative effects is accounted for in the model.

We also calculated the overall ranking of interventions according to their relative risk compared to control group. Due to the skewness of the data, the NMA relative risks and rank results are reported as medians rather than means (as in the direct comparisons) to give a more accurate representation of the 'most likely' value. The median rank for each intervention was derived from the resulting distribution and these are presented on a rank plot with the associated 95% credible intervals.

A key assumption behind NMA is that the network is consistent. In other words, it is assumed that the direct and indirect treatment effect estimates do not disagree with one another. Discrepancies between direct and indirect estimates of effect may result from several possible causes. First, there is chance and if this is the case then the network meta-analysis results are likely to be more precise as they pool together more data than conventional meta-analysis estimates alone. Second, there could be differences between the trials included in terms of their clinical or methodological characteristics.

This heterogeneity is a problem for network meta-analysis but may be dealt with by subgroup analysis, meta-regression or by carefully defining inclusion criteria. Inconsistency, caused by heterogeneity, was assessed subjectively by comparing the relative risks from the direct evidence (from pair-wise meta-analysis) to the relative risks from the combined direct and indirect evidence (from NMA). We further tested for inconsistency by developing inconsistency models for networks of binary outcomes using the TSD 4 template from the University of Bristol website (https://www.bris.ac.uk/cobm/research/mpes/mtc.html). We compared the posterior mean of the residual deviance between the consistency and inconsistency models to see which was a better fit to the data (closest to the number of trial arms in each network) and checked the difference in deviance information criterion (DIC) values between the two models was small (less than 3-5) or if it was larger, that the smaller DIC and hence better fitting model was the consistency model. No inconsistency was identified.

M.1.3 Results

M.1.3.1 Deep vein thrombosis (symptomatic and asymptomatic)

Included studies

44 studies were identified as reporting on DVT outcomes. After excluding papers that reported zero events in each arm and papers reporting on combinations that did not connect to any other intervention in the network, 42 studies involving 26 treatments were included in the network for DVT (symptomatic and asymptomatic). The network can be seen in Figure 827 and the trial data for each of the studies included in the NMA are presented in **Table 238**.

Figure 827: Network diagram for DVT (symptomatic and asymptomatic)

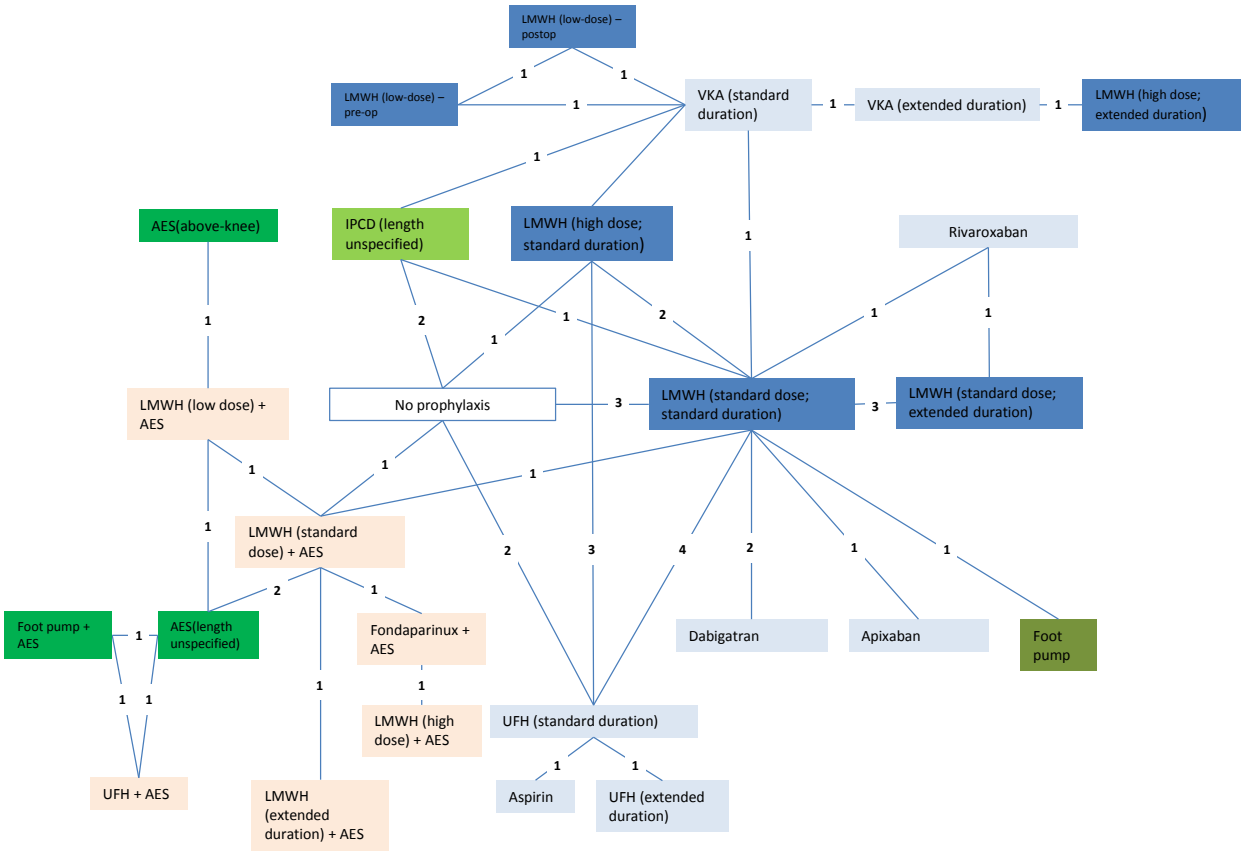


Table 238: Study data for DVT network meta-analysis

Study	Comparison	Intervention 1	Intervention 2	Comparison		Intervention 1		Intervention 2	
				N	NA	N	NA	N	NA
Kalodiki 1996 [472]	No prophylaxis	LMWH (standard dose; standard duration)	LMWH (standard dose) + AES	13	14	12	32	8	32
Bergqvist 1996B [92]	No prophylaxis	LMWH (standard dose; standard duration)	-	43	116	21	117	-	-
Tørholm 1991 [941]	No prophylaxis	LMWH (standard dose; standard duration)	-	19	54	9	58	-	-
Hampson 1974 [382]	No prophylaxis	UFH (standard duration)	-	28	52	22	48	-	-
Mannucci 1976 [604]	No prophylaxis	UFH (standard duration)	-	36	75	14	68	-	-
Turpie 1986 [952]	No prophylaxis	LMWH (high dose; standard	-	20	39	4	37	-	-

Study	Comparison	Intervention 1	Intervention 2	Comparison		Intervention 1		Intervention 2	
		duration)							
Hull 1990	No prophylaxis	IPCD (length unspecified)	-	36	152	77	158	-	-
Gallus 1983 [334]	No prophylaxis	IPCD (length unspecified)	-	25	47	15	43	-	-
Colwell 1994 [204]	LMWH (standard dose; standard duration)	UFH (standard duration)	-	28	136	21	142	8	136
Avikainen 1995 [57]	LMWH (standard dose; standard duration)	UFH (standard duration)	-	1	79	4	79	-	-
Eriksson 1991A [289]	LMWH (standard dose; standard duration)	UFH (standard duration)	-	19	63	25	59	-	-
Planes 1990A (Trial3) [758]	LMWH (standard dose; standard duration)	UFH (standard duration)	-	15	120	27	106	-	-
Planes 1990A (Trial1) [758]	LMWH (standard dose; standard duration)	LMWH (high dose; standard duration)	-	12	150	5	78	-	-
Hardwick 2011 [389]	LMWH (standard dose; standard duration)	IPCD (length unspecified)	-	8	190	8	196	-	-
Comp 2001 [209]	LMWH (standard dose; standard duration)	LMWH (standard dose; extended duration)	-	39	138	15	152	-	-
Lassen 1998 [528]	LMWH (standard dose; standard duration)	LMWH (standard dose; extended duration)	-	12	102	5	113	-	-
Planes 1996 [757]	LMWH (standard dose; standard duration)	LMWH (standard dose; extended duration)	-	17	88	6	85	-	-
Eriksson 2011 [292]	LMWH (standard dose; standard duration)	Dabigatran	-	67	783	60	791	-	-
Eriksson 2007 [288]	LMWH (standard dose; standard duration)	Dabigatran	-	57	897	45	880	-	-
Warwick 1998 [994]	LMWH (standard dose; standard	Foot pump	-	18	138	24	136	-	-

Study	Comparison	Intervention 1	Intervention 2	Comparison		Intervention 1		Intervention 2	
	duration)								
Lassen 2010 [535]	LMWH (standard dose; standard duration)	Apixaban	-	68	1911	22	1944	-	-
Kakkar 2008 [467]	LMWH (standard dose; standard duration)	Rivaroxaban	-	71	869	14	864	-	-
Francis 1997A [315]	LMWH (standard dose; standard duration)	VKA (standard duration)	-	49	190	28	192	-	-
Kakkar 2000 [468]	UFH (standard duration)	LMWH (high dose; standard duration)	-	24	116	9	101	-	-
Levine 1991 [551]	UFH (standard duration)	LMWH (high dose; standard duration)	-	61	263	50	258	-	-
Manganelli 1998 [601]	UFH (standard duration)	UFH (extended duration)	-	4	33	6	28	-	-
Zanasi 1988 [1039]	UFH (standard duration)	Aspirin	-	10	25	7	19	-	-
Fuji 2008A [328]	LMWH (standard dose) + AES	LMWH (low dose) + AES	AES (length unspecified)	27	80	21	81	36	86
Dahl 1997 [226]	LMWH (standard dose) + AES	LMWH (extended duration) + AES	-	33	104	22	114	-	-
Lassen 2002 [526]	LMWH (standard dose) + AES	Fondaparinux + AES	-	83	918	36	908	-	-
Samama 1997 [844]	LMWH (standard dose) + AES	AES (length unspecified)	-	11	78	28	75	-	-
Warwick 1995A [996]	LMWH (standard dose) + AES	AES (length unspecified)	-	22	78	33	78	-	-
Paeiment 1987 [722]	IPCD (length unspecified)	VKA (standard duration)	-	11	66	12	72	-	-
Lassen 1991 [529]	AES (above-knee)	LMWH (low dose) + AES	-	53	1558	12	1595	-	-
Eriksson 2008 [291]	LMWH (standard dose; extended duration)	Rivaroxaban	-	81	338	36	337	44	336
Hull 2000 [440]	VKA (standard duration)	LMWH (low dose; pre-op)	LMWH (low dose; post-op)	8	176	3	184	-	-
Prandoni 2002 [771]	VKA (standard duration)	VKA (extended duration)	-	29	93	44	97	-	-

Study	Comparison	Intervention 1	Intervention 2	Comparison		Intervention 1		Intervention 2	
Turpie 2002K [954]	Fondaparinux + AES	LMWH (high dose) + AES	-	44	784	65	796	-	-
Moskovitz 1978[657]	AES (length unspecified)	UFH + AES	-	19	28	8	32	-	-
Fordyce 1992 [312]	AES (length unspecified)	Foot pump + AES		4	39	16	40	-	-
Samama 2002 [845]	LMWH (high dose; extended duration)	VKA (extended duration)	-	20	636	15	643	-	-
Santori 1994 [850]	UFH + AES	Foot pump + AES		23	65	9	67	-	-

N; number of events, NA; number analysed

NMA results

Table 239 summarises the results of the conventional meta-analyses in terms of risk ratios generated from studies directly comparing different interventions, together with the results of the NMA in terms of risk ratios for every possible treatment comparison.

Table 239: Risk ratios for DVT (symptomatic and asymptomatic)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
Versus no prophylaxis	LMWH (standard dose; standard duration)	0.46 (0.33, 0.63)	0.46 (0.23, 0.81)
	UFH (standard duration)	0.61 (0.45, 0.85)	0.60 (0.28, 1.03)
	LMWH (standard dose) + AES	0.27 (0.15, 0.50)	0.14 (0.07, 0.59)
	LMWH (high dose; standard duration)	0.21 (0.08, 0.56)	0.28 (0.10, 0.67)
	IPCD	0.53 (0.40, 0.69)	0.80 (0.34, 1.41)
	LMWH (standard dose; extended duration)	-	0.19 (0.05, 0.57)
	Dabigatran	-	0.40 (0.11, 1.05)
	Foot pump	-	0.62 (0.11, 1.83)
	Apixaban	-	0.16 (0.03, 0.76)
	Rivaroxaban	-	0.06 (0.01, 0.29)
	VKA (standard duration)	-	0.44 (0.11, 1.13)
	UFH (extended duration)	-	0.96 (0.15, 2.92)
	Aspirin	-	0.54 (0.07, 1.87)
	LMWH (low dose) + AES	-	0.13 (0.02, 0.89)
	LMWH (extended duration) + AES	-	0.08 (0.01, 0.61)
	Fondaparinux + AES	-	0.07 (0.01, 0.49)
	AES (length unspecified)	-	0.30 (0.08, 1.46)
	LMWH (low dose; pre-op)	-	0.19 (0.02, 1.00)
	LMWH (low dose; post-op)	-	0.23 (0.03, 1.12)
	VKA (extended duration)	-	0.16 (0.01, 1.08)
	AES (above-knee)	-	0.23 (0.02, 2.04)
	LMWH (high dose) + AES	-	0.10 (0.01, 1.07)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	UFH + AES		0.27 (0.04, 1.82)
	Foot pump + AES	-	0.32 (0.04, 2.11)
	LMWH (high dose; extended duration)		0.12 (0.00, 1.20)
Versus LMWH (standard dose; standard duration)	UFH (standard duration)	1.27 (0.95, 1.70)*	1.28 (0.72, 2.36)
	LMWH (standard dose) + AES	0.67 (0.32, 1.41)*	0.33 (0.10, 1.65)
	LMWH (high dose; standard duration)	0.40 (0.22, 0.72)*	0.61 (0.26, 1.28)
	IPCD	0.97 (0.37, 2.53)*	1.67 (0.77, 3.74)
	LMWH (standard dose; extended duration)	0.36 (0.23, 0.55)	0.41 (0.16, 0.95)
	Dabigatran	0.85 (0.66, 1.09)*	0.87 (0.30, 2.06)
	Foot pump	1.35 (0.77, 2.38)*	1.30 (0.29, 4.12)
	Apixaban	0.32 (0.20, 0.51)*	0.36 (0.07, 1.43)
	Rivaroxaban	0.20 (0.11, 0.35)*	0.14 (0.04, 0.51)
	VKA (standard duration)	0.57 (0.37, 0.86)*	0.94 (0.29, 2.52)
	UFH (extended duration)	-	1.97 (0.35, 7.54)
	Aspirin	-	1.15 (0.17, 4.55)
	LMWH (low dose) + AES	-	0.28 (0.04, 2.39)
	LMWH (extended duration) + AES	-	0.18 (0.02, 1.61)
	Fondaparinux + AES	-	0.14 (0.02, 1.31)
	AES (length unspecified)	-	0.66 (0.14, 4.01)
	LMWH (low dose; pre-op)	-	0.41 (0.05, 2.13)
	LMWH (low dose; post-op)	-	0.50 (0.07, 2.46)
	VKA (extended duration)	-	0.34 (0.03, 2.37)
	AES (above-knee)	-	0.50 (0.07, 5.45)
	LMWH (high dose) + AES	-	0.21 (0.02, 2.79)
	UFH + AES	-	0.58 (0.07, 4.94)
	Foot pump + AES	-	0.69 (0.08, 5.68)
	LMWH (high dose; extended duration)	-	0.25 (0.01, 2.65)
Versus UFH (standard duration)	LMWH (standard dose) + AES	-	0.25 (0.08, 1.32)
	LMWH (high dose; standard duration)	0.66 (0.50, 0.87)	0.48 (0.21, 0.94)
	IPCD	-	1.30 (0.54, 3.17)
	LMWH (standard dose; extended duration)	-	0.32 (0.10, 0.89)
	Dabigatran	-	0.68 (0.20, 1.88)
	Foot pump	-	1.03 (0.20, 3.55)
	Apixaban	-	0.28 (0.05, 1.25)
	Rivaroxaban	-	0.11 (0.03, 0.45)
	VKA (standard duration)	-	0.74 (0.20, 2.17)
	UFH (extended duration)	0.57 (0.18, 1.81)	1.53 (0.31, 5.36)
	Aspirin	4.17 (0.88, 19.66)*	0.90 (0.14, 3.17)
	LMWH (low dose) + AES	-	0.22 (0.03, 1.88)
	LMWH (extended duration) + AES	-	0.14 (0.02, 1.27)
	Fondaparinux + AES	-	0.11 (0.01, 1.02)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	AES (length unspecified)	-	0.51 (0.11, 3.17)
	LMWH (low dose; pre-op)	-	0.32 (0.04, 1.76)
	LMWH (low dose; post-op)	-	0.39 (0.03, 4.24)
	VKA (extended duration)	-	0.27 (0.02, 1.93)
	AES (above-knee)	-	0.39 (0.03, 4.24)
	LMWH (high dose) + AES	-	0.17 (0.01, 2.17)
	UFH + AES	-	0.45 (0.05, 3.89)
	Foot pump + AES	-	0.53 (0.06, 4.48)
	LMWH (high dose; extended duration)	-	0.20 (0.01, 2.16)
Versus LMWH (standard dose) + AES	LMWH (high dose; standard duration)	-	1.82 (0.28, 8.24)
	IPCD	-	5.36 (0.99, 13.82)
	LMWH (standard dose; extended duration)	-	1.21 (0.17, 6.59)
	Dabigatran	-	2.61 (0.36, 10.81)
	Foot pump	-	4.10 (0.43, 14.18)
	Apixaban	-	1.06 (0.10, 7.73)
	Rivaroxaban	-	0.42 (0.05, 3.30)
	VKA (standard duration)	-	2.85 (0.38, 11.60)
	UFH (extended duration)	-	6.67 (0.60, 16.55)
	Aspirin	-	3.54 (0.27, 14.52)
	LMWH (low dose) + AES	0.77 (0.48, 1.24)	0.84 (0.18, 3.53)
	LMWH (extended duration) + AES	0.61 (0.38, 0.97)	0.52 (0.10, 2.59)
	Fondaparinux + AES	0.44 (0.30, 0.64)*	0.43 (0.08, 2.03)
	AES (length unspecified)	1.58 (1.22, 2.06)*	2.00 (0.79, 4.61)
	LMWH (low dose; pre-op)	-	1.19 (0.08, 9.72)
	LMWH (low dose; post-op)	-	1.49 (0.11, 10.76)
	VKA (extended duration)	-	1.00 (0.05, 10.12)
	AES (above-knee)	-	1.51 (0.16, 8.73)
	LMWH (high dose) + AES	-	0.63 (0.06, 4.95)
	UFH + AES	-	1.74 (0.29, 7.26)
	Foot pump + AES	-	2.07 (0.36, 8.34)
	LMWH (high dose; extended duration)	-	0.74 (0.02, 10.73)
Versus LMWH (high dose; standard duration)	IPCD	-	2.76 (1.01, 8.59)
	LMWH (standard dose; extended duration)	-	0.68 (0.20, 2.20)
	Dabigatran	-	1.41 (0.40, 4.90)
	Foot pump	-	2.10 (0.41, 9.28)
	Apixaban	-	0.60 (0.10, 3.03)
	Rivaroxaban	-	0.24 (0.05, 1.03)
	VKA (standard duration)	1.35 (0.70, 2.61)*	1.53 (0.40, 5.64)
	UFH (extended duration)	-	3.18 (0.58, 15.07)
	Aspirin	-	1.83 (0.28, 8.93)
	LMWH (low dose) + AES	-	0.47 (0.05, 4.83)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	LMWH (extended duration) + AES	-	0.29 (0.03, 3.28)
	Fondaparinux + AES	-	0.24 (0.02, 2.66)
	AES (length unspecified)	-	1.10 (0.18, 8.35)
	LMWH (low dose; pre-op)	-	0.67 (0.08, 4.33)
	LMWH (low dose; post-op)	-	0.83 (0.10, 5.05)
	VKA (extended duration)	-	0.57 (0.04, 4.71)
	AES (above-knee)	-	0.83 (0.05, 10.87)
	LMWH (high dose) + AES	-	0.36 (0.02, 5.52)
	UFH + AES	-	0.96 (0.09, 9.94)
	Foot pump + AES	-	1.14 (0.11, 11.68)
	LMWH (high dose; extended duration)	-	0.42 (0.02, 5.12)
Versus IPCD	LMWH (standard dose; extended duration)	-	0.25 (0.07, 0.79)
	Dabigatran	-	0.52 (0.14, 1.62)
	Foot pump	-	0.79 (0.14, 2.94)
	Apixaban	-	0.21 (0.03, 1.05)
	Rivaroxaban	-	0.08 (0.02, 0.39)
	VKA (standard duration)	1.00 (0.47, 2.11)*	0.56 (0.17, 1.48)
	UFH (extended duration)	-	1.19 (0.19, 4.86)
	Aspirin	-	0.69 (0.09, 3.01)
	LMWH (low dose) + AES	-	0.17 (0.02, 1.43)
	LMWH (extended duration) + AES	-	0.10 (0.01, 0.98)
	Fondaparinux + AES	-	0.08 (0.01, 0.79)
	AES (length unspecified)	-	0.38 (0.09, 2.44)
	LMWH (low dose; pre-op)	-	0.24 (0.03, 1.27)
	LMWH (low dose; post-op)	-	0.30 (0.04, 1.46)
	VKA (extended duration)	-	0.20 (0.02, 1.39)
	AES (above-knee)	-	0.30 (0.02, 3.21)
	LMWH (high dose) + AES	-	0.13 (0.01, 1.65)
	UFH + AES	-	0.34 (0.04, 2.95)
	Foot pump + AES	-	0.40 (0.05, 3.44)
	LMWH (high dose; extended duration)	-	0.15 (0.01, 1.55)
Versus LMWH (standard dose; extended duration)	Dabigatran	-	2.06 (0.56, 7.82)
	Foot pump	-	3.07 (0.59, 14.78)
	Apixaban	-	0.87 (0.14, 4.73)
	Rivaroxaban	0.22 (0.12, 0.41)*	0.35 (0.10, 1.18)
	VKA (standard duration)	-	2.24 (0.55, 9.29)
	UFH (extended duration)	-	4.68 (0.74, 26.51)
	Aspirin	-	2.67 (0.35, 15.99)
	LMWH (low dose) + AES	-	0.70 (0.07, 7.90)
	LMWH (extended duration) + AES	-	0.43 (0.04, 5.27)
	Fondaparinux + AES	-	0.36 (0.03, 4.31)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	AES (length unspecified)	-	1.64 (0.24, 13.76)
	LMWH (low dose; pre-op)	-	0.98 (0.11, 6.93)
	LMWH (low dose; post-op)	-	1.21 (0.14, 8.14)
	VKA (extended duration)	-	0.83 (0.06, 7.45)
	AES (above-knee)	-	1.23 (0.07, 17.59)
	LMWH (high dose) + AES	-	0.52 (0.03, 8.87)
	UFH + AES	-	1.42 (0.12, 16.35)
	Foot pump + AES	-	1.68 (0.15, 18.95)
	LMWH (high dose; extended duration)	-	0.62 (0.03, 8.12)
Versus Dabigatran	Foot pump	-	1.49 (0.27, 7.25)
	Apixaban	-	0.42 (0.06, 2.34)
	Rivaroxaban	-	0.17 (0.03, 0.82)
	VKA (standard duration)	-	1.09 (0.25, 4.63)
	UFH (extended duration)	-	2.24 (0.35, 13.01)
	Aspirin	-	1.31 (0.16, 7.71)
	LMWH (low dose) + AES	-	0.33 (0.04, 3.71)
	LMWH (extended duration) + AES	-	0.21 (0.02, 2.50)
	Fondaparinux + AES	-	0.17 (0.02, 2.00)
	AES (length unspecified)	-	0.77 (0.14, 6.46)
	LMWH (low dose; pre-op)	-	0.48 (0.05, 3.38)
	LMWH (low dose; post-op)	-	0.59 (0.04, 8.23)
	VKA (extended duration)	-	0.40 (0.03, 3.63)
	AES (above-knee)	-	0.59 (0.04, 8.28)
	LMWH (high dose) + AES	-	0.25 (0.02, 4.14)
	UFH + AES	-	0.68 (0.07, 7.66)
	Foot pump + AES	-	0.80 (0.08, 8.80)
	LMWH (high dose; extended duration)	-	0.30 (0.01, 3.96)
Versus Foot pump	Apixaban	-	0.28 (0.04, 2.07)
	Rivaroxaban	-	0.11 (0.02, 0.74)
	VKA (standard duration)	-	0.73 (0.14, 4.23)
	UFH (extended duration)	-	1.49 (0.20, 11.19)
	Aspirin	-	0.88 (0.10, 6.72)
	LMWH (low dose) + AES	-	0.22 (0.03, 2.93)
	LMWH (extended duration) + AES	-	0.14 (0.01, 1.97)
	Fondaparinux + AES	-	0.11 (0.01, 1.58)
	AES (length unspecified)	-	0.50 (0.10, 5.34)
	LMWH (low dose; pre-op)	-	0.32 (0.03, 2.84)
	LMWH (low dose; post-op)	-	0.40 (0.04, 3.41)
	VKA (extended duration)	-	0.27 (0.02, 3.07)
	AES (above-knee)	-	0.39 (0.03, 6.37)
	LMWH (high dose) + AES	-	0.17 (0.01, 3.15)
	UFH + AES	-	0.44 (0.05, 6.03)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	Foot pump + AES	-	0.52 (0.06, 7.07)
	LMWH (high dose; extended duration)	-	0.20 (0.01, 3.16)
Versus Apixaban	Rivaroxaban	-	0.40 (0.06, 3.02)
	VKA (standard duration)	-	2.57 (0.43, 17.96)
	UFH (extended duration)	-	5.35 (0.64, 48.48)
	Aspirin	-	3.04 (0.30, 28.57)
	LMWH (low dose) + AES	-	0.80 (0.06, 12.74)
	LMWH (extended duration) + AES	-	0.50 (0.04, 8.55)
	Fondaparinux + AES	-	0.41 (0.03, 6.87)
	AES (length unspecified)	-	1.88 (0.21, 23.11)
	LMWH (low dose; pre-op)	-	1.13 (0.09, 11.98)
	LMWH (low dose; post-op)	-	1.38 (0.12, 14.17)
	VKA (extended duration)	-	0.95 (0.05, 12.43)
	AES (above-knee)	-	1.41 (0.07, 28.04)
	LMWH (high dose) + AES	-	0.61 (0.03, 13.84)
	UFH + AES	-	1.63 (0.11, 26.26)
	Foot pump + AES	-	1.92 (0.14, 30.62)
	LMWH (high dose; extended duration)	-	0.71 (0.02, 12.98)
Versus Rivaroxaban	VKA (standard duration)	-	6.41 (1.23, 35.36)
	UFH (extended duration)	-	13.43 (1.70, 96.91)
	Aspirin	-	7.61 (0.84, 58.00)
	LMWH (low dose) + AES	-	2.01 (0.15, 27.57)
	LMWH (extended duration) + AES	-	1.26 (0.09, 18.53)
	Fondaparinux + AES	-	1.03 (0.07, 14.83)
	AES (length unspecified)	-	4.78 (0.50, 49.19)
	LMWH (low dose; pre-op)	-	2.79 (0.27, 24.81)
	LMWH (low dose; post-op)	-	3.42 (0.34, 29.03)
	VKA (extended duration)	-	2.35 (0.15, 26.30)
	AES (above-knee)	-	3.55 (0.17, 60.68)
	LMWH (high dose) + AES	-	1.52 (0.07, 30.36)
	UFH + AES	-	4.11 (0.27, 56.89)
	Foot pump + AES	-	4.83 (0.34, 66.14)
	LMWH (high dose; extended duration)	-	1.75 (0.07, 27.90)
Versus VKA (standard duration)	UFH (extended duration)	-	2.06 (0.31, 12.35)
	Aspirin	-	1.20 (0.14, 7.43)
	LMWH (low dose) + AES	-	0.30 (0.03, 3.47)
	LMWH (extended duration) + AES	-	0.19 (0.02, 2.32)
	Fondaparinux + AES	-	0.15 (0.02, 1.87)
	AES (length unspecified)	-	0.71 (0.13, 6.14)
	LMWH (low dose; pre-op)	0.45 (0.31, 0.64)	0.44 (0.09, 1.64)
	LMWH (low dose; post-op)	0.55 (0.39, 0.76)	0.54 (0.11, 1.91)
	VKA (extended duration)	0.36 (0.10, 1.33)	0.37 (0.04, 1.94)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	AES (above-knee)	-	0.54 (0.04, 7.78)
	LMWH (high dose) + AES	-	0.23 (0.01, 3.87)
	UFH + AES	-	0.62 (0.06, 7.21)
	Foot pump + AES	-	0.74 (0.07, 8.33)
	LMWH (high dose; extended duration)	0.74 (0.38, 1.44)	0.28 (0.02, 2.29)
Versus UFH (extended duration)	Aspirin	-	0.59 (0.06, 4.37)
	LMWH (low dose) + AES	-	0.14 (0.02, 1.98)
	LMWH (extended duration) + AES	-	0.09 (0.01, 1.33)
	Fondaparinux + AES	-	0.07 (0.01, 1.09)
	AES (length unspecified)	-	0.31 (0.07, 3.72)
	LMWH (low dose; pre-op)	-	0.21 (0.02, 2.09)
	LMWH (low dose; post-op)	-	0.26 (0.02, 2.48)
	VKA (extended duration)	-	0.18 (0.01, 2.13)
	AES (above-knee)	-	0.25 (0.02, 4.28)
	LMWH (high dose) + AES		0.11 (0.01, 2.13)
	UFH + AES	-	0.29 (0.03, 4.15)
	Foot pump + AES	-	0.34 (0.04, 4.88)
	LMWH (high dose; extended duration)	-	0.13 (0.00, 2.17)
Versus Aspirin	LMWH (low dose) + AES	-	0.25 (0.03, 4.42)
	LMWH (extended duration) + AES	-	0.16 (0.01, 2.93)
	Fondaparinux + AES	-	0.13 (0.01, 2.36)
	AES (length unspecified)	-	0.57 (0.10, 8.17)
	LMWH (low dose; pre-op)	-	0.37 (0.03, 4.39)
	LMWH (low dose; post-op)	-	0.46 (0.04, 5.28)
	VKA (extended duration)	-	0.31 (0.02, 4.50)
	AES (above-knee)	-	0.45 (0.03, 9.51)
	LMWH (high dose) + AES	-	0.19 (0.01, 4.71)
	UFH + AES	-	0.51 (0.05, 9.06)
	Foot pump + AES	-	0.60 (0.06, 10.77)
	LMWH (high dose; extended duration)	-	0.23 (0.01, 4.53)
Versus LMWH (low dose) + AES	LMWH (extended duration) + AES	-	0.62 (0.07, 5.81)
	Fondaparinux + AES	-	0.51 (0.06, 4.65)
	AES (length unspecified)	1.61 (1.04, 2.52)	2.35 (0.56, 10.69)
	LMWH (low dose; pre-op)	-	1.41 (0.07, 19.95)
	LMWH (low dose; post-op)	-	1.75 (0.09, 22.86)
	VKA (extended duration)	-	1.18 (0.04, 19.61)
	AES (above-knee)	1.45 (1.00, 2.11)	1.75 (0.35, 7.07)
	LMWH (high dose) + AES	-	0.75 (0.05, 9.99)
	UFH + AES	-	2.04 (0.26, 14.28)
	Foot pump + AES	-	2.40 (0.32, 16.79)
	LMWH (high dose; extended duration)	-	0.87 (0.02, 19.76)
Versus LMWH	Fondaparinux + AES	-	0.81 (0.08, 8.23)

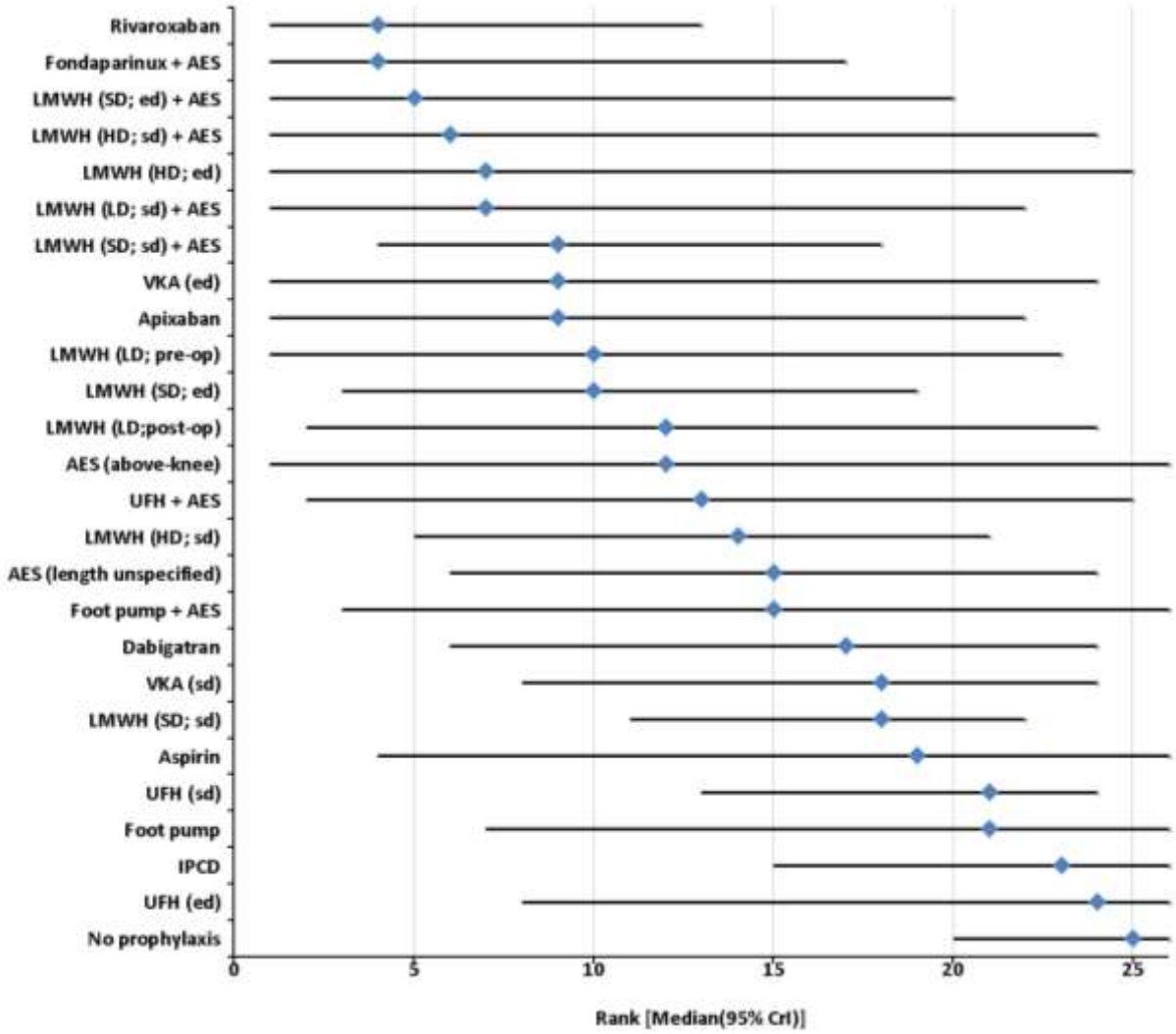
	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
(standard dose; extended duration) + AES	AES (length unspecified)	-	3.80 (0.60, 25.16)
	LMWH (low dose; pre-op)	-	2.25 (0.11, 35.36)
	LMWH (low dose; post-op)	-	2.78 (0.13, 40.08)
	VKA (extended duration)	-	1.89 (0.06, 35.03)
	AES (above-knee)	-	2.84 (0.18, 33.96)
	LMWH (high dose) + AES	-	1.20 (0.07, 17.55)
	UFH + AES	-	3.28 (0.30, 30.52)
	Foot pump + AES	-	3.88 (0.37, 35.78)
	LMWH (high dose; extended duration)	-	1.39 (0.03, 35.31)
Versus fondaparinux + AES	AES (length unspecified)	-	4.65 (0.76, 29.22)
	LMWH (low dose; pre-op)	-	2.76 (0.13, 41.55)
	LMWH (low dose; post-op)	-	3.41 (0.16, 47.41)
	VKA (extended duration)	-	2.30 (0.08, 41.24)
	AES (above-knee)	-	3.46 (0.22, 39.92)
	LMWH (high dose) + AES	1.46 (1.01, 2.11)	1.47 (0.29, 6.50)
	UFH + AES	-	4.04 (0.38, 35.80)
	Foot pump + AES	-	4.75 (0.47, 41.79)
	LMWH (high dose; extended duration)	-	1.70 (0.04, 41.28)
Versus AES (length unspecified)	LMWH (low dose; pre-op)	-	0.60 (0.04, 6.00)
	LMWH (low dose; post-op)	-	0.74 (0.05, 6.71)
	VKA (extended duration)	-	0.50 (0.02, 6.09)
	AES (above-knee)	-	0.76 (0.08, 4.60)
	LMWH (high dose) + AES	-	0.32 (0.03, 3.00)
	UFH + AES	1.46 (1.01, 2.11)	0.87 (0.20, 3.00)
	Foot pump + AES	0.26 (0.09, 0.70)	1.03 (0.24, 3.48)
	LMWH (high dose; extended duration)	-	0.37 (0.01, 6.24)
Versus LMWH (low dose; standard duration; pre-op)	LMWH (low dose; post-op)	1.23 (0.81, 1.85)*	1.22 (0.28, 5.44)
	VKA (extended duration)	-	0.85 (0.07, 8.65)
	AES (above-knee)	-	1.25 (0.06, 31.23)
	LMWH (high dose) + AES	-	0.54 (0.02, 15.05)
	UFH + AES	-	1.45 (0.09, 29.53)
	Foot pump + AES	-	1.70 (0.11, 34.69)
	LMWH (high dose; extended duration)	-	0.64 (0.03, 9.39)
Versus LMWH (low dose; standard duration; post-op)	VKA (extended duration)	-	0.70 (0.06, 6.90)
	AES (above-knee)	-	1.01 (0.05, 24.79)
	LMWH (high dose) + AES	-	0.44 (0.02, 11.93)
	UFH + AES	-	1.17 (0.08, 23.26)
	Foot pump + AES	-	1.38 (0.10, 27.44)
	LMWH (high dose; extended duration)	-	0.52 (0.02, 7.44)
Versus VKA (extended duration)	AES (above-knee)	-	1.48 (0.06, 50.45)
	LMWH (high dose) + AES	-	0.65 (0.02, 24.76)
	UFH + AES	-	1.73 (0.09, 49.88)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	Foot pump + AES	-	2.03 (0.11, 58.64)
	LMWH (high dose; extended duration)	0.74 (0.38, 1.44)	0.76 (0.14, 3.29)
Versus AES (above-knee)	LMWH (high dose) + AES	-	0.43 (0.02, 8.95)
	UFH + AES	-	1.15 (0.11, 14.62)
	Foot pump + AES	-	1.36 (0.13, 17.26)
	LMWH (high dose; extended duration)	-	0.50 (0.01, 17.17)
Versus LMWH (high dose + AES)	UFH + AES	-	2.72 (0.18, 40.86)
	Foot pump + AES	-	3.20 (0.22, 48.42)
	LMWH (high dose; extended duration)	-	1.16 (0.02, 42.98)
Versus UFH + AES	Foot pump + AES	0.38 (0.19, 0.76)	1.18 (0.32, 4.50)
	LMWH (high dose; extended duration)	-	0.43 (0.01, 11.02)
Versus Foot pump + AES	LMWH (high dose; extended duration)	-	0.37 (0.01, 8.98)

**Intervention and comparison numbers have been switched in Review Manager*

Figure 828 shows the rank of each intervention compared to the others. The rank is based on the relative risk compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 26 different interventions being evaluated.

Figure 828: Rank order for interventions based on the relative risk of experiencing DVT



LD = low dose; SD = standard dose; HD = high dose; sd = standard duration; ed = extended duration

Goodness of fit and inconsistency

Both fixed effects and random effects models were fitted to the data. The random effects model had a DIC of 570 compared with 634 for the fixed effects model. The random effects model used for the NMA is a good fit, with a residual deviance of 90 reported. This corresponds well to the total number of trial arms, 88. The between trial standard deviation in the random effects analysis was 0.78 (95% CI 0.52 to 1.16). On evaluating inconsistency by comparing risk ratios, eight inconsistencies were identified. The NMA estimated risk ratio for:

- LMWH at a standard dose for a standard duration plus AES versus no prophylaxis (0.14 [0.07, 0.59]) lay outside of the confidence interval of the risk ratio estimated for the direct comparison (0.27 [0.15, 0.50])
- IPCD versus no prophylaxis (0.80 [0.34, 1.41]) lay outside of the confidence interval of the risk ratio estimated for the direct comparison (0.53 [0.40, 0.69])
- VKA at a standard duration versus LMWH at a standard dose and standard duration (0.94 [0.29, 2.52]) lay outside of the confidence interval of the risk ratio estimated for the direct comparison (0.57 [0.37, 0.86])
- LMWH at a high dose and standard duration versus UFH (0.48 [0.21, 0.94]) lay outside of the confidence interval of the risk ratio estimated for the direct comparison (0.66 [0.50, 0.87])

- LMWH at a high dose and extended duration versus VKA at a standard duration (0.28 [0.02, 2.29]) lay outside of the confidence interval of the risk ration estimated for the direct comparison (0.74 [0.38, 1.44])
- Foot pump plus AES (length unspecified) versus AES (length unspecified) (1.03 [0.24, 3.48]) lay outside of the confidence interval of the risk ratio estimated for the direct comparison (0.26 [0.09, 0.70])
- UFH plus AES (length unspecified) versus AES (length unspecified) (0.87 [0.20, 3.00]) lay outside of the confidence interval of the risk ratio estimated for the direct comparison (1.46 [1.01, 2.11])
- Foot pump plus AES (length unspecified) versus UFH plus AES (length unspecified) (1.18 [0.32, 4.50]) lay outside of the confidence interval of the risk ration estimated for the direct comparison (0.38 [0.19, 0.76])

An inconsistency model was run and the DIC statistics were as follows in **Table 240**. The difference in the DIC is small (<3-5) with the consistency model having the lower DIC value. This suggests that it fits the data better than the inconsistency model.

Table 240: Posterior mean of the residual deviance (resdev) and DIC for the RE network meta-analysis and inconsistency models – DVT

	DIC	ResDev
Consistency model	570.092	90
Inconsistency model	570.268	90

M.1.3.2 Pulmonary embolism

Included studies

37 studies were identified as reporting on PE outcomes. After excluding papers that reported zero events in each arm and papers reporting on combinations that did not connect to any other intervention in the network, 30 studies involving 23 treatments were included in the network for PE. The network can be seen in **Figure 829** and the trial data for each of the studies included in the NMA are presented in **Table 241**.

Figure 829: Network diagram for PE

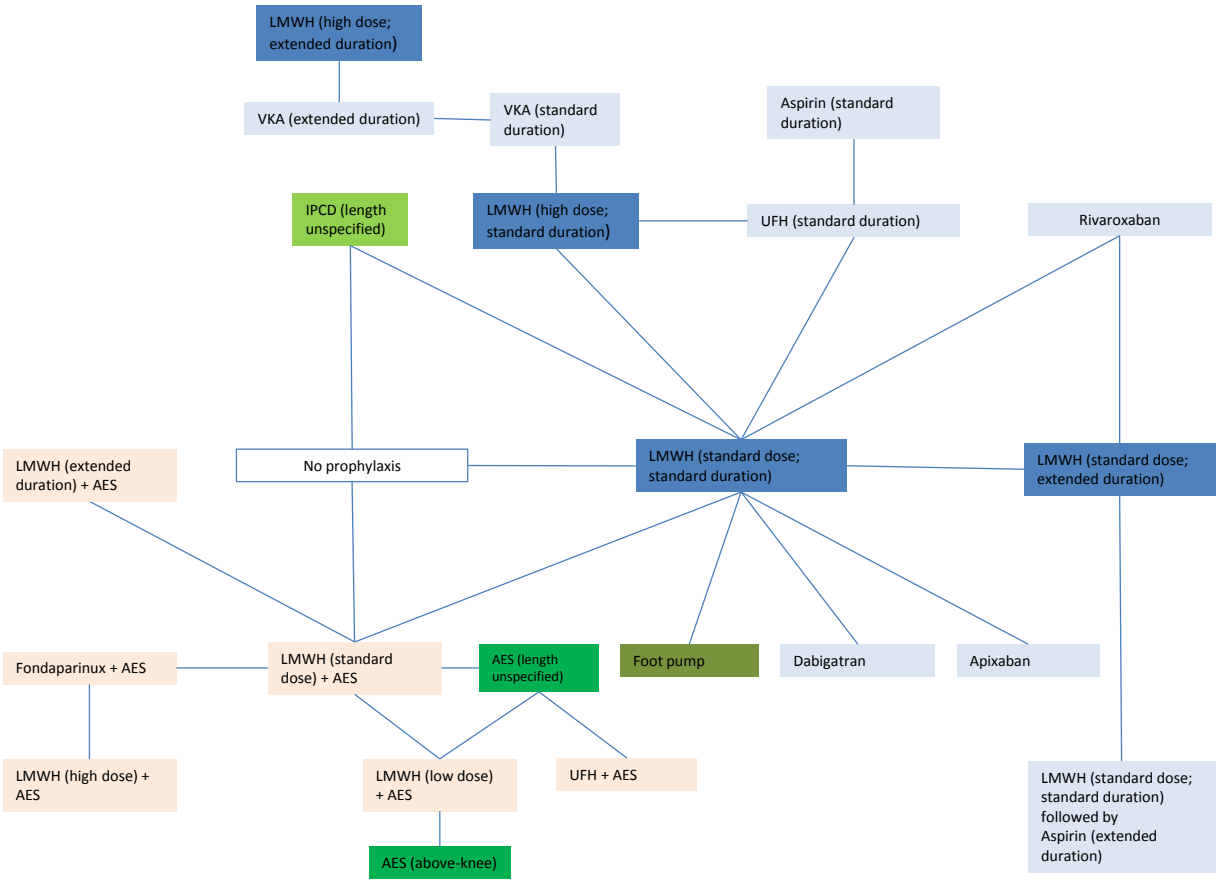


Table 241: Study data for PE network meta-analysis

Study	Comparison	Intervention 1	Intervention 2	Comparison		Intervention 1		Intervention 2	
				N	NA	N	NA	N	NA
Kalodiki 1996 [472]	No prophylaxis	LMWH (standard dose; standard duration)	LMWH (standard dose) + AES	5	14	3	32	2	32
Bergqvist 1996 [92]	No prophylaxis	LMWH (standard dose; standard duration)	-	2	116	0	117	-	-

Study	Comparison	Intervention 1	Intervention 2	Comparison		Intervention 1		Intervention 2	
Torholm 1991 [941]	No prophylaxis	LMWH (standard dose; standard duration)	-	1	54	0	58	-	-
Hull 1990 [441]	No prophylaxis	IPCD (length unspecified)	-	1	158	1	152	-	-
Hardwick 2011 [389]	LMWH (standard dose; standard duration)	IPCD (length unspecified)	-	2	196	2	194	-	-
Avikainen 1995 [57]	LMWH (standard dose; standard duration)	UFH (standard duration)	-	0	84	1	83	-	-
Colwell 1994 [204]	LMWH (standard dose; standard duration)	UFH (standard duration)	LMWH (high dose; standard duration)	1	203	4	209	0	195
Eriksson 1991A[289]	LMWH (standard dose; standard duration)	UFH (standard duration)	-	1	67	2	69	-	-
Planès 1990 [758]	LMWH (standard dose; standard duration)	UFH (standard duration)	-	0	120	1	106	-	-
Comp 2001 [208]	LMWH (standard dose; standard duration)	LMWH (standard dose; extended duration)	-	1	211	0	224	-	-
Eriksson 2011 [292]	LMWH (standard dose; standard duration)	Dabigatran	-	2	992	1	1001	-	-
Eriksson 2007 [288]	LMWH (standard dose; standard duration)	Dabigatran	-	3	897	5	880	-	-
Warwick 1998 [994]	LMWH (standard dose; standard duration)	Foot pump	-	0	138	1	136	-	-
Lassen 2010 [534]	LMWH (standard dose; standard duration)	Apixaban	-	5	2699	3	2708	-	-
Kakkar 2008 [467]	LMWH (standard dose; standard duration)	Rivaroxaban	-	4	869	1	864	-	-
Dahl 1997 [227]	LMWH (standard dose)	LMWH (extended	-	3	106	0	111	-	-

Study	Comparison	Intervention 1	Intervention 2	Comparison		Intervention 1		Intervention 2	
	+ AES	duration) + AES							
Lassen 2002 [526]	LMWH (standard dose) + AES	Fondaparinux + AES	-	3	1123	3	1129	-	-
Fuji 2008A [328]	LMWH (standard dose) + AES	LMWH (low dose) + AES	AES (length unspecified)	1	80	0	81	0	86
Warwick 1995A [992]	LMWH (standard dose) + AES	AES (length unspecified)	-	1	78	2	78	-	-
Kakkar 2000 [468]	LMWH (high dose; standard duration)	UFH (standard duration)	-	1	125	2	134	-	-
Levine 1991 [551]	LMWH (high dose; standard duration)	UFH (standard duration)	-	1	332	1	333	-	-
Colwell 1999 [203]	LMWH (high dose; standard duration)	VKA (standard duration)	-	6	1516	9	1495	-	-
Samama 2002 [845]	LMWH (high dose; extended duration)	VKA (extended duration)	-	0	643	4	636	-	-
Zanasi 1988 [1039]	UFH (standard duration)	Aspirin (standard duration)	-	1	25	1	19	-	-
Eriksson 2008 [291]	LMWH (standard dose; extended duration)	Rivaroxaban	-	1	1558	4	1595	-	-
Anderson 2013 [40]	LMWH (standard dose; extended duration)	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	3	398	0	380	-	-
Turpie 2002K [954]	Fondaparinux + AES	LMWH (high dose) + AES	-	5	1126	0	1128	-	-
Moskovtiz 1978 [657]	AES (length unspecified)	UFH + AES	-	1	32	3	35	-	-
Lassen 1991 [529]	LMWH (low dose) + AES	AES (above-knee)	-	2	93	1	97	-	-
Prandoni 2002 [771]	VKA (standard duration)	VKA (extended duration)	-	1	176	0	184	-	-

N; number of events, NA; number analysed

NMA results

Table 242 summarises the results of the conventional meta-analyses in terms of risk ratios generated from studies directly comparing different interventions, together with the results of the NMA in terms of risk ratios for every possible treatment comparison.

Table 242: Risk ratios for PE

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
Versus no prophylaxis	LMWH (standard dose; standard duration)	0.15 (0.04, 0.58)	0.25 (0.06, 0.89)
	LMWH (standard dose) + AES	0.17 (0.04, 0.80)	0.12 (0.02, 0.82)
	IPCD (length unspecified)	1.04 (0.07, 16.47)	0.41 (0.05, 2.97)
	UFH (standard duration)	-	0.65 (0.10, 4.02)
	Rivaroxaban	-	0.07 (0.00, 0.78)
	LMWH (standard dose; extended duration)	-	0.02 (0.00, 0.34)
	LMWH (high dose; standard duration)	-	0.21 (0.02, 2.09)
	Dabigatran	-	0.29 (0.04, 1.87)
	Foot pump	-	1.18 (0.03, 29.88)
	Apixaban	-	0.14 (0.01, 1.21)
	AES (length unspecified)	-	0.12 (0.01, 2.08)
	LMWH (low dose) + AES	-	0.03 (0.00, 1.87)
	Fondaparinux + AES	-	0.12 (0.01, 1.95)
	LMWH (extended duration) + AES	-	0.01 (0.00, 0.31)
	Aspirin (standard duration)	-	3.43 (0.09, 45.71)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.00 (0.00, 0.10)
	VKA (standard duration)	-	0.33 (0.02, 4.32)
	UFH + AES	-	0.45 (0.01, 18.78)
	AES (above-knee)	-	0.17 (0.00, 24.69)
	LMWH (high dose) + AES	-	0.00 (0.00, 0.30)
	VKA (extended duration)		0.06 (0.00, 4.46)
	LMWH (high dose; extended duration)		0.00 (0.00, 0.81)
Versus LMWH (standard dose; standard duration)	LMWH (standard dose) + AES	0.67 (0.12, 3.73)	0.52 (0.05, 3.82)
	IPCD (length unspecified)	1.01 (0.14, 7.10)*	1.63 (0.23, 11.08)
	UFH (standard duration)	3.01 (0.82,11.03)*	2.60 (0.73, 10.33)
	Rivaroxaban	0.25 (0.03, 2.25)*	0.29 (0.02, 2.14)
	LMWH (standard dose; extended duration)	0.30 (0.01, 7.37)	0.08 (0.00, 1.00)
	LMWH (high dose; standard duration)	0.35 (0.01, 8.47)	0.87 (0.11, 5.55)
	Dabigatran	1.21 (0.37, 3.96)*	1.19 (0.27, 4.76)
	Foot pump	-	4.51 (0.15, 118.90)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	Apixaban	0.60 (0.14, 2.50)*	0.57 (0.08, 3.18)
	AES (length unspecified)	-	0.49 (0.02, 9.58)
	LMWH (low dose) + AES	-	0.14 (0.00, 8.53)
	Fondaparinux + AES	0.25 (0.03, 2.25)*	0.51 (0.03, 8.51)
	LMWH (extended duration) + AES	-	0.03 (0.00, 1.41)
	Aspirin (standard duration)	-	13.34 (0.44, 181.20)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.00 (0.00, 0.33)
	VKA (standard duration)	-	1.34 (0.11, 12.45)
	UFH + AES	-	1.88 (0.03, 83.70)
	AES (above-knee)	-	0.69 (0.00, 109.60)
	LMWH (high dose) + AES	-	0.02 (0.00, 1.26)
	VKA (extended duration)	-	0.25 (0.00, 14.26)
	LMWH (high dose; extended duration)	-	0.01 (0.00, 2.76)
Versus LMWH (standard dose; standard duration) + AES	IPCD (length unspecified)	-	3.22 (0.22, 45.98)
	UFH (standard duration)	-	5.30 (0.48, 54.12)
	Rivaroxaban	-	0.53 (0.02, 11.48)
	LMWH (standard dose; extended duration)	-	0.15 (0.00, 4.70)
	LMWH (high dose; standard duration)	0.97 (0.17, 5.47)*	1.71 (0.09, 28.52)
	Dabigatran	-	2.32 (0.19, 29.85)
	Foot pump	-	10.44 (0.16, 143.60)
	Apixaban	-	1.10 (0.07, 18.05)
	AES (length unspecified)	0.97 (0.17, 21.61)*	0.97 (0.11, 8.04)
	LMWH (low dose) + AES	0.33 (0.01, 7.96)	0.29 (0.00, 9.28)
	Fondaparinux + AES	-	1.00 (0.13, 7.52)
	LMWH (extended duration) + AES	-	0.07 (0.00, 1.37)
	Aspirin (standard duration)	-	34.54 (0.52, 148.70)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.01 (0.00, 1.13)
	VKA (standard duration)	-	2.66 (0.10, 50.54)
	UFH + AES	-	3.64 (0.13, 90.72)
	AES (above-knee)	-	1.38 (0.00, 128.90)
	LMWH (high dose) + AES	-	0.04 (0.00, 1.49)
	VKA (extended duration)	-	0.47 (0.00, 48.12)
	LMWH (high dose; extended duration)	-	0.02 (0.00, 8.29)
Versus IPCD	UFH (standard duration)	-	1.61 (0.16, 16.85)
	Rivaroxaban	-	0.17 (0.01, 2.96)
	LMWH (standard dose; extended	-	0.05 (0.00, 1.21)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	duration)		
	LMWH (high dose; standard duration)	-	0.54 (0.03, 7.90)
	Dabigatran	-	0.73 (0.06, 7.96)
	Foot pump	-	2.88 (0.05, 123.10)
	Apixaban	-	0.35 (0.02, 4.70)
	AES (length unspecified)	-	0.30 (0.01, 9.30)
	LMWH (low dose) + AES	-	0.08 (0.00, 7.49)
	Fondaparinux + AES	-	0.31 (0.01, 8.70)
	LMWH (extended duration) + AES	-	0.02 (0.00, 1.30)
	Aspirin (standard duration)	-	8.03 (0.16, 206.90)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.00 (0.00, 0.31)
	VKA (standard duration)	-	0.83 (0.04, 15.75)
	UFH + AES	-	1.16 (0.02, 74.21)
	AES (above-knee)	-	0.42 (0.00, 96.92)
	LMWH (high dose) + AES	-	0.01 (0.00, 1.17)
	VKA (extended duration)	-	0.15 (0.00, 14.26)
	LMWH (high dose; extended duration)	-	0.01 (0.00, 2.22)
Versus UFH (standard duration)	Rivaroxaban	-	0.11 (0.01, 1.19)
	LMWH (standard dose; extended duration)	-	0.03 (0.00, 0.52)
	LMWH (high dose; standard duration)	0.35 (0.08, 1.47)	0.34 (0.05, 1.40)
	Dabigatran	-	0.45 (0.06, 2.97)
	Foot pump	-	1.77 (0.04, 56.95)
	Apixaban	-	0.21 (0.02, 1.85)
	AES (length unspecified)	-	0.18 (0.01, 4.70)
	LMWH (low dose) + AES	-	0.05 (0.00, 3.85)
	Fondaparinux + AES	-	0.19 (0.01, 4.11)
	LMWH (extended duration) + AES		0.01 (0.00, 0.65)
	Aspirin (standard duration)	2.88 (0.46, 18.06)*	4.66 (0.21, 75.89)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.00 (0.00, 0.15)
	VKA (standard duration)	-	0.52 (0.05, 3.60)
	UFH + AES	-	0.70 (0.01, 39.25)
	AES (above-knee)	-	0.26 (0.00, 48.78)
	LMWH (high dose) + AES	-	0.01 (0.00, 0.57)
	VKA (extended duration)		0.10 (0.00, 4.67)
	LMWH (high dose; extended duration)		0.00 (0.00, 0.92)
Versus	LMWH (standard dose; extended	0.31 (0.05, 1.78)	0.28 (0.02, 2.17)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
Rivaroxaban	duration)		
	LMWH (high dose; standard duration)	-	3.06 (0.18, 75.17)
	Dabigatran	-	4.20 (0.33, 82.88)
	Foot pump	-	16.83 (0.30, 1021.00)
	Apixaban	-	2.01 (0.12, 45.80)
	AES (length unspecified)	-	1.81 (0.04, 86.58)
	LMWH (low dose) + AES	-	0.50 (0.00, 64.91)
	Fondaparinux + AES	-	1.88 (0.05, 79.40)
	LMWH (extended duration) + AES	-	0.11 (0.00, 11.74)
	Aspirin (standard duration)	-	47.43 (0.94, 1872.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.02 (0.00, 0.84)
	VKA (standard duration)	-	4.77 (0.20, 143.70)
	UFH + AES	-	6.97 (0.07, 664.60)
	AES (above-knee)	-	2.56 (0.00, 697.00)
	LMWH (high dose) + AES	-	0.07 (0.00, 9.59)
	VKA (extended duration)	-	0.88 (0.00, 113.30)
	LMWH (high dose; extended duration)	-	0.04 (0.00, 18.95)
Versus LMWH (standard dose; extended duration)	LMWH (high dose; standard duration)	-	11.42 (0.41, 493.60)
	Dabigatran	-	15.57 (0.77, 598.20)
	Foot pump	-	64.15 (0.82, 6018.00)
	Apixaban	-	7.48 (0.29, 311.80)
	AES (length unspecified)	-	6.64 (0.12, 558.20)
	LMWH (low dose) + AES	-	1.84 (0.00, 346.30)
	Fondaparinux + AES	3.91 (0.44, 34.92)*	6.99 (0.13, 512.20)
	LMWH (extended duration) + AES	-	0.40 (0.00, 63.43)
	Aspirin (standard duration)	-	175.90 (2.45, 12110.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	0.15 (0.01, 2.89)*	0.07 (0.00, 1.46)
	VKA (standard duration)	-	17.66 (0.48, 931.10)
	UFH + AES	-	25.95 (0.21, 4081.00)
	AES (above-knee)	-	9.84 (0.01, 3985.00)
	LMWH (high dose) + AES	-	0.27 (0.00, 54.28)
	VKA (extended duration)		3.27 (0.00, 650.10)
	LMWH (high dose; extended duration)		0.13 (0.00, 96.85)
Versus LMWH (high dose; standard	Dabigatran	-	1.36 (0.13, 16.37)
	Foot pump	-	5.31 (0.10, 274.50)
	Apixaban	-	0.65 (0.05, 9.72)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
duration)	AES (length unspecified)	-	0.57 (0.02, 20.87)
	LMWH (low dose) + AES	-	0.15 (0.00, 16.59)
	Fondaparinux + AES	-	0.59 (0.02, 18.62)
	LMWH (extended duration) + AES	-	0.04 (0.00, 2.89)
	Aspirin (standard duration)	-	14.19 (0.47, 387.50)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.01 (0.00, 0.62)
	VKA (standard duration)	0.66 (0.23, 1.84)	1.53 (0.37, 6.16)
	UFH + AES	-	2.22 (0.03, 162.40)
	AES (above-knee)	-	0.78 (0.00, 205.60)
	LMWH (high dose) + AES	-	0.02 (0.00, 2.37)
	VKA (extended duration)	-	0.30 (0.00, 10.82)
	LMWH (high dose; extended duration)	-	0.01 (0.00, 2.07)
Versus Dabigatran	Foot pump	-	3.85 (0.10, 142.40)
	Apixaban	-	0.48 (0.04, 4.69)
	AES (length unspecified)	-	0.41 (0.02, 11.16)
	LMWH (low dose) + AES	-	0.11 (0.00, 9.14)
	Fondaparinux + AES	-	0.43 (0.02, 10.35)
	LMWH (extended duration) + AES	-	0.03 (0.00, 1.57)
	Aspirin (standard duration)	-	11.07 (0.29, 226.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.00 (0.00, 0.36)
	VKA (standard duration)	-	1.13 (0.07, 16.88)
	UFH + AES	-	1.60 (0.02, 92.90)
	AES (above-knee)	-	0.58 (0.00, 114.40)
	LMWH (high dose) + AES	-	0.02 (0.00, 1.42)
	VKA (extended duration)	-	0.21 (0.00, 16.13)
	LMWH (high dose; extended duration)	-	0.01 (0.00, 2.81)
Versus Foot pump	Apixaban	-	0.12 (0.00, 5.59)
	AES (length unspecified)	-	0.09 (0.00, 9.71)
	LMWH (low dose) + AES	-	0.03 (0.00, 6.62)
	Fondaparinux + AES	-	0.10 (0.00, 9.98)
	LMWH (extended duration) + AES	-	0.01 (0.00, 1.18)
	Aspirin (standard duration)	-	2.49 (0.03, 224.30)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.00 (0.00, 0.26)
	VKA (standard duration)	-	0.29 (0.00, 17.57)
	UFH + AES	-	0.38 (0.00, 69.71)
	AES (above-knee)	-	0.14 (0.00, 78.93)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	LMWH (high dose) + AES	-	0.00 (0.00, 1.08)
	VKA (extended duration)	-	0.05 (0.00, 12.09)
	LMWH (high dose; extended duration)	-	0.00 (0.00, 1.54)
Versus Apixaban	AES (length unspecified)	-	0.87 (0.03, 30.52)
	LMWH (low dose) + AES	-	0.24 (0.00, 23.71)
	Fondaparinux + AES	-	0.90 (0.03, 27.94)
	LMWH (extended duration) + AES	-	0.06 (0.00, 4.03)
	Aspirin (standard duration)	-	22.98 (0.56, 601.70)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.01 (0.00, 0.89)
	VKA (standard duration)	-	2.38 (0.12, 44.65)
	UFH + AES	-	3.36 (0.04, 231.40)
	AES (above-knee)	-	1.23 (0.00, 292.10)
	LMWH (high dose) + AES	-	0.04 (0.00, 3.49)
	VKA (extended duration)	-	0.43 (0.00, 37.71)
	LMWH (high dose; extended duration)	-	0.02 (0.00, 6.53)
Versus AES (length unspecified)	LMWH (low dose) + AES	-	0.30 (0.00, 9.69)
	Fondaparinux + AES	-	1.02 (0.06, 19.24)
	LMWH (extended duration) + AES	-	0.06 (0.00, 2.97)
	Aspirin (standard duration)	-	31.53 (0.32, 593.60)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.01 (0.00, 1.87)
	VKA (standard duration)	-	2.75 (0.06, 106.00)
	UFH + AES	2.74 (0.30, 25.05)	3.59 (0.30, 63.62)
	AES (above-knee)	-	1.43 (0.00, 186.90)
	LMWH (high dose) + AES	-	0.04 (0.00, 2.98)
	VKA (extended duration)	-	0.47 (0.00, 76.14)
	LMWH (high dose; extended duration)	-	0.02 (0.00, 11.98)
Versus LMWH (low dose) + AES	Fondaparinux + AES	-	3.57 (0.07, 1617.00)
	LMWH (extended duration) + AES	-	0.22 (0.00, 154.80)
	Aspirin (standard duration)	-	105.40 (0.46, 51270.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.03 (0.00, 53.02)
	VKA (standard duration)	-	10.18 (0.08, 5399.00)
	UFH + AES	-	13.70 (0.16, 8649.00)
	AES (above-knee)	1.00 (0.06, 15.76)	4.55 (0.14, 390.60)
	LMWH (high dose) + AES	-	0.14 (0.00, 130.20)
	VKA (extended duration)		1.71 (0.00, 2387.00)

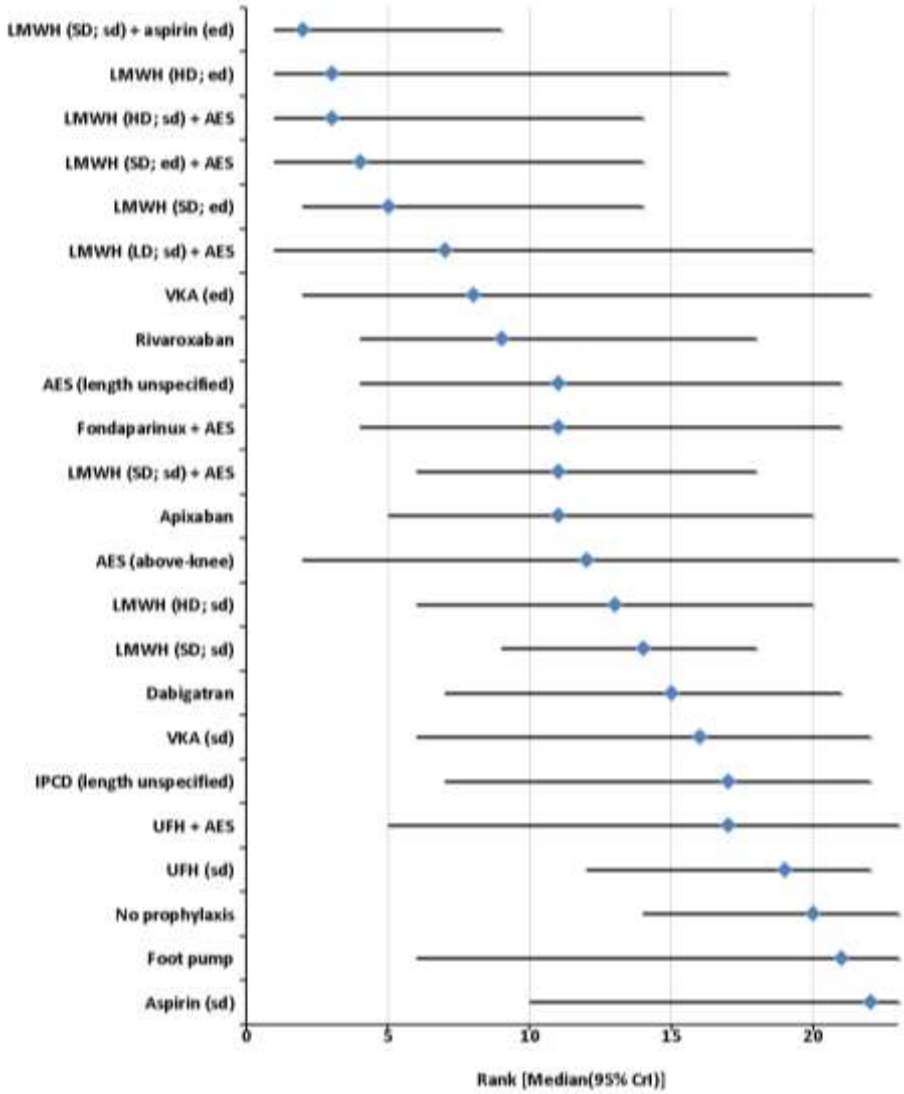
	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	LMWH (high dose; extended duration)		0.07 (0.00, 248.80)
Versus fondaparinux + AES	LMWH (extended duration) + AES	-	0.06 (0.00, 2.67)
	Aspirin (standard duration)	-	30.57 (0.33, 561.70)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.01 (0.00, 1.73)
	VKA (standard duration)	-	2.65 (0.06, 93.52)
	UFH + AES	-	3.69 (0.08, 153.80)
	AES (above-knee)	1.00 (0.06, 15.76)	1.38 (0.00, 216.10)
	LMWH (high dose) + AES	0.09 (0.01, 1.64)	0.05 (0.00, 0.76)
	VKA (extended duration)	-	0.46 (0.00, 70.47)
	LMWH (high dose; extended duration)	-	0.02 (0.00, 11.65)
Versus LMWH (standard dose; extended duration) + AES	Aspirin (standard duration)	-	464.20 (2.80, 242800.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.15 (0.00, 254.00)
	VKA (standard duration)	-	43.65 (0.43, 30520.00)
	UFH + AES	-	64.47 (0.55, 48030.00)
	AES (above-knee)	-	26.19 (0.01, 37000.00)
	LMWH (high dose) + AES	-	0.66 (0.00, 571.60)
	VKA (extended duration)	-	8.20 (0.00, 13090.00)
	LMWH (high dose; extended duration)	-	0.34 (0.00, 1307.00)
Versus aspirin (standard duration)	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.00 (0.00, 0.08)
	LMWH (high dose) + AES	-	0.11 (0.00, 4.01)
	UFH + AES	-	0.13 (0.00, 20.61)
	AES (above-knee)	-	0.05 (0.00, 24.21)
	VKA (standard duration)	-	0.00 (0.00, 0.32)
	VKA (extended duration)	-	0.02 (0.00, 2.85)
	LMWH (high dose; extended duration)	-	0.00 (0.00, 0.44)
Versus LMWH (standard dose; standard duration) + aspirin (extended duration)	LMWH (high dose) + AES	-	291.70 (2.02, 392100.00)
	UFH + AES	-	437.20 (1.06, 869900.00)
	AES (above-knee)	-	169.70 (0.05, 610700.00)
	VKA (standard duration)	-	4.35 (0.00, 11340.00)
	VKA (extended duration)	-	51.11 (0.02, 143200.00)
	LMWH (high dose; extended duration)	-	2.14 (0.00, 12350.00)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
Versus LMWH (high dose) + AES	UFH + AES	-	1.43 (0.02, 133.70)
	AES (above-knee)	-	0.51 (0.00, 161.90)
	VKA (standard duration)	-	0.01 (0.00, 1.86)
	VKA (extended duration)	-	0.20 (0.00, 5.27)
	LMWH (high dose; extended duration)	-	0.01 (0.00, 1.07)
Versus UFH + AES	AES (above-knee)	-	0.39 (0.00, 99.84)
	VKA (standard duration)	-	0.01 (0.00, 1.58)
	VKA (extended duration)	-	0.12 (0.00, 41.97)
	LMWH (high dose; extended duration)	-	0.00 (0.00, 5.61)
Versus AES (above-knee)	VKA (standard duration)	-	0.03 (0.00, 57.82)
	VKA (extended duration)	-	0.33 (0.00, 1053.00)
	LMWH (high dose; extended duration)	-	0.01 (0.00, 100.60)
Versus VKA (standard duration)	VKA (extended duration)	0.32 (0.01, 7.78)	12.18 (0.01, 23630.00)
	LMWH (high dose; extended duration)	0.11 (0.01, 2.04)	0.54 (0.00, 2480.00)
Versus VKA (extended duration	LMWH (high dose; extended duration)	-	0.06 (0.00, 0.99)

**Intervention and comparison numbers have been switched in Review Manager*

Figure 830 shows the rank of each intervention compared to the others. The rank is based on the relative risk compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 23 different interventions being evaluated.

Figure 830: Rank order for interventions based on the relative risk of experiencing PE



LD = low dose; SD = standard dose; HD = high dose; sd = standard duration; ed = extended duration

Goodness of fit and inconsistency

Both fixed effects and random effects models were fitted to the data. The random effects model had a DIC of 255 compared with 276 for the fixed effects model. The random effects model used for the NMA is a good fit, with a residual deviance of 61 reported. This corresponds well to the total number of trial arms, 62. The between trial standard deviation in the random effects analysis was 0.41 (95% CI 0.14 to 1.04). On evaluating inconsistency by comparing risk ratios, one inconsistency was identified. The NMA estimated risk ratio for VKA at an extended duration versus VKA at a standard duration (12.18 [1.01, 23630.00]) lay outside of the confidence interval of the risk ratio estimated for the direct comparison (0.32 [0.01, 7.78]). An inconsistency model was run and the DIC statistics were as follows in Table 243. The difference in the DIC is small (<3-5) with the consistency model having the lower DIC value. This suggests that it fits the data better than the inconsistency model.

Table 243: Posterior mean of the residual deviance (resdev) and DIC for the RE network meta-analysis and inconsistency models – PE

	DIC	ResDev
Consistency model	255.025	61

Inconsistency model	258.386	63

M.1.3.3 Major bleeding

Included studies

28 studies were identified as reporting on major bleeding outcomes. After excluding papers that reported zero events in each arm and papers reporting on combinations that did not connect to any other intervention in the network, 24 studies involving 15 treatments were included in the network for PE. The network can be seen in **Figure 831** and the trial data for each of the studies included in the NMA are presented in

Table 244.

Figure 831: Network diagram for major bleeding

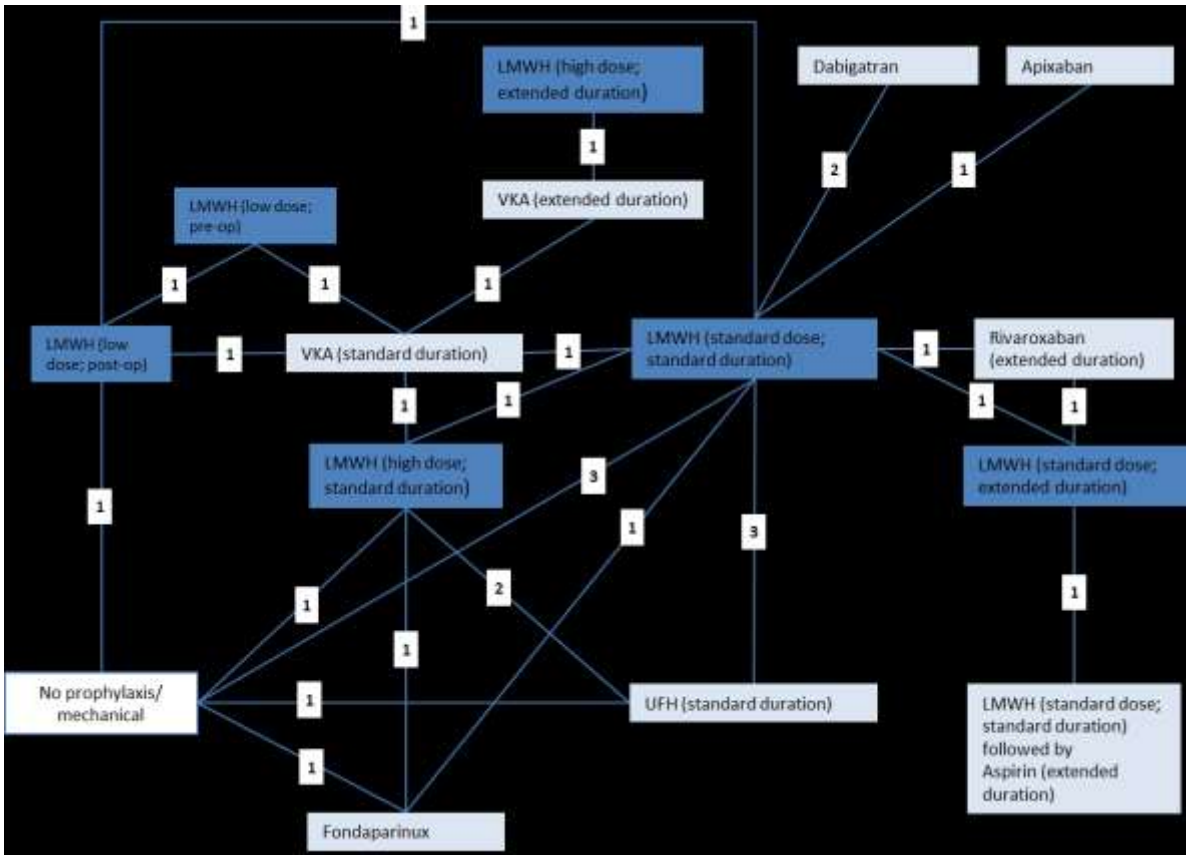


Table 244: Study data for major bleeding network meta-analysis

Study	Comparison	Intervention 1	Intervention 2	Comparison	Intervention 1	Intervention 2

Study	Comparison	Intervention 1	Intervention 2	Comparison		Intervention 1		Intervention 2	
				N	NA	N	NA	N	NA
Moskovitz 1978 [657]	No prophylaxis/ mechanical	UFH (standard duration)	-	3	35	0	32	-	-
Turpie 1986 [952]	No prophylaxis/ mechanical	LMWH (high dose; standard duration)	-	1	50	2	50	-	-
Fuji 2008A [328]	No prophylaxis/ mechanical	LMWH (standard dose; standard duration)	LMWH (low dose; post-op)	0	101	2	102	1	100
Hardwick 2011 [389]	No prophylaxis/ mechanical	LMWH (standard dose; standard duration)	-	0	198	11	194	-	-
Samama 1997 [844]	No prophylaxis/ mechanical	LMWH (standard dose; standard duration)	-	1	75	1	78	-	-
Fuji 2008 [325]	No prophylaxis/ mechanical	Fondaparinux	-	0	82	2	81	-	-
Levine 1991 [551]	UFH (standard duration)	LMWH (high dose; standard duration)	-	19	332	11	333	-	-
Colwell 1994 [204]	UFH (standard duration)	LMWH (high dose; standard duration)	LMWH (standard dose; standard duration)	13	209	8	195	3	203
Eriksson 1991A [289]	UFH (standard duration)	LMWH (standard dose; standard duration)	-	5	69	1	67	-	-
Plànes 1990 [758]	UFH (standard duration)	LMWH (standard dose; standard duration)	-	0	106	2	120	-	-
Turpie 2002K[954]	LMWH (high dose; standard duration)	Fondaparinux	-	11	1129	20	1128	-	-
Colwell 1999 [203]	LMWH (high dose; standard duration)	VKA (standard duration)	-	6	1516	4	1495	-	-
Lassen 2002[526]	LMWH (standard dose; standard duration)	Fondaparinux	-	32	1133	47	1140	-	-

Study	Comparison	Intervention 1	Intervention 2	Comparison		Intervention 1		Intervention 2	
Francis 1997 [315]	LMWH (standard dose; standard duration)	VKA (standard duration)	-	6	271	4	279	-	-
Eriksson 2011 [292]	LMWH (standard dose; standard duration)	Dabigatran	-	9	1003	14	1010	-	-
Eriksson 2007 [288]	LMWH (standard dose; standard duration)	Dabigatran	-	18	1154	23	1146	-	-
Lassen 2010 [534]	LMWH (standard dose; standard duration)	Apixaban	-	18	2659	22	2673	-	-
Kakkar 2008 [467]	LMWH (standard dose; standard duration)	Rivaroxaban	-	19	1257	23	1252	-	-
Lassen 1998 [527]	LMWH (standard dose; standard duration)	LMWH (standard dose; extended duration)	-	1	141	0	140	-	-
Hull 2000[440]	LMWH (low dose; post-op)	VKA (standard duration)	LMWH (low dose; pre-op)	32	487	22	489	44	496
Prandoni 2002 [771]	VKA (standard duration)	VKA (extended duration)	-	0	176	1	184	-	-
Eriksson 2008 [291]	LMWH (standard dose; extended duration)	Rivaroxaban	-	33	2225	40	2266	-	-
Anderson 2013 [40]	LMWH (standard dose; extended duration)	LMWH (st; st duration) + aspirin (extended)	-	1	400	0	386	-	-
Samama 2002 [845]	LMWH (high dose; extended duration)	VKA (extended duration)	-	10	643	37	636	-	-

N; number of events, NA; number analysed

NMA results

Table 245 summarises the results of the conventional meta-analyses in terms of odd ratios generated from studies directly comparing different interventions, together with the results of the NMA in terms of odd ratios for every possible treatment comparison. Relative risks were not calculated for this outcome as data was only available for non-surgical site bleeding (intracranial haemorrhage + gastrointestinal bleeding) from the observational study used as the source of baseline risk.[451]

Table 245: Odd ratios for major bleeding

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
Versus no prophylaxis/ mechanical	UFH (standard duration)	7.00 (0.35, 140.99)	3.58 (0.89, 13.67)
	LMWH (high dose; standard duration)	0.49 (0.04, 5.58)	2.47 (0.67, 9.56)
	LMWH (standard dose; standard duration)	7.66 (1.76, 33.31)	2.55 (0.82, 8.70)
	Fondaparinux	5.19 (0.25, 109.77)	4.28 (1.07, 18.66)
	LMWH (low dose; post-op)	3.06 (0.12, 76.02)	2.20 (0.35, 13.35)
	VKA (standard duration)	-	1.54 (0.31, 7.94)
	Dabigatran	-	3.63 (0.74, 18.48)
	Apixaban	-	3.16 (0.47, 21.15)
	Rivaroxaban	-	2.74 (0.42, 16.16)
	LMWH (standard dose; extended duration)	-	1.99 (0.21, 14.60)
	LMWH (low dose; pre-op)	-	3.13 (0.41, 23.59)
	VKA (extended duration)	-	8.21 (0.13, 7883.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.37 (0.00, 26.96)
	LMWH (high dose; extended duration)	-	2.06 (0.02, 2194.00)
Versus UFH	LMWH (high dose; standard duration)	0.60 (0.33, 1.06)	0.69 (0.28, 2.01)
	LMWH (standard dose; standard duration)	0.34 (0.14, 0.84)	0.71 (0.28, 2.13)
	Fondaparinux	-	1.18 (0.36, 5.06)
	LMWH (low dose; post-op)	-	0.61 (0.11, 3.68)
	VKA (standard duration)	-	0.43 (0.10, 2.01)
	Dabigatran	-	1.00 (0.25, 4.99)
	Apixaban	-	0.87 (0.16, 5.91)
	Rivaroxaban	-	0.76 (0.14, 4.22)
	LMWH (standard dose; extended duration)	-	0.55 (0.07, 3.86)
	LMWH (low dose; pre-op)	-	0.87 (0.13, 6.53)
	VKA (extended duration)	-	2.29 (0.04, 2198.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.10 (0.00, 7.53)
	LMWH (high dose; extended	-	0.57 (0.01, 621.20)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	duration)		
Versus LMWH (high dose; standard duration)	LMWH (standard dose; standard duration)	0.35 (0.09, 1.34)	1.04 (0.38, 2.83)
	Fondaparinux	1.83 (0.87, 3.85)*	1.71 (0.58, 5.66)
	LMWH (low dose; post-op)	-	0.89 (0.17, 4.54)
	VKA (standard duration)	0.68 (0.19, 2.40)	0.62 (0.16, 2.36)
	Dabigatran	-	1.46 (0.34, 6.58)
	Apixaban	-	1.27 (0.21, 7.77)
	Rivaroxaban	-	1.11 (0.19, 5.73)
	LMWH (standard dose; extended duration)	-	0.80 (0.09, 5.27)
	LMWH (low dose; pre-op)	-	1.26 (0.20, 8.08)
	VKA (extended duration)	-	3.28 (0.06, 2993.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.15 (0.00, 10.57)
	LMWH (high dose; extended duration)	-	0.83 (0.01, 851.90)
Versus LMWH (standard dose; standard duration)	Fondaparinux	1.48 (0.94, 2.34)*	1.66 (0.58, 5.15)
	LMWH (low dose; post-op)	0.51 (0.05, 5.66)	0.86 (0.18, 3.95)
	VKA (standard duration)	0.64 (0.18, 2.30)*	0.60 (0.16, 2.14)
	Dabigatran	1.38 (0.84, 2.28)*	1.41 (0.48, 4.27)
	Apixaban	1.22 (0.65, 2.26)*	1.23 (0.27, 5.51)
	Rivaroxaban	1.22 (0.65, 2.28)*	1.07 (0.25, 3.97)
	LMWH (standard dose; extended duration)	0.33 (0.01, 8.25)	0.78 (0.11, 3.85)
	LMWH (low dose; pre-op)	-	1.22 (0.20, 7.15)
	VKA (extended duration)	-	3.14 (0.06, 2820.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.14 (0.00, 8.94)
	LMWH (high dose; extended duration)	-	0.79 (0.01, 815.60)
Versus Fondaparinux	LMWH (low dose; post-op)	-	0.51 (0.08, 2.97)
	VKA (standard duration)	-	0.36 (0.07, 1.67)
	Dabigatran	-	0.85 (0.18, 3.89)
	Apixaban	-	0.74 (0.11, 4.58)
	Rivaroxaban	-	0.64 (0.10, 3.42)
	LMWH (standard dose; extended duration)	-	0.47 (0.05, 3.11)
	LMWH (low dose; pre-op)	-	0.73 (0.09, 5.23)
	VKA (extended duration)	-	1.90 (0.03, 1816.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.09 (0.00, 6.02)
	LMWH (high dose; extended	-	0.48 (0.01, 500.80)

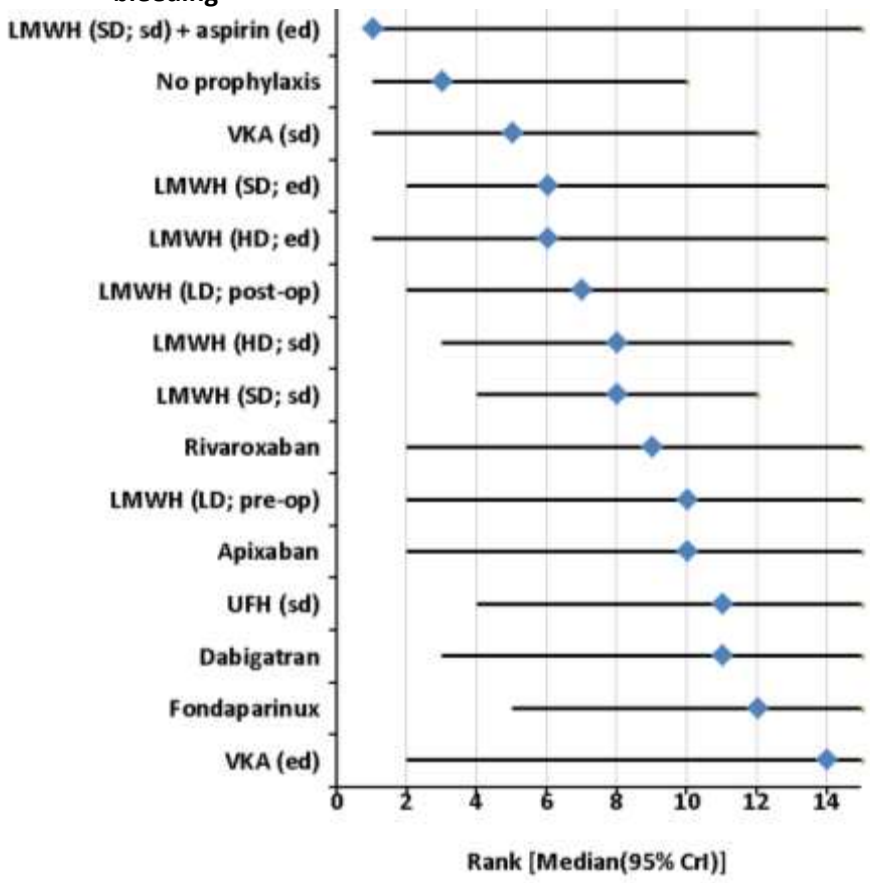
	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	duration)		
Versus LMWH (low dose; post-op)	VKA (standard duration)	-	0.70 (0.20, 2.61)
	Dabigatran	-	1.66 (0.26, 11.40)
	Apixaban	-	1.43 (0.17, 12.73)
	Rivaroxaban	-	1.25 (0.15, 9.64)
	LMWH (standard dose; extended duration)	-	0.90 (0.08, 8.49)
	LMWH (low dose; pre-op)	1.38 (0.86, 2.22)	1.42 (0.35, 5.91)
	VKA (extended duration)	-	3.68 (0.07, 3220.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.17 (0.00, 14.06)
	LMWH (high dose; extended duration)	-	0.93 (0.01, 927.10)
Versus VKA (standard duration)	Dabigatran	-	2.36 (0.45, 12.91)
	Apixaban	-	2.05 (0.29, 14.69)
	Rivaroxaban	-	1.77 (0.26, 11.11)
	LMWH (standard dose; extended duration)	-	1.29 (0.13, 10.07)
	LMWH (low dose; pre-op)	2.07 (1.22, 3.50)	2.03 (0.49, 8.27)
	VKA (extended duration)	2.89 (0.12, 71.31)	5.18 (0.12, 4147.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.24 (0.00, 18.31)
	LMWH (high dose; extended duration)	0.26 (0.13, 0.52)	1.30 (0.02, 1200.00)
Versus Dabigatran	Apixaban	-	0.87 (0.13, 5.46)
	Rivaroxaban	-	0.76 (0.12, 4.06)
	LMWH (standard dose; extended duration)	-	0.55 (0.06, 3.69)
	LMWH (low dose; pre-op)	-	0.86 (0.10, 6.78)
	VKA (extended duration)	-	2.26 (0.04, 2161.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.10 (0.00, 7.14)
	LMWH (high dose; extended duration)		0.57 (0.01, 607.50)
Versus Apixaban	Rivaroxaban	-	0.88 (0.10, 6.31)
	LMWH (standard dose; extended duration)	-	0.63 (0.05, 5.52)
	LMWH (low dose; pre-op)	-	0.99 (0.10, 9.99)
	VKA (extended duration)	-	2.64 (0.04, 2645.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.12 (0.00, 9.43)
	LMWH (high dose; extended	-	0.66 (0.01, 737.70)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	duration)		
Versus Rivaroxaban	LMWH (standard dose; extended duration)	0.82 (0.51, 1.30)	0.73 (0.18, 2.54)
	LMWH (low dose; pre-op)	-	1.14 (0.12, 11.40)
	VKA (extended duration)	-	3.01 (0.05, 3189.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.14 (0.00, 7.28)
	LMWH (high dose; extended duration)	-	0.76 (0.01, 905.60)
Versus LMWH (standard dose; extended duration)	LMWH (low dose; pre-op)	-	1.58 (0.15, 21.45)
	VKA (extended duration)	-	4.24 (0.06, 4892.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	0.35 (0.01, 8.51)*	0.20 (0.00, 8.19)
	LMWH (high dose; extended duration)	-	1.06 (0.01, 1347.00)
Versus LMWH (low dose; standard duration; pre-op)	VKA (extended duration)	-	2.62 (0.05, 2269.00)
	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.12 (0.00, 10.62)
	LMWH (high dose; extended duration)	-	0.66 (0.01, 652.50)
Versus VKA (extended duration	LMWH (standard dose; standard duration) + aspirin (extended duration)	-	0.04 (0.00, 15.62)
	LMWH (high dose; extended duration)	-	0.25 (0.05, 1.14)
Versus LMWH (standard dose; standard duration) + aspirin (extended duration)	LMWH (high dose; extended duration)	-	6.97 (0.01, 64290.00)

**Intervention and comparison numbers have been switched in Review Manager*

Figure 832 shows the rank of each intervention compared to the others. The rank is based on the relative risk compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 14 different interventions being evaluated.

Figure 832: Rank order for interventions based on the relative risk of experiencing major bleeding



LD = low dose; SD = standard dose; HD = high dose; sd = standard duration; ed = extended duration

Goodness of fit and inconsistency

Both fixed effects and random effects models were fitted to the data. The random effects model had a DIC of 275 compared with 276 for the fixed effects model. The random effects model used for the NMA is a good fit, with a residual deviance of 55 reported. This corresponds well to the total number of trial arms, 51. The between trial standard deviation in the random effects analysis was 0.56 (95% CI 0.19 to 1.27). On evaluating inconsistency by comparing odd ratios, one inconsistency was identified. The NMA estimated odd ratio for LMWH at a standard dose for an extended duration versus VKA at a standard duration (1.30 [0.02, 1200.00]) lay outside of the confidence interval of the odd ratio estimated for the direct comparison (0.26 [0.13, 0.52]). An inconsistency model was run and the DIC statistics were as follows in Table 246. The difference in the DIC is small (<3-5) which suggests that there is no obvious inconsistency in the network. The consistency model has a smaller DIC suggesting that it is a better fit to the data than the inconsistency model.

Table 246: Posterior mean of the residual deviance (resdev) and DIC for the RE network meta-analysis and inconsistency models – major bleeding

	DIC	ResDev
Consistency model	275.34	55
Inconsistency model	277.695	55

M.1.4 Discussion

Based on the results of conventional meta-analyses of direct evidence, as has been previously presented in Chapter 26 and appendix H, deciding upon the most clinical and cost effective prophylaxis intervention in patients undergoing elective hip replacement surgery is challenging. In order to overcome the difficulty of interpreting the conclusions from numerous separate comparisons, network meta-analysis of the direct evidence was performed. The findings of the NMA were used to facilitate the committee in their decision-making when developing recommendations.

Our analyses were divided into three critical outcomes. 42 studies informed the DVT network where 26 different individual or combination treatments were evaluated including five mechanical interventions, fourteen pharmacological interventions, and six interventions that combined both mechanical and pharmacological prophylaxis. 30 studies informed the PE network of 23 different treatments, including four mechanical interventions, eleven pharmacological interventions, and six interventions that combined both mechanical and pharmacological prophylaxis. The major bleeding network included 24 studies evaluating 15 treatments, 14 of which were pharmacological as for this outcome any mechanical prophylaxis measures were combined with the no prophylaxis intervention as it is believed that mechanical prophylaxis has no associated bleeding risk.

In the DVT network, the top three interventions were rivaroxaban, fondaparinux plus AES and LMWH at a standard dose for an extended duration plus AES. The bottom three interventions were no prophylaxis, UFH at an extended duration and IPCD (length unspecified). Five of the six interventions that represented a combination of mechanical and pharmacological prophylaxis featured in the top ten best ranked treatments. The treatment believed to most represent standard practice, LMWH at a standard dose for a standard duration plus AES, ranked at 7. There was a lot of uncertainty about the estimates with the credible intervals for some of the interventions being very wide, some interventions' ranks spanning across from 1 to 26.

In the PE network, the top intervention was the combination treatment of LMWH at a standard dose for a standard duration followed by aspirin at an extended duration. The second and third ranked treatments were LMWH at a high dose for an extended duration and LMWH at a high dose for a standard duration plus AES. The bottom three interventions were aspirin at a standard duration, foot pump and no prophylaxis. The intervention LMWH at a standard dose for a standard duration with AES was ranked eleventh. There was also considerable uncertainty in the PE network with wide credible intervals for a majority of the interventions, particularly for LMWH (high dose, standard duration) plus AES and LMWH (low dose, standard duration) plus AES with credible intervals spanning from 1 to 20.; and for AES (above-knee) and apixaban with credible intervals spanning from 2 to 23.

In the major bleeding network the highest ranked intervention was the combination treatment of LMWH at a standard dose for a standard duration followed by aspirin at an extended duration. This was followed by no prophylaxis and VKA at a standard duration.. The bottom three interventions were VKA at an extended duration, fondaparinux and dabigatran. There was a lot of uncertainty within the major bleeding network with very wide credible intervals for all of the interventions. These very wide credible intervals account for the unusual rank of no prophylaxis as the second best intervention in terms of major bleeding.

In summary, the three outcomes chosen for analyses were considered to be among the most critical for assessing clinical effectiveness of different VTE prophylaxis strategies. All three networks seemed to fit well, as demonstrated by DIC and residual deviance statistics. However due to the sparse nature of the networks, and low event rates, the credible intervals around the ranking of treatments in all three networks were wide suggesting considerable uncertainty about these results.

M.1.5 Conclusion

This analysis allowed us to combine findings from many different comparisons presented in the review even when direct comparative data was lacking.

The committee and orthopaedic subgroup noted the wide credible intervals particularly for the PE and major bleeding network meta-analyses. They both also noted that even with the high levels of uncertainty, interventions such as LMWH at a standard dose for a standard duration followed by aspirin for an extended duration and LMWH in combination with AES, present possible clinical effectiveness in terms of the outcomes of DVT (symptomatic and asymptomatic), PE and major bleeding. .

For details of the rationale and discussion leading to recommendations, please refer to the section linking the evidence to the recommendations (section 26.6, chapter 26).

M.1.6 WinBUGS codes

M.1.6.1 WinBUGS code for number of patients with DVT (symptomatic and asymptomatic)

```
#Random effects model for multi-arm trials (any number of arms)

model{

for(i in 1:NS){

  w[i,1] <-0

  delta[i,t[i,1]]<-0

  mu[i] ~ dnorm(0,.0001) # vague priors for trial baselines

  for (k in 1:na[i]){

    r[i,k] ~ dbin(p[i,t[i,k]],n[i,k]) # binomial likelihood

    logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]  # model

#Deviance residuals for data i

  rhat[i,k] <- p[i,t[i,k]] * n[i,k]                                    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))

   }

  sdev[i]<- sum(dev[i,1:na[i]])

  for (k in 2:na[i]){

# trial-specific LOR distributions

    delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])

    md[i,t[i,k]] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions

    taud[i,t[i,k]] <- tau *2*(k-1)/k     #precision of LOR distributions

#adjustment, multi-arm RCTs
```

```
   w[i,k] <- (delta[i,t[i,k]]  - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
   sw[i,k] <-sum(w[i,1:k-1])/(k-1)
  }
 }
d[1]<-0
for (k in 2:NT){d[k] ~ dnorm(0,.0001) } # vague priors for basic parameters
#sd ~ dunif(0,5)        # vague prior for random effects standard deviation
#tau <- 1/pow(sd,2)
sd.sq ~ dlnorm(m.tau,prec.tau)  # empirical prior for between-trial Var
prec.tau <- pow(sd.tau,-2)
tau <- pow(sd.sq,-1)   # between-trial precision = (1/between-trial variance)
sd <- sqrt(sd.sq)

#A ~ dnorm(meanA, precA)  # A is on log-odds scale
#precA <- pow(sdA,-2)     # turn st dev into precision

v[4] ~ dbeta(a, b)    # distribution for prob event on LMWH (std/std)+AES
b <- N-a
N <- 85642
a <- 4746
for (k in 1:3){       # treatments below 4
  logit(v[k]) <- logit(v[4]) - lor[k,4]       # note change in sign
  rr[k] <- v[k]/v[1]     # calculate relative risk
 }

for (k in 5:NT){    # treatments above 4
  logit(v[k]) <- logit(v[4]) + lor[4,k]
  rr[k] <- v[k]/v[1]     # calculate relative risk
 }
rr[4] <- v[4]/v[1]
sumdev <- sum(sdev[])    # Calculate residual deviance
```

```
# Ranking and prob{treatment k is best}
for (k in 1:NT){
  rk[k] <- rank(rr[],k)
  best[k] <- equals(rank(rr[],k),1)
 }
# pairwise ORs and RRs
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]
    lrr[c,k] <- log(rr[k]) - log(rr[c])
    log(rrisk[c,k]) <- lrr[c,k]
   }
 }
}


# NT=no. treatments, NS=no. studies;
# NB : set up M vectors each r[,]. n[,] and t[,],  where M is the Maximum number of treatments
#         per trial in the dataset. In this dataset M is 3.



list(NT=26, NS=42,
# meanA and sdA are the  posterior mean and sd of log-odds of event
#meanA=-1.673, sdA=0.2529,
#Empirical prior Table IV (Turner et al) intervention: Non-Pharma v Pharma;
# outcome type: general physical health indicators
m.tau= -1.26, sd.tau=1.25 )

 r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1]  t[,2]  t[,3]     t[,4]     t[,5]    na[]

13        14        12        32        8         32        NA        NA        NA        NA        1         2         4
          NA        NA        3

43        116       21        117       NA        NA        NA        NA        NA        NA        1         2         NA
          NA        NA        2
```

19	54 NA	9 NA	58 2	NA	NA	NA	NA	NA	NA	1	2	NA
28	52 NA	22 NA	48 2	NA	NA	NA	NA	NA	NA	1	3	NA
36	75 NA	14 NA	68 2	NA	NA	NA	NA	NA	NA	1	3	NA
20	39 NA	4 NA	37 2	NA	NA	NA	NA	NA	NA	1	5	NA
36	152 NA	77 NA	158 2	NA	NA	NA	NA	NA	NA	1	6	NA
25	47 NA	15 NA	43 2	NA	NA	NA	NA	NA	NA	1	6	NA
28	136 NA	21 NA	142 3	8	136	NA	NA	NA	NA	2	3	5
1	79 NA	4 NA	79 2	NA	NA	NA	NA	NA	NA	2	3	NA
19	63 NA	25 NA	59 2	NA	NA	NA	NA	NA	NA	2	3	NA
15	120 NA	27 NA	106 2	NA	NA	NA	NA	NA	NA	2	3	NA
12	150 NA	5 NA	78 2	NA	NA	NA	NA	NA	NA	2	5	NA
8	190 NA	8 NA	196 2	NA	NA	NA	NA	NA	NA	2	6	NA
39	138 NA	15 NA	152 2	NA	NA	NA	NA	NA	NA	2	7	NA
12	102 NA	5 NA	113 2	NA	NA	NA	NA	NA	NA	2	7	NA
17	88 NA	6 NA	85 2	NA	NA	NA	NA	NA	NA	2	7	NA
67	783 NA	60 NA	791 2	NA	NA	NA	NA	NA	NA	2	8	NA
57	897 NA	45 NA	880 2	NA	NA	NA	NA	NA	NA	2	8	NA
18	138 NA	24 NA	136 2	NA	NA	NA	NA	NA	NA	2	9	NA
68	1911 NA	22 NA	1944 2	NA	NA	NA	NA	NA	NA	2	10	NA
71	869 NA	14 NA	864 2	NA	NA	NA	NA	NA	NA	2	11	NA

49	190 NA	28 NA	192 2	NA	NA	NA	NA	NA	NA	2	12	NA
24	116 NA	9 NA	101 2	NA	NA	NA	NA	NA	NA	3	5	NA
61	263 NA	50 NA	258 2	NA	NA	NA	NA	NA	NA	3	5	NA
4	33 NA	6 NA	28 2	NA	NA	NA	NA	NA	NA	3	13	NA
10	25 NA	7 NA	19 2	NA	NA	NA	NA	NA	NA	3	14	NA
27	80 NA	21 NA	81 3	36	86	NA	NA	NA	NA	4	15	18
33	104 NA	22 NA	114 2	NA	NA	NA	NA	NA	NA	4	16	NA
83	918 NA	36 NA	908 2	NA	NA	NA	NA	NA	NA	4	17	NA
11	78 NA	28 NA	75 2	NA	NA	NA	NA	NA	NA	4	18	NA
22	78 NA	33 NA	78 2	NA	NA	NA	NA	NA	NA	4	18	NA
11	66 NA	12 NA	72 2	NA	NA	NA	NA	NA	NA	6	12	NA
53	1558 NA	12 NA	1595 2	NA	NA	NA	NA	NA	NA	7	11	NA
81	338 NA	36 NA	337 3	44	336	NA	NA	NA	NA	12	19	20
8	176 NA	3 NA	184 2	NA	NA	NA	NA	NA	NA	12	21	NA
29	93 NA	44 NA	97 2	NA	NA	NA	NA	NA	NA	15	22	NA
44	784 NA	65 NA	796 2	NA	NA	NA	NA	NA	NA	17	23	NA
19	28 NA	8 NA	32 2	NA	NA	NA	NA	NA	NA	18	24	NA
4	39 NA	16 NA	40 2	NA	NA	NA	NA	NA	NA	18	25	NA
20	636 NA	15 NA	643 2	NA	NA	NA	NA	NA	NA	21	26	NA
23	65 NA	9 NA	67 2	NA	NA	NA	NA	NA	NA	24	25	NA

```
END


 INITS
list(
d=c(NA,0,0,0,0,  0,0,0,1,2,   3,4,2,4,2,   1,2,-1,-2,0,   2,3,1,4,0,  -1), # one for each treatment,
sd.sq=1,
mu=c(-2,0,2,0,0,   0,3,0,1,0,   0,2,1,1, 3,   2,-2,0,2,0,   0,0,3,0,1,   0,0,2,1, 1,   3, 2,1,0,4,  1, 2,0,2,-3, 1,1) )
list(
d=c(NA,0,0,4,0,  0,3,0,0,3,   4,4,1,0,-1,   -3,0,2,1,4,  2,1,2,2,1,   0), # one for each treatment,
sd.sq=0.1,
mu=c(0,0,-2,0,3,   0,0,2,0,0,  0,2,0,2,1,   4,0,0,-2,0,   3,0,0,2,0,   0,0,2,0,2,   1,4, 2,0, -3,   1,2,1,0,0, 1,1) )
list(
d=c(NA,0,1,1,0,  0,0,0,1,2,  3,4,2,1,0,  3,1,3,4,-2,  0,1,-3,4,2,  1), # one for each treatment,
sd.sq=2,
mu=c(0,0,3,0,0,   0,0,0,3,3,  0,0,4,2,1,   1,0,0,3,0,   0,0,0,0,3,  3,0,0,4,2,   1,1,1, 2,4,      0,-1,2,1,3, 2,1) )
```

M.1.6.2 WinBUGS code for inconsistency model for number of patients with DVT

```
VTE - inconsistency model - Elective hip DVT
==============================
42 studies
26 treatments
==============================
# Binomial likelihood, logit link, inconsistency model
# Random effects model
model{                  # *** PROGRAM STARTS
for(i in 1:ns){          # LOOP THROUGH STUDIES
   delta[i,1]<-0         # treatment effect is zero in control arm
   mu[i] ~ dnorm(0,.0001)  # vague priors for trial baselines
   for (k in 1:na[i])  {   # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
```

```
      logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
        +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
    }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {  # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
    }
 }
totresdev <- sum(resdev[])   # Total Residual Deviance
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
   for (k in (c+1):nt)  { d[c,k] ~ dnorm(0,.0001) }
 }
#sd ~ dunif(0,5)  # vague prior for between-trial standard deviation
#var <- pow(sd,2) # between-trial variance
#tau <- 1/var     # between-trial precision
sd.sq ~ dlnorm(m.tau,prec.tau)  # empirical prior for between-trial Var
prec.tau <- pow(sd.tau,-2)
tau <- pow(sd.sq,-1)   # between-trial precision = (1/between-trial variance)
sd <- sqrt(sd.sq)

} # *** PROGRAM ENDS

 Data
# DVT
# nt=no. treatments, ns=no. studies
list(nt=26,ns=42, m.tau= -1.26, sd.tau=1.25)
```

r[,1]	n[,1]	r[,2]	n[,2]	r[,3]	n[,3]	r[,4]	n[,4]	r[,5]	n[,5]	t[,1]	t[,2]	t[,3]	t[,4]	t[,5]	na[]
13	14	12	32	8	32	NA	NA	NA	NA	1	2	4			
	NA	NA	3												
43	116	21	117	NA	NA	NA	NA	NA	NA	1	2	NA			
	NA	NA	2												
19	54	9	58	NA	NA	NA	NA	NA	NA	1	2	NA			
	NA	NA	2												
28	52	22	48	NA	NA	NA	NA	NA	NA	1	3	NA			
	NA	NA	2												
36	75	14	68	NA	NA	NA	NA	NA	NA	1	3	NA			
	NA	NA	2												
20	39	4	37	NA	NA	NA	NA	NA	NA	1	5	NA			
	NA	NA	2												
36	152	77	158	NA	NA	NA	NA	NA	NA	1	6	NA			
	NA	NA	2												
25	47	15	43	NA	NA	NA	NA	NA	NA	1	6	NA			
	NA	NA	2												
28	136	21	142	8	136	NA	NA	NA	NA	2	3	5			
	NA	NA	3												
1	79	4	79	NA	NA	NA	NA	NA	NA	2	3	NA			
	NA	NA	2												
19	63	25	59	NA	NA	NA	NA	NA	NA	2	3	NA			
	NA	NA	2												
15	120	27	106	NA	NA	NA	NA	NA	NA	2	3	NA			
	NA	NA	2												
12	150	5	78	NA	NA	NA	NA	NA	NA	2	5	NA			
	NA	NA	2												
8	190	8	196	NA	NA	NA	NA	NA	NA	2	6	NA			
	NA	NA	2												
39	138	15	152	NA	NA	NA	NA	NA	NA	2	7	NA			
	NA	NA	2												
12	102	5	113	NA	NA	NA	NA	NA	NA	2	7	NA			
	NA	NA	2												
17	88	6	85	NA	NA	NA	NA	NA	NA	2	7	NA			
	NA	NA	2												
67	783	60	791	NA	NA	NA	NA	NA	NA	2	8	NA			
	NA	NA	2												
57	897	45	880	NA	NA	NA	NA	NA	NA	2	8	NA			
	NA	NA	2												

18	138 NA	24 NA	136 2	NA	NA	NA	NA	NA	NA	2	9	NA
68	1911 NA	22 NA	1944 2	NA	NA	NA	NA	NA	NA	2	10	NA
71	869 NA	14 NA	864 2	NA	NA	NA	NA	NA	NA	2	11	NA
49	190 NA	28 NA	192 2	NA	NA	NA	NA	NA	NA	2	12	NA
24	116 NA	9 NA	101 2	NA	NA	NA	NA	NA	NA	3	5	NA
61	263 NA	50 NA	258 2	NA	NA	NA	NA	NA	NA	3	5	NA
4	33 NA	6 NA	28 2	NA	NA	NA	NA	NA	NA	3	13	NA
10	25 NA	7 NA	19 2	NA	NA	NA	NA	NA	NA	3	14	NA
27	80 NA	21 NA	81 3	36	86	NA	NA	NA	NA	4	15	18
33	104 NA	22 NA	114 2	NA	NA	NA	NA	NA	NA	4	16	NA
83	918 NA	36 NA	908 2	NA	NA	NA	NA	NA	NA	4	17	NA
11	78 NA	28 NA	75 2	NA	NA	NA	NA	NA	NA	4	18	NA
22	78 NA	33 NA	78 2	NA	NA	NA	NA	NA	NA	4	18	NA
11	66 NA	12 NA	72 2	NA	NA	NA	NA	NA	NA	6	12	NA
53	1558 NA	12 NA	1595 2	NA	NA	NA	NA	NA	NA	7	11	NA
81	338 NA	36 NA	337 3	44	336	NA	NA	NA	NA	12	19	20
8	176 NA	3 NA	184 2	NA	NA	NA	NA	NA	NA	12	21	NA
29	93 NA	44 NA	97 2	NA	NA	NA	NA	NA	NA	15	22	NA
44	784 NA	65 NA	796 2	NA	NA	NA	NA	NA	NA	17	23	NA
19	28 NA	8 NA	32 2	NA	NA	NA	NA	NA	NA	18	24	NA

```
4	39	16	40	NA	NA	NA	NA	NA	NA	18	25	NA
	NA	NA	2

20	636	15	643	NA	NA	NA	NA	NA	NA	21	26	NA
	NA	NA	2

23	65	9	67	NA	NA	NA	NA	NA	NA	24	25	NA
	NA	NA	2


END



 INITS

#chain 1

list(sd.sq=1,  mu=c(-2,0,2,0,0,   0,3,0,1,0,   0,2,1,1, 3,   2,-2,0,2,0,   0,0,3,0,1,   0,0,2,1,1,   3, 2,1,0,4,  1,
2,0,2,0,  1,2),

d = structure(.Data = c(

	NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

	NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

	NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

	NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

	NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

	NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

	NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

	NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

	NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

	NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

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	NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,

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	NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,
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NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0  ),
.Dim = c(25,26))   )


# chain 2
list(sd.sq=1.5,  mu=c(0,0,-2,0,3,   0,0,2,0,0,  0,2,0,2,1,   4,0,0,-2,0,   3,0,0,2,0,   0,0,2,0,2,  1,4,2,0,-3,
1,2,1,0, 2,    2,0),
d = structure(.Data = c(
        NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
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NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA, NA,NA,5),

.Dim = c(25,26)))

chain 3

list(sd.sq=3, mu=c(0,0,3,0,0, 0,0,0,3,3, 0,0,4,2,1,1,0,0,3,0,0, 0,0,0,3,3, 0,0,4,2,1,1, 1, 2,4, 0,-1,2,1,1,
0,-1),

d = structure(.Data = c(

NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

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NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,
NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3
),

.Dim = c(25,26)))

M.1.6.3 WinBUGS code for number of patients with PE

```
#Random effects model for multi-arm trials (any number of arms)

model{

for(i in 1:NS){

  w[i,1] <-0

  delta[i,t[i,1]]<-0

  mu[i] ~ dnorm(0,.0001) # vague priors for trial baselines

  for (k in 1:na[i]){

    r[i,k] ~ dbin(p[i,t[i,k]],n[i,k]) # binomial likelihood

    logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]  # model

#Deviance residuals for data i

  rhat[i,k] <- p[i,t[i,k]] * n[i,k]                                    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))

   }

  sdev[i]<- sum(dev[i,1:na[i]])

  for (k in 2:na[i]){

# trial-specific LOR distributions

    delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])

    md[i,t[i,k]] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions

    taud[i,t[i,k]] <- tau *2*(k-1)/k     #precision of LOR distributions
```

```
#adjustment, multi-arm RCTs
   w[i,k] <- (delta[i,t[i,k]]  - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
   sw[i,k] <-sum(w[i,1:k-1])/(k-1)
  }
 }
d[1]<-0
for (k in 2:NT){d[k] ~ dnorm(0,.0001) } # vague priors for basic parameters
#sd ~ dunif(0,5)        # vague prior for random effects standard deviation
#tau <- 1/pow(sd,2)
sd.sq ~ dlnorm(m.tau,prec.tau)  # empirical prior for between-trial Var
prec.tau <- pow(sd.tau,-2)
tau <- pow(sd.sq,-1)   # between-trial precision = (1/between-trial variance)
sd <- sqrt(sd.sq)

#A ~ dnorm(meanA, precA)  # A is on log-odds scale
#precA <- pow(sdA,-2)     # turn st dev into precision

v[3] ~ dbeta(a, b)    # distribution for prob event on LMWH (std/std)+AES
b <- N-a
N <- 85642
a <- 583
for (k in 1:2){       # treatments below 3
  logit(v[k]) <- logit(v[3]) - lor[k,3]       # note change in sign
  rr[k] <- v[k]/v[1]     # calculate relative risk
 }

for (k in 4:NT){    # treatments above 3
  logit(v[k]) <- logit(v[3]) + lor[3,k]
  rr[k] <- v[k]/v[1]     # calculate relative risk
 }
```

```
rr[3] <- v[3]/v[1]
sumdev <- sum(sdev[])    # Calculate residual deviance
# Ranking and prob{treatment k is best}
for (k in 1:NT){
  rk[k] <- rank(rr[],k)
  best[k] <- equals(rank(rr[],k),1)
 }
# pairwise ORs and RRs
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]
    lrr[c,k] <- log(rr[k]) - log(rr[c])
    log(rrisk[c,k]) <- lrr[c,k]
   }
 }
}

# NT=no. treatments, NS=no. studies;
# NB : set up M vectors each r[,]. n[,] and t[,],  where M is the Maximum number of treatments
#         per trial in the dataset. In this dataset M is 4.

list(NT=23, NS=30,
# meanA and sdA are the  posterior mean and sd of log-odds of event
#meanA=-1.673, sdA=0.2529,
#Empirical prior Table IV (Turner et al) intervention: Non-Pharma v Pharma;
# outcome type: general physical health indicators
m.tau= -1.26, sd.tau=1.25  )

  r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1]  t[,2]  t[,3]     t[,4]     t[,5]    na[]
 5 14 3 32 2 32 NA NA NA NA 1 2 3 NA NA 3
 2.5 117 0.5 118 NA NA NA NA NA NA 1 2 NA NA NA 2
```

1.5 55 0.5 59 NA NA NA NA NA NA 1 2 NA NA NA 2

1 158 1 152 NA NA NA NA NA NA 1 4 NA NA NA 2

2 196 2 194 NA NA NA NA NA NA 2 4 NA NA NA 2

1.5 204 4.5 210 0.5 196 NA NA NA NA 2 5 8 NA NA 3

0.5 85 1.5 84 NA NA NA NA NA NA 2 5 NA NA NA 2

1 67 2 69 NA NA NA NA NA NA 2 5 NA NA NA 2

0.5 121 1.5 107 NA NA NA NA NA NA 2 5 NA NA NA 2

4 869 1 864 NA NA NA NA NA NA 2 6 NA NA NA 2

1.5 212 0.5 225 NA NA NA NA NA NA 2 7 NA NA NA 2

2 992 1 1001 NA NA NA NA NA NA 2 9 NA NA NA 2

3 897 5 880 NA NA NA NA NA NA 2 9 NA NA NA 2

0.5 139 1.5 137 NA NA NA NA NA NA 2 10 NA NA NA 2

5 2699 3 2708 NA NA NA NA NA NA 2 11 NA NA NA 2

1.5 81 0.5 87 0.5 82 NA NA NA NA 3 12 13 NA NA 3

1 78 2 78 NA NA NA NA NA NA 3 12 NA NA NA 2

3 1123 3 1129 NA NA NA NA NA NA 3 14 NA NA NA 2

3.5 107 0.5 112 NA NA NA NA NA NA 3 15 NA NA NA 2

2 134 1 125 NA NA NA NA NA NA 5 8 NA NA NA 2

1 332 1 333 NA NA NA NA NA NA 5 8 NA NA NA 2

0.5 26 1.5 20 NA NA NA NA NA NA 5 16 NA NA NA 2

4 1595 1 1558 NA NA NA NA NA NA 6 7 NA NA NA 2

3.5 399 0.5 381 NA NA NA NA NA NA 7 17 NA NA NA 2

6 1516 9 1495 NA NA NA NA NA NA 8 18 NA NA NA 2

1 32 3 35 NA NA NA NA NA NA 12 19 NA NA NA 2

0.5 94 1.5 98 NA NA NA NA NA NA 13 20 NA NA NA 2

5.5 1127 0.5 1129 NA NA NA NA NA NA 14 21 NA NA NA 2

1.5 177 0.5 185 NA NA NA NA NA NA 18 22 NA NA NA 2

4.5 637 0.5 644 NA NA NA NA NA NA 22 23 NA NA NA 2

END

```
list(
d=c(NA,0,0,0,0,   0,0,0,0,0,  0,0,0,0,0,   0,0,0,0,0,  0,0, 0), # one for each treatment,
sd.sq=1,
mu=c(0,0,0,0,0,   0,0,0,0,0,   0,0,0,0,0,   0, 0,0,0,0,   0,0,0,0,0,    0,0,0,0,0) )

list(
d=c(NA,0,0,0,0,   0,0,0,0,1,  0,0,0,0,-1,   0,0,0,0,1,  0,-1, 0), # one for each treatment,
sd.sq=0.1,
mu=c(-1,-1,-1,-1,-1,   -1,-1,-1,-1,-1,   -1,-1,-1,-1,-1,   -1, -1,-1,-1,-1,   -1,-1,-1,-1,-1,   -1,-1,-1,-1,-1) )

list(
d=c(NA,0,0,0,2,   -2,0,0,0,1,  0,0,0,0,-1,   2,0,0,0,1,  -2,-1, -1), # one for each treatment,
sd.sq=2,
mu=c(0,1,-1,0,2,   0,1,-1,-2,0,   1,2,0,2,0,   0, 2,1,0,-2,  0,2,1,-2,0,  2,1,1,0,0) )
```

M.1.6.4 WinBUGS code for inconsistency model for number of patients with PE

```
VTE - inconsistency model - Elective hip PE
==============================
30 studies
23 treatments
==============================
# Binomial likelihood, logit link, inconsistency model
# Random effects model
model{                  # *** PROGRAM STARTS
for(i in 1:ns){          # LOOP THROUGH STUDIES
   delta[i,1]<-0         # treatment effect is zero in control arm
   mu[i] ~ dnorm(0,.0001)  # vague priors for trial baselines
   for (k in 1:na[i])  {   # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
```

```
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
        +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
    }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {  # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
    }
 }
totresdev <- sum(resdev[])   # Total Residual Deviance
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
   for (k in (c+1):nt)  { d[c,k] ~ dnorm(0,.0001) }
 }
#sd ~ dunif(0,5)  # vague prior for between-trial standard deviation
#var <- pow(sd,2) # between-trial variance
#tau <- 1/var     # between-trial precision
sd.sq ~ dlnorm(m.tau,prec.tau)  # empirical prior for between-trial Var
prec.tau <- pow(sd.tau,-2)
tau <- pow(sd.sq,-1)   # between-trial precision = (1/between-trial variance)
sd <- sqrt(sd.sq)

} # *** PROGRAM ENDS


 Data
# DVT
# nt=no. treatments, ns=no. studies
list(nt=23,ns=30, m.tau= -1.26, sd.tau=1.25)


  r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1]  t[,2]  t[,3]     t[,4]     t[,5]    na[]
 5 14 3 32 2 32 NA NA NA NA 1 2 3 NA NA 3
```

2.5 117 0.5 118 NA NA NA NA NA NA 1 2 NA NA NA 2

1.5 55 0.5 59 NA NA NA NA NA NA 1 2 NA NA NA 2

1 158 1 152 NA NA NA NA NA NA 1 4 NA NA NA 2

2 196 2 194 NA NA NA NA NA NA 2 4 NA NA NA 2

1.5 204 4.5 210 0.5 196 NA NA NA NA 2 5 8 NA NA 3

0.5 85 1.5 84 NA NA NA NA NA NA 2 5 NA NA NA 2

1 67 2 69 NA NA NA NA NA NA 2 5 NA NA NA 2

0.5 121 1.5 107 NA NA NA NA NA NA 2 5 NA NA NA 2

4 869 1 864 NA NA NA NA NA NA 2 6 NA NA NA 2

1.5 212 0.5 225 NA NA NA NA NA NA 2 7 NA NA NA 2

2 992 1 1001 NA NA NA NA NA NA 2 9 NA NA NA 2

3 897 5 880 NA NA NA NA NA NA 2 9 NA NA NA 2

0.5 139 1.5 137 NA NA NA NA NA NA 2 10 NA NA NA 2

5 2699 3 2708 NA NA NA NA NA NA 2 11 NA NA NA 2

1.5 81 0.5 87 0.5 82 NA NA NA NA 3 12 13 NA NA 3

1 78 2 78 NA NA NA NA NA NA 3 12 NA NA NA 2

3 1123 3 1129 NA NA NA NA NA NA 3 14 NA NA NA 2

3.5 107 0.5 112 NA NA NA NA NA NA 3 15 NA NA NA 2

2 134 1 125 NA NA NA NA NA NA 5 8 NA NA NA 2

1 332 1 333 NA NA NA NA NA NA 5 8 NA NA NA 2

0.5 26 1.5 20 NA NA NA NA NA NA 5 16 NA NA NA 2

4 1595 1 1558 NA NA NA NA NA NA 6 7 NA NA NA 2

3.5 399 0.5 381 NA NA NA NA NA NA 7 17 NA NA NA 2

6 1516 9 1495 NA NA NA NA NA NA 8 18 NA NA NA 2

1 32 3 35 NA NA NA NA NA NA 12 19 NA NA NA 2

0.5 94 1.5 98 NA NA NA NA NA NA 13 20 NA NA NA 2

5.5 1127 0.5 1129 NA NA NA NA NA NA 14 21 NA NA NA 2

1.5 177 0.5 185 NA NA NA NA NA NA 18 22 NA NA NA 2

4.5 637 0.5 644 NA NA NA NA NA NA 22 23 NA NA NA 2

END

INITS

```
#chain 1
list(sd.sq=1,  mu=c(0,0,3,0,0,   0,2,0,-1,0,   4,0,3,1,0,    0, 2,1,3,-2,   4,2,1,-3,0,   3,1,0,3,-2),
d = structure(.Data = c(
        NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
        NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0
),
.Dim = c(22,23))   )

# chain 2
list(sd.sq=1.5,  mu=c(0,2,1,0,-2,   0,3,0,4,0,    2,0,1,3,0,    0, 2,1,3,-2,    4,2,1,-3,0,   3,2,-1,0,0),
d = structure(.Data = c(
        NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
```

```
        NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,
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        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5
),
.Dim = c(22,23))  )

# chain 3
list(sd.sq=3,  mu=c(0,3,3,0,4,   0,1,0,-2,0,   1,2,0,2,0,   0, 2,1,3,-2,    4,2,1,-3,0,   3,1,1,0,-1),
d = structure(.Data = c(
        NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
```

```
NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
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NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,
NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,
NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,
NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,
NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,
NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,
NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,
NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,
NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3
),
.Dim = c(22,23))  )
```

M.1.6.5 WinBUGS code for number of patients with major bleeding

```
#Random effects model for multi-arm trials (any number of arms)
model{
for(i in 1:NS){
  w[i,1] <-0
  delta[i,t[i,1]]<-0
  mu[i] ~ dnorm(0,.0001) # vague priors for trial baselines
  for (k in 1:na[i]){
    r[i,k] ~ dbin(p[i,t[i,k]],n[i,k]) # binomial likelihood
    logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]  # model
#Deviance residuals for data i
  rhat[i,k] <- p[i,t[i,k]] * n[i,k]                    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
```

```
  }
 sdev[i]<- sum(dev[i,1:na[i]])
 for (k in 2:na[i]){
# trial-specific LOR distributions
   delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])
   md[i,t[i,k]] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions
   taud[i,t[i,k]] <- tau *2*(k-1)/k     #precision of LOR distributions
#adjustment, multi-arm RCTs
   w[i,k] <- (delta[i,t[i,k]]  - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
   sw[i,k] <-sum(w[i,1:k-1])/(k-1)
  }
 }
d[1]<-0
for (k in 2:NT){d[k] ~ dnorm(0,.0001) } # vague priors for basic parameters
#sd ~ dunif(0,5)        # vague prior for random effects standard deviation
#tau <- 1/pow(sd,2)
sd.sq ~ dlnorm(m.tau,prec.tau)  # empirical prior for between-trial Var
prec.tau <- pow(sd.tau,-2)
tau <- pow(sd.sq,-1)   # between-trial precision = (1/between-trial variance)
sd <- sqrt(sd.sq)

#A ~ dnorm(meanA, precA)  # A is on log-odds scale
#precA <- pow(sdA,-2)     # turn st dev into precision

v[4] ~ dbeta(a, b)    # distribution for prob event on LMWH (std/std)+AES
b <- N-a
N <- 85642
a <- 620
for (k in 1:3){       # treatments below 4
  logit(v[k]) <- logit(v[4]) - lor[k,4]       # note change in sign
  rr[k] <- v[k]/v[1]     # calculate relative risk
```

```
 }

for (k in 5:NT){    # treatments above 4
  logit(v[k]) <- logit(v[4]) + lor[4,k]
  rr[k] <- v[k]/v[1]     # calculate relative risk
 }

rr[4] <- v[4]/v[1]
sumdev <- sum(sdev[])    # Calculate residual deviance
# Ranking and prob{treatment k is best}
for (k in 1:NT){
  rk[k] <- rank(rr[],k)
  best[k] <- equals(rank(rr[],k),1)
 }
# pairwise ORs and RRs
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]
    lrr[c,k] <- log(rr[k]) - log(rr[c])
    log(rrisk[c,k]) <- lrr[c,k]
   }
 }
}

# NT=no. treatments, NS=no. studies;
# NB : set up M vectors each r[,]. n[,] and t[,],  where M is the Maximum number of treatments
#         per trial in the dataset. In this dataset M is 3.

list(NT=15, NS=24,
# meanA and sdA are the  posterior mean and sd of log-odds of event
#meanA=-1.673, sdA=0.2529,
```

#Empirical prior Table IV (Turner et al) intervention: Non-Pharma v Pharma;

outcome type: adverse events

m.tau= -0.84, sd.tau=1.24)

r[,1]	n[,1]	r[,2]	n[,2]	r[,3]	n[,3]	r[,4]	n[,4]	r[,5]	n[,5]	t[,1]	t[,2]	t[,3]
	t[,4]	t[,5]	na[]									
3.5	36	0.5	33	NA	NA	NA	NA	NA	NA	1	2	NA
	NA	NA	2									
1	50	2	50	NA	NA	NA	NA	NA	NA	1	3	NA
	NA	NA	2									
0.5	102	2.5	103	1.5	101	NA	NA	NA	NA	1	4	6
	NA	NA	3									
0.5	199	11.5	195	NA	NA	NA	NA	NA	NA	1	4	NA
	NA	NA	2									
1	75	1	78	NA	NA	NA	NA	NA	NA	1	4	NA
	NA	NA	2									
0.5	83	2.5	82	NA	NA	NA	NA	NA	NA	1	5	NA
	NA	NA	2									
19	332	11	333	NA	NA	NA	NA	NA	NA	2	3	NA
	NA	NA	2									
13	209	8	195	3	203	NA	NA	NA	NA	2	3	4
	NA	NA	3									
5	69	1	67	NA	NA	NA	NA	NA	NA	2	4	NA
	NA	NA	2									
0.5	107	2.5	121	NA	NA	NA	NA	NA	NA	2	4	NA
	NA	NA	2									
11	1129	20	1128	NA	NA	NA	NA	NA	NA	3	5	NA
	NA	NA	2									
6	1516	4	1495	NA	NA	NA	NA	NA	NA	3	7	NA
	NA	NA	2									
32	1133	47	1140	NA	NA	NA	NA	NA	NA	4	5	NA
	NA	NA	2									
6	271	4	279	NA	NA	NA	NA	NA	NA	4	7	NA
	NA	NA	2									
9	1003	14	1010	NA	NA	NA	NA	NA	NA	4	8	NA
	NA	NA	2									
18	1154	23	1146	NA	NA	NA	NA	NA	NA	4	8	NA
	NA	NA	2									

18	2659 NA	22 NA	2673 2	NA	NA	NA	NA	NA	NA	4	9	NA
19	1257 NA	23 NA	1252 2	NA	NA	NA	NA	NA	NA	4	10	NA
1.5	142 NA	0.5 NA	141 2	NA	NA	NA	NA	NA	NA	4	11	NA
32	487 NA	22 NA	489 3	44	496	NA	NA	NA	NA	6	7	12
0.5	177 NA	1.5 NA	185 2	NA	NA	NA	NA	NA	NA	7	13	NA
40	2266 NA	33 NA	2275 2	NA	NA	NA	NA	NA	NA	10	11	NA
1.5	401 NA	0.5 NA	386 2	NA	NA	NA	NA	NA	NA	11	14	NA
37	636 NA	10 NA	643 2	NA	NA	NA	NA	NA	NA	13	15	NA

END

INITS

list(

d=c(NA,0,0,0,0, 0,0,0,1,2, 3,4,1,0,0), # one for each treatment

sd.sq=1,

mu=c(-2,0,2,0,0, 0,3,0,1,0, 0,2,1, 1, 3, 2,0, 0,1,2, 1,2,1,1))

list(

d=c(NA,0,0,4,0, 0,3,0,0,3, 4,4,2,1,2), # one for each treatment

sd.sq=0.1,

mu=c(0,0,-2,0,3, 0,0,2,0,0, 0,2,0,2,1, 4,3,0,3,4, 1,0,-1,0))

list(

d=c(NA,0,1,1,0, 0,0,0,1,2, 3,4,1,2,1), # one for each treatment

sd.sq=2,

mu=c(0,0,3,0,0, 0,0,0,3,3, 0,0,4,2,1, 1,-1,0,2,3, 2,-3,0,2))

M.1.6.6 WinBUGS code for inconsistency model for number of patients with major bleeding

```
VTE - inconsistency model - Elective hip - major bleeding
==============================
24 studies
15 treatments
==============================
# Binomial likelihood, logit link, inconsistency model
# Random effects model
model{                  # *** PROGRAM STARTS
for(i in 1:ns){          # LOOP THROUGH STUDIES
   delta[i,1]<-0         # treatment effect is zero in control arm
   mu[i] ~ dnorm(0,.0001)  # vague priors for trial baselines
   for (k in 1:na[i])  {   # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
        +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
    }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {  # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
    }
 }
totresdev <- sum(resdev[])   # Total Residual Deviance
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
   for (k in (c+1):nt)  { d[c,k] ~ dnorm(0,.0001) }
 }
#sd ~ dunif(0,5)  # vague prior for between-trial standard deviation
```

```
#var <- pow(sd,2) # between-trial variance

#tau <- 1/var     # between-trial precision

sd.sq ~ dlnorm(m.tau,prec.tau)  # empirical prior for between-trial Var

prec.tau <- pow(sd.tau,-2)

tau <- pow(sd.sq,-1)   # between-trial precision = (1/between-trial variance)

sd <- sqrt(sd.sq)


} # *** PROGRAM ENDS


 Data

# DVT

# nt=no. treatments, ns=no. studies

list(nt=15,ns=24, m.tau= -0.84, sd.tau=1.24)


 r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1]  t[,2]  t[,3]     t[,4]     t[,5]    na[]

3.5     36      0.5     33      NA      NA      NA      NA      NA      NA      1       2       NA
        NA      NA      2

1       50      2       50      NA      NA      NA      NA      NA      NA      1       3       NA
        NA      NA      2

0.5     102     2.5     103     1.5     101     NA      NA      NA      NA      1       4       6
        NA      NA      3

0.5     199     11.5    195     NA      NA      NA      NA      NA      NA      1       4       NA
        NA      NA      2

1       75      1       78      NA      NA      NA      NA      NA      NA      1       4       NA
        NA      NA      2

0.5     83      2.5     82      NA      NA      NA      NA      NA      NA      1       5       NA
        NA      NA      2

19      332     11      333     NA      NA      NA      NA      NA      NA      2       3       NA
        NA      NA      2

13      209     8       195     3       203     NA      NA      NA      NA      2       3       4
        NA      NA      3

5       69      1       67      NA      NA      NA      NA      NA      NA      2       4       NA
        NA      NA      2

0.5     107     2.5     121     NA      NA      NA      NA      NA      NA      2       4       NA
        NA      NA      2
```

11	1129 NA	20 NA	1128 2	NA	NA	NA	NA	NA	NA	3	5	NA
6	1516 NA	4 NA	1495 2	NA	NA	NA	NA	NA	NA	3	7	NA
32	1133 NA	47 NA	1140 2	NA	NA	NA	NA	NA	NA	4	5	NA
6	271 NA	4 NA	279 2	NA	NA	NA	NA	NA	NA	4	7	NA
9	1003 NA	14 NA	1010 2	NA	NA	NA	NA	NA	NA	4	8	NA
18	1154 NA	23 NA	1146 2	NA	NA	NA	NA	NA	NA	4	8	NA
18	2659 NA	22 NA	2673 2	NA	NA	NA	NA	NA	NA	4	9	NA
19	1257 NA	23 NA	1252 2	NA	NA	NA	NA	NA	NA	4	10	NA
1.5	142 NA	0.5 NA	141 2	NA	NA	NA	NA	NA	NA	4	11	NA
32	487 NA	22 NA	489 3	44	496	NA	NA	NA	NA	6	7	12
0.5	177 NA	1.5 NA	185 2	NA	NA	NA	NA	NA	NA	7	13	NA
40	2266 NA	33 NA	2275 2	NA	NA	NA	NA	NA	NA	10	11	NA
1.5	401 NA	0.5 NA	386 2	NA	NA	NA	NA	NA	NA	11	14	NA
37	636 NA	10 NA	643 2	NA	NA	NA	NA	NA	NA	13	15	NA

END

INITS

#chain 1

list(sd.sq=1, mu=c(-2,0,2,0,0, 0,3,0,1,0, 0,2,1,1,3, 2,-2,1,1,0, 0,0,0,0),

d = structure(.Data = c(

NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,

```
        NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0),
.Dim = c(14,15))   )

# chain 2
list(sd.sq=1.5,  mu=c(0,0,-2,0,3,  0,0,2,0,0,   0,2,0,2,1,  4,0,2,-1,1,    0,1,0,0),
d = structure(.Data = c(
        NA,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5 ),
.Dim = c(14,15))  )
```

```
# chain 3

list(sd.sq=3,  mu=c(0,0,3,0,0,  0,0,0,3,3,  0,0,4,2,1,  1,0,3,0,0,    2,1,0,0),

d = structure(.Data = c(

        NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

        NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

        NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

        NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

        NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,

        NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,

        NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,

        NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,

        NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,

        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,

        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,

        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,

        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,

        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3),

.Dim = c(14,15))  )
```

M.2 Network meta-analysis for elective knee replacement surgery

M.2.1 Introduction

The results of conventional meta-analyses of direct evidence alone (as presented in the GRADE profiles for Chapter 27 and forest plots in appendix L) does not help inform which intervention is most effective as VTE prophylaxis in patients undergoing elective knee replacement surgery. The challenge of interpretation has arisen for two reasons:

- In isolation, each pair-wise comparison does not inform the choice among the different treatments; in addition direct evidence is not available for some pair-wise comparisons in a randomised controlled trial.
- There are frequently multiple overlapping comparisons that could potentially give inconsistent estimates of effect.

To overcome these problems, a hierarchical Bayesian network meta-analysis (NMA) was performed. This type of analysis allows for the synthesis of data from direct and indirect comparisons without

breaking randomisation and allows for the ranking of different interventions. In this case the outcomes were defined as:

- Deep vein thrombosis (DVT; symptomatic and asymptomatic)
- Pulmonary embolism (PE)
- Major bleeding

The analysis also provided estimates of effect (with 95% credible intervals) for each intervention compared to one another and compared to a single baseline risk (in this case the baseline treatment was no prophylaxis or in the case of the major bleeding outcome a combination of no prophylaxis and mechanical prophylaxis). These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on the best available evidence.

Conventional fixed effects meta-analysis assumes that the relative effect of one treatment compared to another is the same across an entire set of trials. In a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials.

Network meta-analysis requires an additional assumption over conventional meta-analysis. The additional assumption is that intervention A has the same effect on people in trials of intervention A compared to intervention B as it does for people in trials of intervention A versus intervention C, and so on. Thus, in a random effects network meta-analysis, the assumption is that intervention A has the same effect distribution across trials of A versus B, A versus C and so on.

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.

M.2.2 Methods

M.2.2.1 Study selection

To estimate the relative risks, we performed an NMA that simultaneously used all the relevant RCT evidence from the clinical evidence review. As with conventional meta-analyses, this type of analysis does not break the randomisation of the evidence, nor does it make any assumptions about adding the effects of different interventions. The effectiveness of a particular treatment strategy combination will be derived only from randomised controlled trials that had that particular combination in a trial arm.

M.2.2.2 Outcome measures

The NMA evidence reviews for interventions considered three clinical efficacy outcomes identified from the clinical evidence review; number of people with DVT, number of people with PE and number of people with major bleeding. Other outcomes were not considered for the NMA as they were infrequently reported across the studies. The committee considered that these outcomes were the most critical clinical outcomes for testing effectiveness of VTE prophylaxis.

M.2.2.3 Comparability of interventions

The interventions compared in the model were those found in the randomised controlled trials and included in the clinical evidence review already presented in Chapter 27 of the full guideline and in appendix H. If an intervention was evaluated in a study that met the inclusion criteria for the network (that is if it reported at least one of the outcomes of interest and matched the inclusion criteria for the meta-analysis) then it was included in the network meta-analysis, otherwise it was excluded.

The treatments included in each network are shown in Table 247.

Table 247: Treatments included in the network meta-analysis

Network 1: Number of people with DVT	Network 2: Number of people with PE	Network 3: Number of people with major bleeding
No prophylaxis	No prophylaxis	No prophylaxis/mechanical
LMWH (standard dose; standard duration)	LMWH (standard dose; standard duration)	LMWH (standard dose; standard duration)
LMWH (high dose; standard duration)	AES	LMWH (high dose; standard duration)
AES (length unspecified)	IPCD	Fondaparinux
Dabigatran	Dabigatran	LMWH (low dose; standard duration)
IPCD (length unspecified)	Rivaroxaban	Apixaban
Foot pump	Apixaban	Dabigatran
Foot pump + AES	LMWH (standard dose; extended duration)	Rivaroxaban
Rivaroxaban	LMWH (standard dose; standard duration) + AES	LMWH (standard dose; extended duration)
Aspirin	LMWH (low dose; standard duration) + AES	UFH
LMWH (standard duration; extended duration)	LMWH (high dose; standard duration)	VKA
Apixaban	VKA	-
VKA	UFH	-
UFH	-	-
Fondaparinux + AES	-	-
LMWH (standard dose; standard duration) + AES	-	-
LMWH (low dose; standard duration) + AES	-	-
LMWH high dose; standard duration) + AES	-	-
UFH + AES	-	-

M.2.2.4 Baseline risks

The baseline risk is defined as the risk of achieving the outcome of interest in the baseline treatment arm of the included trials. This figure is useful because it allows us to convert the results of the NMA from odds ratios to relative risks. However, the majority of these trials were older studies that reported very high risk of DVT and PE in the no prophylaxis arm that the orthopaedic subgroup considered to be not reflective of the baseline risk in the UK. Hence, for the purpose of calculating the relative risks of these events for presentation in this appendix, the baseline risk values were obtained from data from the UK National Joint Registry (NJR).[450] For full details of the calculation of baseline risk, please refer to HE write-up (appendix P, section P.1.3.3).

M.2.2.5 Statistical analysis

A hierarchical Bayesian network meta-analysis (NMA) was performed using the software WinBUGS. We adapted a three-arm random effects model template for the networks, from the University of Bristol website (https://www.bris.ac.uk/cobm/research/mpes/mtc.html). This model accounts for the correlation between study level effects induced by multi-arm trials.

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 outcome subgroup, a diagram of the evidence network is presented in section M.2.3.

The model used was a random effects logistic regression model, with parameters estimated by Markov chain Monte Carlo simulation. As it was a Bayesian analysis, for each parameter the evidence distribution is weighted by a distribution of prior beliefs. Due to the sparse nature of the networks (few studies per direct treatment comparison), the between-study heterogeneity parameter is imprecisely estimated in a random effects model. Therefore it is beneficial to apply informative priors in order to restrict the prior distribution for heterogeneity to avoid unreasonably wide credible intervals. Turner et al (2015)[946] derived a novel set of predictive distributions for the degree of heterogeneity across 80 different settings. Appropriate predictive distributions for heterogeneity were chosen from Turner et al (2015)[946] and used directly as informative priors. The log normal (μ, σ^2) predictive distributions obtained for the between-study heterogeneity in a future meta-analysis presented in Table IV[946] were selected according to the outcome and treatment comparison. For the DVT and PE NMAs the distributions defined by the outcome of "general physical health indicators" and by the intervention/comparison type "non-pharmacological vs. pharmacological" were chosen (LN[-1.26, 1.25^2]). For the major bleeding NMA the distributions defined by the outcome of "adverse events" and by the intervention/comparison type "non-pharmacological vs. pharmacological" were chosen (LN[-0.84, 1.24^2]). These distributions were chosen as they represented outcomes measured by an assessor, whose method of measurement as well as judgement may influence the outcome (as studies provided slightly variable ways of defining these critical outcomes), and the interaction aspect encompassed both the pharmacological and mechanical prophylaxis options covered in our review protocol.

For the analyses, a series of 60,000 burn-in simulations were run to allow convergence and then a further 60,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots.

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.

The results, in terms of relative risk, of pair-wise meta-analyses are presented in the clinical evidence review (Chapter 27, and appendix H).

The aim of the NMA was to calculate treatment specific log odds ratios and relative risks for response to be consistent with the comparative effectiveness results presented elsewhere in the clinical evidence review and for ease of interpretation. Let BO, $\tilde{\theta}$, $\widetilde{\mathrm{OR}}$ and p denote the baseline odds, treatment specific odds, treatment specific log odds ratio and treatment specific absolute probability respectively. Then:

$$\tilde{\boldsymbol{\theta}} = \boldsymbol{Ln}\left(\widetilde{\boldsymbol{OR}}\right) + \boldsymbol{Ln}(\boldsymbol{BO})$$

And:

$$\boldsymbol{p} = \frac{\boldsymbol{e}^{\tilde{\boldsymbol{\theta}}}}{\mathbf{1} + \boldsymbol{e}^{\tilde{\boldsymbol{\theta}}}}$$

Once the treatment specific probabilities for response are calculated, we divide them by the baseline probability (p_b) to get treatment specific relative risks (rr_b):

$$p_b = \frac{e^{BO}}{1 + e^{BO}}$$

$$rr_b = \frac{p}{p_b}$$

This approach has the advantage that baseline and relative effects are both modelled on the same log odds scale, and also ensures that the uncertainty in the estimation of both baseline and relative effects is accounted for in the model.

We also calculated the overall ranking of interventions according to their relative risk compared to control group. Due to the skewness of the data, the NMA relative risks and rank results are reported as medians rather than means (as in the direct comparisons) to give a more accurate representation of the 'most likely' value. The median rank for each intervention was derived from the resulting distribution and these are presented on a rank plot with the associated 95% credible intervals.

A key assumption behind NMA is that the network is consistent. In other words, it is assumed that the direct and indirect treatment effect estimates do not disagree with one another. Discrepancies between direct and indirect estimates of effect may result from several possible causes. First, there is chance and if this is the case then the network meta-analysis results are likely to be more precise as they pool together more data than conventional meta-analysis estimates alone. Second, there could be differences between the trials included in terms of their clinical or methodological characteristics.

This heterogeneity is a problem for network meta-analysis but may be dealt with by subgroup analysis, meta-regression or by carefully defining inclusion criteria. Inconsistency, caused by heterogeneity, was assessed subjectively by comparing the relative risks from the direct evidence (from pair-wise meta-analysis) to the relative risks from the combined direct and indirect evidence (from NMA). We further tested for inconsistency by developing inconsistency models for networks of binary outcomes using the TSD 4 template from the University of Bristol website (https://www.bris.ac.uk/cobm/research/mpes/mtc.html). We compared the posterior mean of the residual deviance between the consistency and inconsistency models to see which was a better fit to the data (closest to the number of trial arms in each network) and checked the difference in deviance information criterion (DIC) values between the two models was small (less than 3-5) or if it was larger, that the smaller DIC and hence better fitting model was the consistency model. No inconsistency was identified.

M.2.3 Results

M.2.3.1 Deep vein thrombosis (symptomatic and asymptomatic)

Included studies

26 studies were identified as reporting on DVT (symptomatic and asymptomatic) outcomes. After excluding papers that reported zero events in each arm and papers reporting on combinations that did not connect to any other intervention in the network, 23 studies involving 19 treatments were included in the network for DVT. The network can be seen in **Figure 833** and the trial data for each of the studies included in the NMA are presented in **Table 248**.

Figure 833: Network diagram for DVT

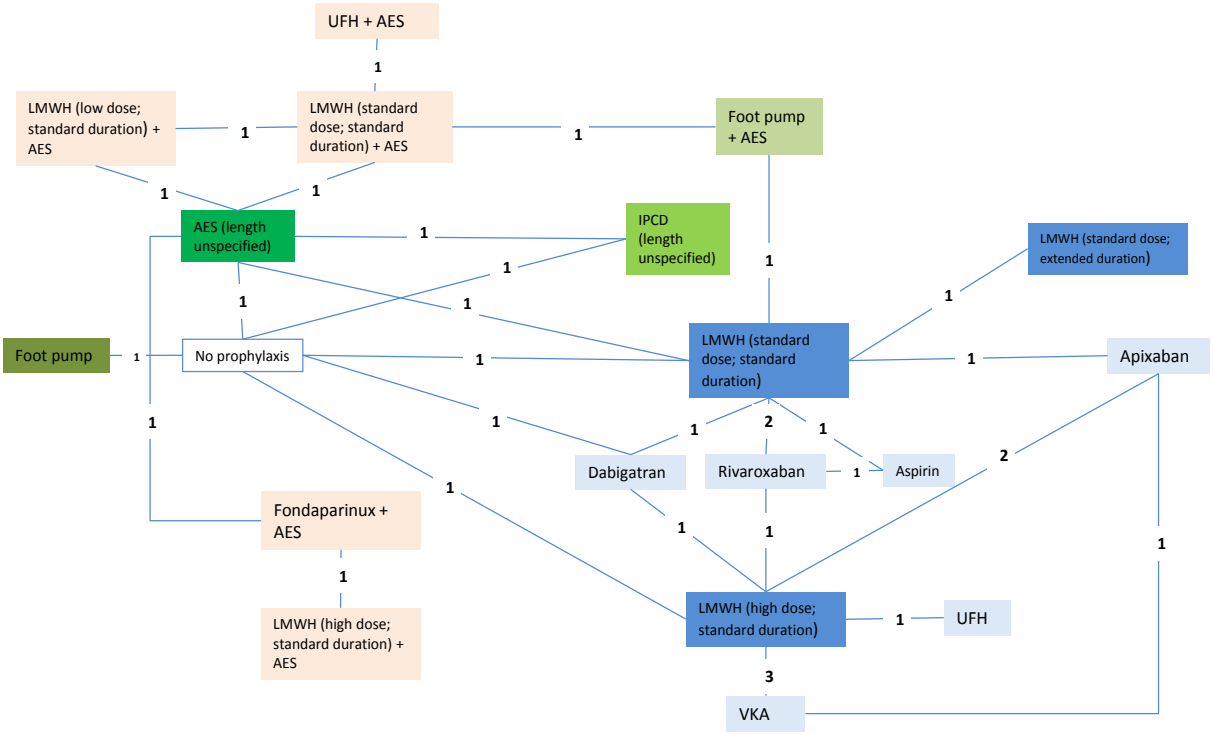


Table 248: Study data for DVT network meta-analysis

Study	Comparison	Intervention 1	Intervention 2	Intervention 3	Comparison		Intervention 1		Intervention 2		Intervention 3	
					N	NA	N	NA	N	NA		
Chin 2009 [177]	No prophylaxis	LMWH (standard dose; standard duration)	AES (length unspecified)	IPCD (length unspecified)	24	110	6	110	14	110	9	110
Leclerc 1992 [543]	No prophylaxis	LMWH (high dose; standard duration)	-	-	37	64	11	65	-	-	-	-
Wilson 1992 [1014]	No prophylaxis	Foot pump	-	-	19	32	5	28	-	-	-	-
Fuji 2010[320]	No prophylaxis	Dabigatran	-	-	57	101	23	96	-	-	-	-
Blanchard 1999A [106]	LMWH (standard dose; standard duration)	IPCD (length unspecified)	-	-	16	67	34	63	-	-	-	-
Norgren 1998 [700]	LMWH (standard dose; standard duration)	Foot pump + AES	-	-	0	14	4	15	-	-	-	-
Zou 2014 [1052]	LMWH (standard dose; standard duration)	Rivaroxaban	Aspirin	-	14	112	3	102	18	110	-	-
Lassen 2008 [525]	LMWH (standard dose; standard	Rivaroxaban	-	-	160	878	79	824	-	-	-	-

Study	Comparison	Intervention 1	Intervention 2	Intervention 3	Comparison		Intervention 1		Intervention 2		Intervention 3	
	duration)											
Eriksson 2007 [293]	LMWH (standard dose; standard duration)	Dabigatran	-	-	192	685	182	675	-	-	-	-
Comp 2001 [208]	LMWH (standard dose; standard duration)	LMWH (standard duration; extended duration)	-	-	37	144	33	155	-	-	-	-
Lassen 2010 [535]	LMWH (standard dose; standard duration)	Apixaban	-	-	243	997	142	971	-	-	-	-
Turpie 2009 [956]	LMWH (high dose; standard duration)	Rivaroxaban	-	-	86	959	61	965	-	-	-	-
Ginsberg 2009 [792]	LMWH (high dose; standard duration)	Dabigatran	-	-	158	643	181	604	-	-	-	-
Lassen 2007[532]	LMWH (high dose; standard duration)	Apixaban	VKA	-	15	109	21	208	29	109	-	-
Lassen 2009 [536]	LMWH (high dose; standard duration)	Apixaban	-	-	92	1122	89	1142	-	-	-	-
Fitzgerald	LMWH (high	VKA	-	-	44	173	79	176	-	-	-	-

Study	Comparison	Intervention 1	Intervention 2	Intervention 3	Comparison		Intervention 1		Intervention 2		Intervention 3	
2001 [308]	dose; standard duration)											
Leclerc 1996 [544]	LMWH (high dose; standard duration)	VKA	-	-	76	206	109	211	-	-	-	-
Colwell 1995D [205]	LMWH (high dose; standard duration)	UFH	-	-	56	145	77	143	-	-	-	-
Cho 2013 [178]	AES (length unspecified)	Fondaparinux + AES	-	-	19	74	5	74	-	-	-	-
Fuji 2008A [328]	AES (length unspecified)	LMWH (standard dose; standard duration) + AES	LMWH low dose; standard duration) + AES	-	48	79	34	78	26	74	-	-
Warwick 2002 [995]	Foot pump + AES	LMWH (standard dose; standard duration) + AES	-	-	57	99	48	89	-	-	-	-
Bauer 2001 [78]	Fondaparinux + AES	LMWH (high dose; standard duration) + AES	-	-	45	361	98	361	-	-	-	-
Fauno 1994 [301]	LMWH (standard dose; standard duration) + AES	UFH + AES	-	-	21	91	25	93	-	-	-	-

N; number of events, NA; number analysed

NMA results - DVT

Table 249summarises the results of the conventional meta-analyses in terms of risk ratios generated from studies directly comparing different interventions, together with the results of the NMA in terms of risk ratios for every possible treatment comparison.

Table 249: Risk ratios for DVT (symptomatic and asymptomatic)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
Versus no prophylaxis	LMWH (standard dose; standard duration)	0.25 (0.11, 0.59)	0.26 (0.15, 0.43)
	LMWH (high dose; standard duration)	0.29 (0.16, 0.52)	0.18 (0.10, 0.30)
	AES (length unspecified)	0.58 (0.32, 1.07)	0.88 (0.55, 1.56)
	Dabigatran	0.42 (0.29, 0.63)	0.25 (0.14, 0.42)
	IPCD (length unspecified)	0.38 (0.18, 0.77)	0.61 (0.32, 1.04)
	Foot pump	0.30 (0.13, 0.70)	0.20 (0.05, 0.63)
	Foot pump + AES	-	0.55 (0.25, 1.48)
	Rivaroxaban	-	0.12 (0.06, 0.22)
	Aspirin	-	0.41 (0.16, 0.94)
	LMWH (standard dose; extended duration)	-	0.21 (0.08, 0.49)
	Apixaban	-	0.15 (0.07, 0.26)
	VKA	-	0.35 (0.17, 0.65)
	UFH	-	0.31 (0.13, 0.69)
	Fondaparinux + AES	-	0.35 (0.16, 0.67)
	LMWH (standard dose; standard duration) + AES	-	0.42 (0.24, 1.00)
	LMWH (low dose; standard duration) + AES	-	0.56 (0.26, 1.32)
	LMWH high dose; standard duration) + AES	-	0.77 (0.31, 1.57)
	UFH + AES	-	0.50 (0.19, 1.50)
Versus LMWH (standard dose; standard duration)	LMWH (high dose; standard duration)	-	0.69 (0.44, 1.05)
	AES (length unspecified)	2.33 (0.93, 5.85)*	3.45 (1.83, 7.10)
	Dabigatran	1.29 (1.09, 1.53)*	0.97 (0.64, 1.52)
	IPCD (length unspecified)	2.05 (1.32, 3.17)*	2.33 (1.31, 4.19)
	Foot pump	-	0.77 (0.18, 2.70)
	Foot pump + AES	8.44 (0.50, 143.77)*	2.15 (0.81, 6.66)
	Rivaroxaban	0.50 (0.39, 0.64)*	0.46 (0.28, 0.70)
	Aspirin	1.31 (0.69, 2.50)*	1.59 (0.71, 3.32)
	LMWH (standard dose; extended duration)	0.83 (0.55, 1.25)	0.80 (0.38, 1.63)
	Apixaban	0.60 (0.50, 0.72)*	0.57 (0.35, 0.88)
	VKA	-	1.33 (0.71, 2.43)
	UFH	-	1.21 (0.54, 2.59)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	Fondaparinux + AES	-	1.35 (0.68, 2.59)
	LMWH (standard dose; standard duration) + AES	-	1.67 (0.70, 4.69)
	LMWH (low dose; standard duration) + AES	-	2.17 (0.87, 5.97)
	LMWH high dose; standard duration) + AES	-	2.94 (1.25, 6.49)
	UFH + AES	-	1.97 (0.62, 6.92)
Versus LMWH (high dose; standard duration)	AES (length unspecified)	-	5.04 (2.52, 10.94)
	Dabigatran	1.22 (1.02, 1.46)*	1.41 (0.93, 2.26)
	IPCD (length unspecified)	-	3.40 (1.74, 6.70)
	Foot pump	-	1.13 (0.26, 3.98)
	Foot pump + AES	-	3.13 (1.10, 10.34)
	Rivaroxaban	0.70 (0.51, 0.97)*	0.67 (0.39, 1.06)
	Aspirin	-	2.31 (0.96, 5.32)
	LMWH (standard dose; extended duration)	-	1.16 (0.49, 2.69)
	Apixaban	0.99 (0.77, 1.28)*	0.82 (0.53, 1.25)
	VKA	1.58 (1.33, 1.87)*	1.94 (1.23, 3.06)
	UFH	1.39 (1.08, 1.80)*	1.76 (0.89, 3.38)
	Fondaparinux + AES	-	1.97 (1.02, 3.71)
	LMWH (standard dose; standard duration) + AES	-	2.43 (0.96, 7.27)
	LMWH (low dose; standard duration) + AES	-	3.17 (1.21, 9.19)
	LMWH high dose; standard duration) + AES	-	4.27 (1.86, 9.50)
	UFH + AES	-	2.88 (0.86, 10.61)
Versus AES (length unspecified)	Dabigatran	-	0.28 (0.13, 0.56)
	IPCD (length unspecified)	0.64 (0.29, 1.42)	0.68 (0.32, 1.23)
	Foot pump	-	0.22 (0.05, 0.82)
	Foot pump + AES	-	0.62 (0.29, 1.46)
	Rivaroxaban	-	0.13 (0.05, 0.28)
	Aspirin	-	0.46 (0.16, 1.12)
	LMWH (standard dose; extended duration)	-	0.23 (0.08, 0.59)
	Apixaban	-	0.16 (0.07, 0.34)
	VKA	-	0.39 (0.16, 0.82)
	UFH	-	0.35 (0.12, 0.84)
	Fondaparinux + AES	0.26 (0.11, 0.67)	0.39 (0.17, 0.76)
	LMWH (standard dose; standard duration) + AES	0.58 (0.40, 0.83)	0.48 (0.29, 0.93)
	LMWH (low dose; standard duration) + AES	0.72 (0.53, 0.98)	0.63 (0.32, 1.21)
	LMWH high dose; standard duration) + AES	-	0.87 (0.34, 1.70)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	UFH + AES	-	0.57 (0.23, 1.47)
Versus Dabigatran	IPCD (length unspecified)	-	2.39 (1.22, 4.66)
	Foot pump	-	0.79 (0.18, 2.76)
	Foot pump + AES	-	2.20 (0.79, 7.17)
	Rivaroxaban	-	0.47 (0.25, 0.79)
	Aspirin	-	1.63 (0.66, 3.73)
	LMWH (standard dose; extended duration)	-	0.82 (0.34, 1.86)
	Apixaban	-	0.58 (0.33, 0.97)
	VKA	-	1.37 (0.72, 2.51)
	UFH	-	1.24 (0.54, 2.65)
	Fondaparinux + AES	-	1.39 (0.66, 2.76)
	LMWH (standard dose; standard duration) + AES	-	1.71 (0.68, 5.04)
	LMWH (low dose; standard duration) + AES	-	2.23 (0.85, 6.41)
	LMWH high dose; standard duration) + AES	-	3.01 (1.23, 6.91)
	UFH + AES	-	2.02 (0.61, 7.35)
Versus IPCD (length unspecified)	Foot pump	-	0.33 (0.07, 1.21)
	Foot pump + AES	-	0.91 (0.36, 2.87)
	Rivaroxaban	-	0.20 (0.09, 0.40)
	Aspirin	-	0.68 (0.25, 1.68)
	LMWH (standard dose; extended duration)	-	0.34 (0.13, 0.85)
	Apixaban	-	0.24 (0.12, 0.48)
	VKA	-	0.57 (0.26, 1.24)
	UFH	-	0.52 (0.20, 1.28)
	Fondaparinux + AES	-	0.58 (0.26, 1.26)
	LMWH (standard dose; standard duration) + AES	-	0.70 (0.33, 1.99)
	LMWH (low dose; standard duration) + AES	-	0.93 (0.39, 2.55)
	LMWH high dose; standard duration) + AES	-	1.26 (0.49, 3.00)
	UFH + AES	-	0.84 (0.28, 2.90)
Versus foot pump	Foot pump + AES	-	2.80 (0.62, 17.30)
	Rivaroxaban	-	0.59 (0.16, 2.65)
	Aspirin	-	2.06 (0.46, 10.59)
	LMWH (standard dose; extended duration)	-	1.04 (0.24, 5.28)
	Apixaban	-	0.73 (0.20, 3.27)
	VKA	-	1.73 (0.45, 8.09)
	UFH	-	1.57 (0.37, 7.75)
	Fondaparinux + AES	-	1.75 (0.45, 8.29)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	LMWH (standard dose; standard duration) + AES	-	2.18 (0.52, 12.54)
	LMWH (low dose; standard duration) + AES	-	2.83 (0.66, 16.01)
	LMWH high dose; standard duration) + AES	-	3.81 (0.90, 19.29)
	UFH + AES	-	2.57 (0.51, 17.00)
Versus foot pump + AES	Rivaroxaban	-	0.21 (0.06, 0.63)
	Aspirin	-	0.74 (0.19, 2.29)
	LMWH (standard dose; extended duration)	-	0.37 (0.09, 1.24)
	Apixaban	-	0.26 (0.08, 0.76)
	VKA	-	0.62 (0.18, 1.77)
	UFH	-	0.56 (0.14, 1.76)
	Fondaparinux + AES	-	0.63 (0.19, 1.75)
	LMWH (standard dose; standard duration) + AES	0.94 (0.73, 1.21)	0.77 (0.42, 1.48)
	LMWH (low dose; standard duration) + AES	-	1.01 (0.39, 2.44)
	LMWH high dose; standard duration) + AES	-	1.39 (0.38, 3.64)
	UFH + AES	-	0.92 (0.34, 2.33)
Versus Rivaroxaban	Aspirin	-	3.47 (1.53, 7.98)
	LMWH (standard dose; extended duration)	-	1.74 (0.74, 4.22)
	Apixaban	-	1.24 (0.71, 2.25)
	VKA	-	2.91 (1.54, 5.91)
	UFH	-	2.64 (1.18, 6.17)
	Fondaparinux + AES	-	2.96 (1.40, 6.43)
	LMWH (standard dose; standard duration) + AES	-	3.67 (1.34, 11.97)
	LMWH (low dose; standard duration) + AES	-	4.78 (1.72, 15.07)
	LMWH high dose; standard duration) + AES	-	6.43 (2.61, 16.07)
	UFH + AES	-	4.35 (1.24, 17.22)
Versus Aspirin	LMWH (standard dose; extended duration)	-	0.50 (0.17, 1.47)
	Apixaban	-	0.36 (0.15, 0.86)
	VKA	-	0.84 (0.33, 2.22)
	UFH	-	0.76 (0.26, 2.25)
	Fondaparinux + AES	-	0.85 (0.32, 2.34)
	LMWH (standard dose; standard duration) + AES	-	1.04 (0.37, 3.85)
	LMWH (low dose; standard duration) + AES	-	1.37 (0.45, 4.90)

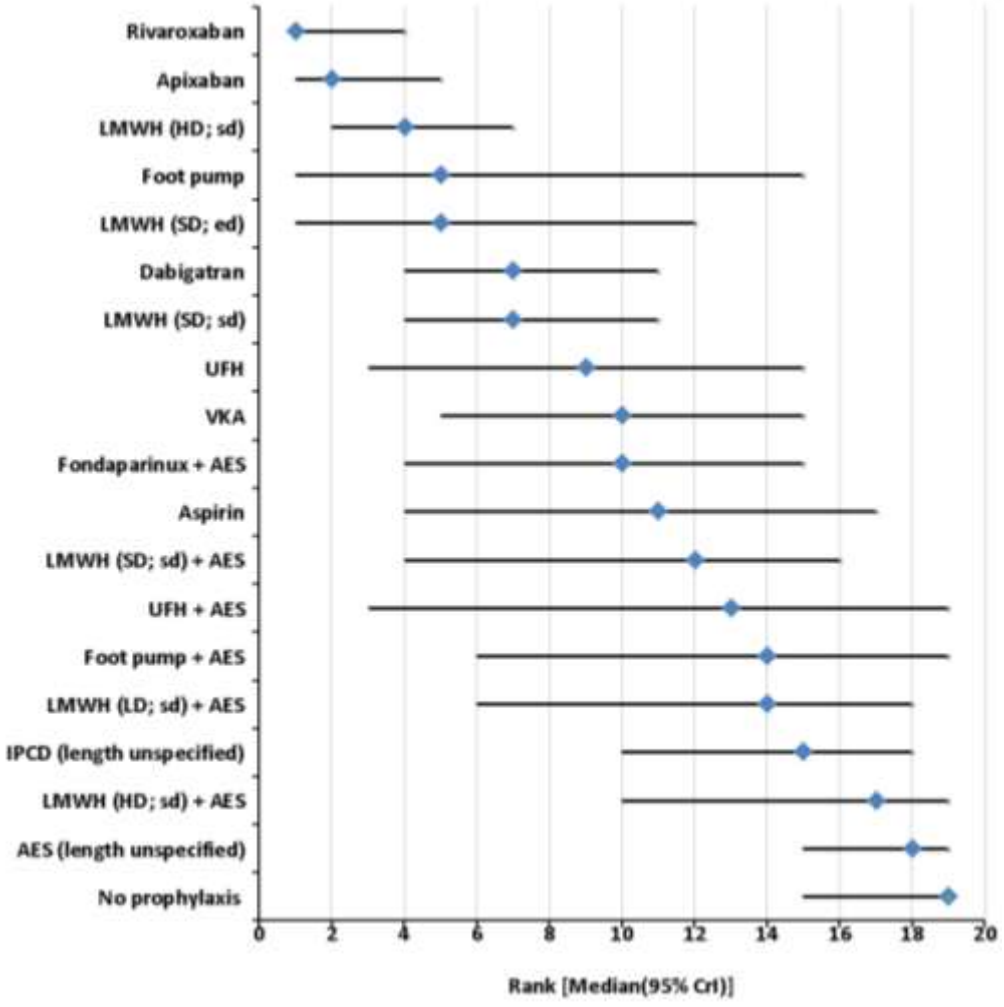
	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	LMWH high dose; standard duration) + AES	-	1.85 (0.62, 5.60)
	UFH + AES	-	1.24 (0.34, 5.42)
Versus LMWH (standard dose; extended duration)	Apixaban	-	0.71 (0.30, 1.69)
	VKA	-	1.67 (0.65, 4.43)
	UFH	-	1.52 (0.52, 4.47)
	Fondaparinux + AES	-	1.70 (0.63, 4.61)
	LMWH (standard dose; standard duration) + AES	-	2.09 (0.68, 7.77)
	LMWH (low dose; standard duration) + AES	-	2.73 (0.86, 9.91)
	LMWH high dose; standard duration) + AES	-	3.69 (1.22, 11.11)
	UFH + AES	-	2.49 (0.64, 10.94)
Versus Apixaban	VKA	-	2.35 (1.29, 4.42)
	UFH	-	2.14 (0.97, 4.67)
	Fondaparinux + AES	-	2.39 (1.25, 4.54)
	LMWH (standard dose; standard duration) + AES	-	2.96 (1.13, 9.12)
	LMWH (low dose; standard duration) + AES	-	3.85 (1.43, 11.47)
	LMWH high dose; standard duration) + AES	-	5.19 (2.26, 11.67)
	UFH + AES	-	3.49 (1.02, 13.17)
Versus VKA	UFH	-	0.91 (0.40, 1.99)
	Fondaparinux + AES	-	1.01 (0.47, 2.18)
	LMWH (standard dose; standard duration) + AES	-	1.24 (0.49, 3.95)
	LMWH (low dose; standard duration) + AES	-	1.62 (0.60, 5.06)
	LMWH high dose; standard duration) + AES	-	2.20 (0.88, 5.40)
	UFH + AES	-	1.47 (0.44, 5.73)
Versus UFH	Fondaparinux + AES	-	1.12 (0.45, 2.81)
	LMWH (standard dose; standard duration) + AES	-	1.37 (0.48, 4.98)
	LMWH (low dose; standard duration) + AES	-	1.80 (0.60, 6.29)
	LMWH high dose; standard duration) + AES	-	2.42 (0.87, 6.89)
	UFH + AES	-	1.62 (0.45, 7.00)
Versus Fondaparinux + AES	LMWH (standard dose; standard duration) + AES	-	1.23 (0.51, 3.73)
	LMWH (low dose; standard duration) + AES	-	1.61 (0.63, 4.71)
	LMWH high dose; standard duration) + AES	2.18 (1.58, 3.00)	2.17 (1.26, 3.79)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	UFH + AES	-	1.46 (0.45, 5.43)
Versus LMWH (standard dose; standard duration) + AES	LMWH (low dose; standard duration) + AES	1.24 (0.83, 1.85)	1.31 (0.61, 2.48)
	LMWH high dose; standard duration) + AES	-	1.81 (0.55, 3.92)
	UFH + AES	-	1.19 (0.54, 2.35)
Versus LMWH (low dose; standard duration) + AES	LMWH high dose; standard duration) + AES	-	1.37 (0.43, 3.45)
	UFH + AES	-	0.91 (0.33, 2.51)
Versus LMWH (high dose; standard duration) + AES	UFH + AES	-	0.66 (0.22, 2.60)

** Intervention and comparison have been switched in Review Manager*

Figure 834 shows the rank of each intervention compared to the others. The rank is based on the relative risk compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 19 different interventions being evaluated.

Figure 834: Rank order for interventions based on the relative risk of experiencing DVT



LD = low dose; SD = standard dose; HD = high dose; sd = standard duration; ed = extended duration

Goodness of fit and inconsistency

Both fixed effects and random effects models were fitted to the data. The random effects model had a DIC of 352 compared with 350 for the fixed effects model. The random effects model used for the NMA is a good fit, with a residual deviance of 51 reported. This corresponds well to the total number of trial arms, 51. The DIC statistics were as follows in Table 250. The between trial standard deviation in the random effects analysis was 0.24 (95% CI 0.09 to 0.56). On evaluating inconsistency by comparing risk ratios, three inconsistencies were identified. Firstly, the NMA estimated risk ratio for VKA compared to LMWH at a high dose and standard duration (1.94 [1.23, 3.06]) lay outside of the confidence interval of the risk ratio estimated for the direct comparison (1.58 [1.33, 1.87]). Secondly, the NMA estimated risk ratio for dabigatran versus no prophylaxis (0.25 [0.14, 0.42]) lay outside of the confidence interval of the risk ration estimated for the direct comparison (0.42 [0.29, 0.63]). Lastly, the NMA estimated risk ratio for dabigatran compared to LMWH at a standard dose and standard duration (0.97 [0.64, 1.52]) lay outside of the confidence interval of the risk ratio estimated for the direct comparison (1.29 [1.09, 1.53]) An inconsistency model was run and the DIC statistics were as follows in Table 250. The difference in the DIC is small (<3-5) with the consistency model having the lower DIC value. This suggests that it fits the data better than the inconsistency model.

Table 250: Posterior mean of the residual deviance (resdev) and DIC for the RE network meta-analysis and inconsistency models – DVT

	DIC	ResDev
Consistency model	352.435	51
Inconsistency model	357.161	51

M.2.3.2 Pulmonary embolism

Included studies

19 studies were identified as reporting on major bleeding outcomes. After excluding papers that reported zero events in each arm and papers reporting on combinations that did not connect to any other intervention in the network, 12 studies involving 13 treatments were included in the network for PE. The network can be seen in **Figure 835**and the trial data for each of the studies included in the NMA are presented in **Table 251**.

Figure 835: Network diagram for PE

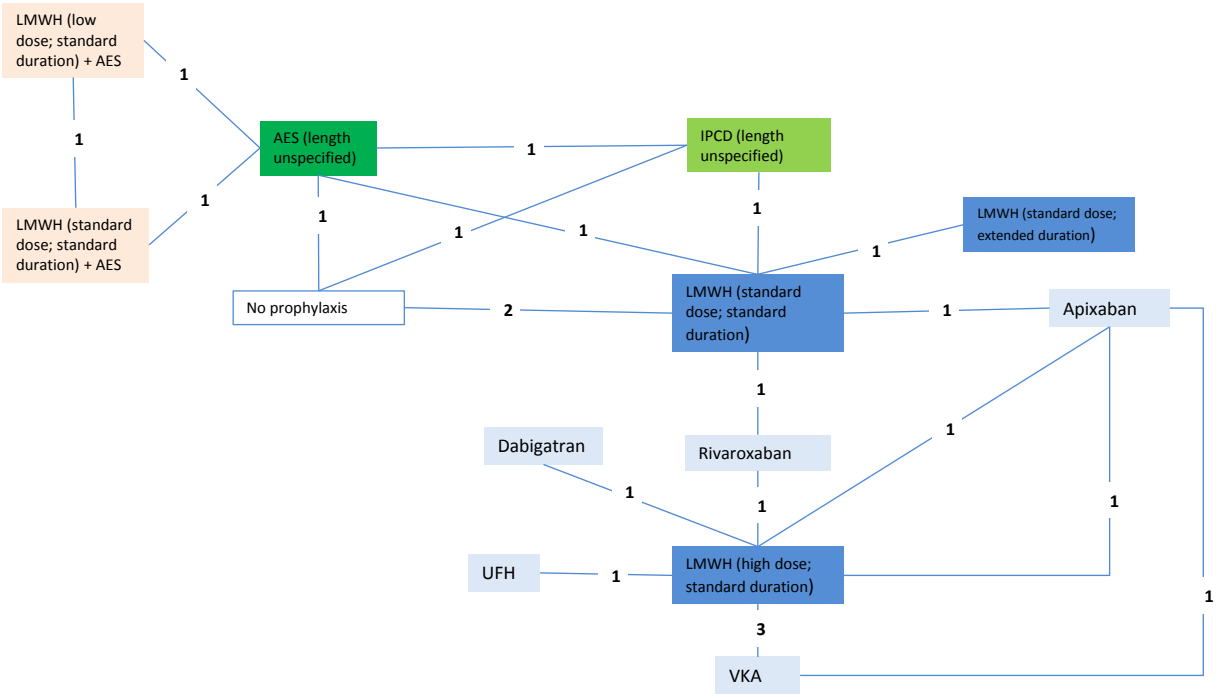


Table 251: Study data for PE network meta-analysis

Study	Comparison	Intervention 1	Intervention 2	Intervention 3	Comparison		Intervention 1		Intervention 2		Intervention 3	
					N	NA	N	NA	N	NA	N	NA
Chin 2009 [177]	No prophylaxis	LMWH (standard dose; standard duration)	AES (length unspecified)	IPCD (length unspecified)	1	110	0	110	1	110	0	110
Lassen 2008 [525]	LMWH (standard dose; standard duration)	Rivaroxaban	-	-	4	1217	0	1201	-	-	-	-
Lassen 2010 [535]	LMWH (standard dose; standard duration)	Apixaban	-	-	1	1449	3	1458	-	-	-	-
Comp 2001 [208]	LMWH (standard dose; standard duration)	LMWH (standard dose; extended duration)	-	-	2	222	0	218	-	-	-	-
Fuji 2008A [328]	AES	LMWH (standard dose; standard duration) + AES	LMWH (low dose; standard duration) + AES	-	1	79	1	74	1	78	-	-
Ginsberg 2009 [792]	Dabigatran	LMWH (high dose; standard duration)	-	-	6	604	5	643	-	-	-	-
Turpie 2009 [956]	Rivaroxaban	LMWH (high dose; standard duration)	-	-	4	1526	8	1508	-	-	-	-
Lassen 2009 [536]	Apixaban	LMWH (high dose; standard duration)	-	-	15	1599	10	1596	-	-	-	-
Lassen 2007[532]	Apixaban	LMWH (high dose; standard duration)	VKA	-	0	208	2	109	0	109	-	-
Fitzgerald 2001 [308]	LMWH (high dose; standard duration)	VKA	-	-	0	173	1	176	-	-	-	-
Leclerc 1996 [543]	LMWH (high dose; standard duration)	VKA	-	-	1	206	3	211	-	-	-	-
Colwell 1995D [205]	LMWH (high dose; standard duration)	UFH	-	-	0	145	2	143	-	-	-	-

N; number of events, NA; number analysed

NMA results - PE

Table 252 summarises the results of the conventional meta-analyses in terms of risk ratios generated from studies directly comparing different interventions, together with the results of the NMA in terms of risk ratios for every possible treatment comparison.

Table 252: Risk ratios for PE

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
Versus no prophylaxis	LMWH (standard dose; standard duration)	0.33 (0.01, 8.09)	0.20 (0.00, 8.57)
	AES (length unspecified)	1.00 (0.06, 15.79)	0.98 (0.04, 24.95)
	IPCD (length unspecified)	0.33 (0.01, 8.09)	0.20 (0.00, 8.53)
	Dabigatran	-	0.47 (0.00, 56.97)
	Rivaroxaban	-	0.08 (0.00, 6.65)
	Apixaban	-	0.52 (0.00, 36.43)
	LMWH (standard duration; extended duration)	-	0.02 (0.00, 3.86)
	LMWH (standard dose; standard duration) + AES	-	1.00 (0.01, 199.30)
	LMWH (low dose; standard duration) + AES	-	0.97 (0.01, 167.70)
	LMWH (high dose; standard duration)	-	0.37 (0.00, 30.66)
	VKA	-	0.63 (0.00, 64.93)
	UFH	-	1.79 (0.00, 625.00)
Versus LMWH (standard dose; standard duration)	AES (length unspecified)	3.00 (0.12, 72.85)*	5.00 (0.12, 3120.00)
	IPCD (length unspecified)	-	0.98 (0.00, 791.60)
	Dabigatran	-	2.45 (0.11, 52.27)
	Rivaroxaban	0.11 (0.01, 2.03)*	0.45 (0.04, 3.62)
	Apixaban	6.00 (0.72, 49.81)*	2.59 (0.32, 21.68)
	LMWH (standard duration; extended duration)	0.20 (0.01, 4.22)	0.11 (0.00, 3.33)
	LMWH (standard dose; standard duration) + AES	-	6.04 (0.02, 9283.00)
	LMWH (low dose; standard duration) + AES	-	5.68 (0.02, 8979.00)
	LMWH (high dose; standard duration)	-	1.90 (0.20, 18.92)
	VKA	-	3.23 (0.20, 52,24)
	UFH	-	9.06 (0.12, 1640.00)
Versus AES (length unspecified)	IPCD (length unspecified)	0.33 (0.01, 8.09)	0.20 (0.00, 8.36)
	Dabigatran	-	0.48 (0.00, 48.08)
	Rivaroxaban	-	0.08 (0.00, 6.65)
	Apixaban	-	0.52 (0.00, 32.84)
	LMWH (standard duration; extended duration)	-	0.01 (0.00, 3.86)
	LMWH (standard dose; standard duration) + AES	1.07 (0.07, 16.76)	1.04 (0.02, 61.02)

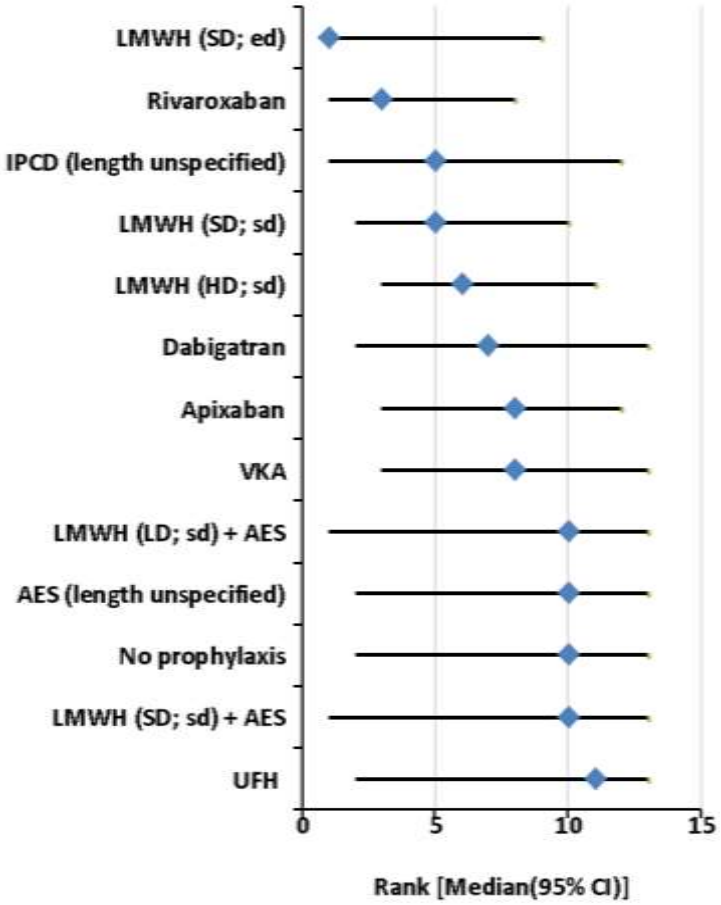
	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	LMWH (low dose; standard duration) + AES	1.01 (0.06, 15.91)	1.00 (0.02, 54.60)
	LMWH (high dose; standard duration)	-	0.37 (0.00, 27.68)
	VKA	-	0.64 (0.00, 52.48)
	UFH	-	1.95 (0.00, 372.20)
Versus IPCD (length unspecified)	Dabigatran	-	2.51 (0.00, 3274.00)
	Rivaroxaban	-	0.45 (0.00, 447.00)
	Apixaban	-	2.68 (0.00, 2584.00)
	LMWH (standard duration; extended duration)	-	0.08 (0.00, 189.20)
	LMWH (standard dose; standard duration) + AES	-	5.96 (0.02, 9804.00)
	LMWH (low dose; standard duration) + AES	-	5.55 (0.02, 8305.00)
	LMWH (high dose; standard duration)	-	1.96 (0.00, 2030.00)
	VKA	-	3.31 (0.00, 3828.00)
	UFH	-	10.55 (0.00, 26060.00)
Versus Dabigatran	Rivaroxaban	-	0.18 (0.01, 2.80)
	Apixaban	-	1.07 (0.08, 14.05)
	LMWH (standard duration; extended duration)	-	0.04 (0.00, 4.37)
	LMWH (standard dose; standard duration) + AES	-	2.40 (0.01, 7128.00)
	LMWH (low dose; standard duration) + AES	-	2.28 (0.00, 6754.00)
	LMWH (high dose; standard duration)	0.78 (0.24, 2.55)	0.79 (0.10, 6.71)
	VKA	-	1.31 (0.09, 21.28)
	UFH	-	3.52 (0.05, 769.80)
Versus Rivaroxaban	Apixaban	-	5.92 (0.73, 64.04)
	LMWH (standard duration; extended duration)	-	0.23 (0.00, 16.74)
	LMWH (standard dose; standard duration) + AES	-	14.28 (0.03, 35160.00)
	LMWH (low dose; standard duration) + AES	-	13.27 (0.03, 32390.00)
	LMWH (high dose; standard duration)	2.02 (0.61, 6.71)	4.23 (0.73, 37.87)
	VKA	-	7.32 (0.65, 116.30)
	UFH	-	20.27 (0.35, 4323.00)
Versus Apixaban	LMWH (standard duration; extended duration)	-	0.04 (0.00, 2.29)
	LMWH (standard dose; standard duration) + AES	-	2.21 (0.01, 4884.00)
	LMWH (low dose; standard duration) + AES	-	2.11 (0.01, 4578.00)
	LMWH (high dose; standard duration)	0.44 (0.18, 1.06)	0.72 (0.17, 3.46)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	VKA	-	1.22 (0.15, 10.54)
	UFH	-	3.25 (0.06, 574.10)
Versus LMWH (standard dose; extended duration)	LMWH (standard dose; standard duration) + AES	-	79.99 (0.07, 785700.00)
	LMWH (low dose; standard duration) + AES	-	74.78 (0.06, 724000.00)
	LMWH (high dose; standard duration)	-	19.13 (0.30, 21100.00)
	VKA	-	33.28 (0.38, 43380.00)
	UFH	-	111.30 (0.35, 330100.00)
Versus LMWH (standard dose; standard duration) + AES	LMWH (low dose; standard duration) + AES	0.95 (0.06, 14.89)	0.95 (0.01, 47.24)
	LMWH (high dose; standard duration)	-	0.32 (0.00, 99.27)
	VKA	-	0.56 (0.00, 140.60)
	UFH	-	1.97 (0.00, 218.00)
Versus LMWH (low dose; standard duration) + AES	LMWH (high dose; standard duration)	-	0.34 (0.00, 135.20)
	VKA	-	0.59 (0.00, 249.50)
	UFH	-	1.94 (0.00, 1050.00)
Versus LMWH (high dose; standard duration)	VKA	1.31 (0.30, 5.79)*	1.68 (0.29, 10.18)
	UFH	3.04 (0.12, 74.05)*	4.38 (0.12, 663.70)
Versus VKA	UFH	-	2.61 (0.04, 533. 70)

** Intervention and comparison have been switched in Review Manager*

Figure 836 shows the rank of each intervention compared to the others. The rank is based on the relative risk compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 13 different interventions being evaluated.

Figure 836: Rank order for interventions based the relative risk of experiencing PE



LD = low dose; SD = standard dose; HD = high dose; sd = standard duration; ed = extended duration

Goodness of fit and inconsistency

Both fixed effects and random effects models were fitted to the data. The random effects model had a DIC of 125 compared with 127 for the fixed effects model. The random effects model used for the NMA is a good fit, with a residual deviance of 32 reported. This corresponds well to the total number of trial arms, 28. The between trial standard deviation in the random effects analysis was 0.67 (95% CI 0.18 to 1.98). No inconsistency was identified between the direct RR and NMA results. The DIC statistics were as follows in **Table 253**.

Table 253: Posterior mean of the residual deviance (resdev) and DIC for the RE network meta-analysis and inconsistency models – PE

	DIC	ResDev
Consistency model	124.870	32
Inconsistency model	125.068	32

M.2.3.3 Major bleeding

Included studies

19 studies were identified as reporting on major bleeding outcomes. All of the studies identified, involving 11 treatments were included in the network for major bleeding. The network can be seen in **Figure 837** and the trial data for each of the studies included in the NMA are presented in **Table 254**.

Figure 837: Network diagram for major bleeding

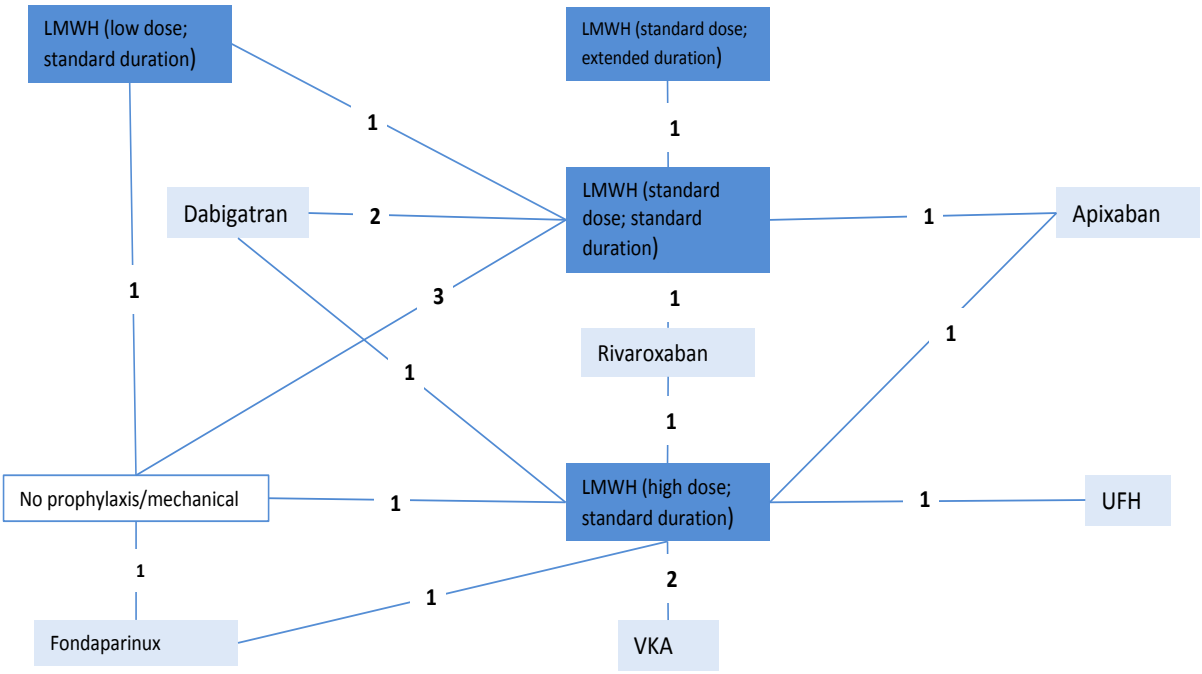


Table 254: Study data for major bleeding network meta-analysis

Study	Comparison	Intervention 1	Intervention 2	Comparison		Intervention 1		Intervention 2	
				N	NA	N	NA	N	NA
Fuji 2008A[328]	No prophylaxis/ mechanical	LMWH (standard dose; standard duration)	LMWH (low dose; standard duration)	4	89	1	91	0	89
Chin 2009 [177]	No prophylaxis/ mechanical	LMWH (standard dose; standard duration)	-	0	110	2	110	-	-
Blanchard 1999A [106]	No prophylaxis/ mechanical	LMWH (standard dose; standard duration)	-	0	63	1	67	-	-
Leclerc 1992 [543]	No prophylaxis/	LMWH (high dose;	-	1	65	0	66	-	-

Study	Comparison	Intervention 1	Intervention 2	Comparison		Intervention 1		Intervention 2	
	mechanical	standard duration)							
Fuji 2008 [325]	No prophylaxis/ mechanical	Fondaparinux	-	1	87	1	84	-	-
Fuji 2010[320]	No prophylaxis/ mechanical	Dabigatran	-	1	124	4	129	-	-
Lassen 2010 [535]	LMWH (standard dose; standard duration)	Apixaban	-	14	1508	9	1501	-	-
Eriksson 2007 [293]	LMWH (standard dose; standard duration)	Dabigatran	-	9	694	10	679	-	-
Mirdamadi 2014 [641]	LMWH (standard dose; standard duration)	Dabigatran	-	2	45	3	45	-	-
Lassen 2008 [525]	LMWH (standard dose; standard duration)	Rivaroxaban	-	17	1277	21	1254	-	-
Comp 2001 [208]	LMWH (standard dose; standard duration)	LMWH (standard dose; extended duration)	-	1	221	0	217	-	-
Bauer 2001[78]	LMWH (high dose; standard duration)	Fondaparinux	-	1	517	11	517	-	-
Lassen 2009 [536]	LMWH (high dose; standard duration)	Apixaban	-	22	1588	11	1596	-	-
Lassen 2007[532]	LMWH (high dose; standard duration)	Apixaban	VKA	0	149	4	305	0	151
Ginsberg 2009 [792]	LMWH (high dose; standard duration)	Dabigatran	-	12	868	5	857	-	-
Turpie 2009 [956]	LMWH (high dose; standard	Rivaroxaban	-	16	1564	27	1584	-	-

Study	Comparison	Intervention 1	Intervention 2	Comparison		Intervention 1		Intervention 2	
	duration)								
Colwell 1995D [205]	LMWH (high dose; standard duration)	UFH	-	3	228	3	225	-	-
Fitzgerald 2001 [308]	LMWH (high dose; standard duration)	VKA	-	9	173	4	176	-	-
Leclerc 1996 [544]	LMWH (high dose; standard duration)	VKA	-	6	336	5	334	-	-

N; number of events, NA; number analysed

NMA results- major bleeding

Table 255 summarises the results of the conventional meta-analyses in terms of odd ratios generated from studies directly comparing different interventions, together with the results of the NMA in terms of odd ratios for every possible treatment comparison. Relative risks were not calculated for this outcome as data was only available for non-surgical site bleeding (intracranial haemorrhage + gastrointestinal bleeding) from the observational study used as the source of baseline risk.[450]

Table 255: Odd ratios for major bleeding

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
Versus no mechanical prophylaxis	LMWH (standard dose; standard duration)	0.98 (0.28, 3.40)	1.09 (0.34, 3.75)
	LMWH (high dose; standard duration)	0.32 (0.01, 8.08)	1.02 (0.24, 3.97)
	Fondaparinux	1.04 (0.06, 16.84)	6.74 (0.79, 76.28)
	LMWH (low dose; standard duration)	0.11 (0.01, 2.00)	0.08 (0.00, 1.76)
	Apixaban	-	0.79 (0.18, 3.99)
	Dabigatran	-	1.08 (0.29, 4.36)
	Rivaroxaban	-	1.55 (0.32, 7.35)
	LMWH (standard dose; extended duration)	-	0.21 (0.00, 10.41)
	UFH	-	1.03 (0.07, 13.19)
	VKA		0.52 (0.08, 2.89)
Versus LMWH (standard dose; standard duration)	LMWH (high dose; standard duration)	-	0.95 (0.27, 2.63)
	Fondaparinux	-	6.18 (0.73, 66.87)
	LMWH (low dose; standard duration)	0.34 (0.01, 8.38)*	0.08 (0.00, 1.62)
	Apixaban	0.64 (0.28, 1.49)*	0.72 (0.23, 2.50)
	Dabigatran	1.21 (0.54, 2.72)*	0.99 (0.35, 2.86)

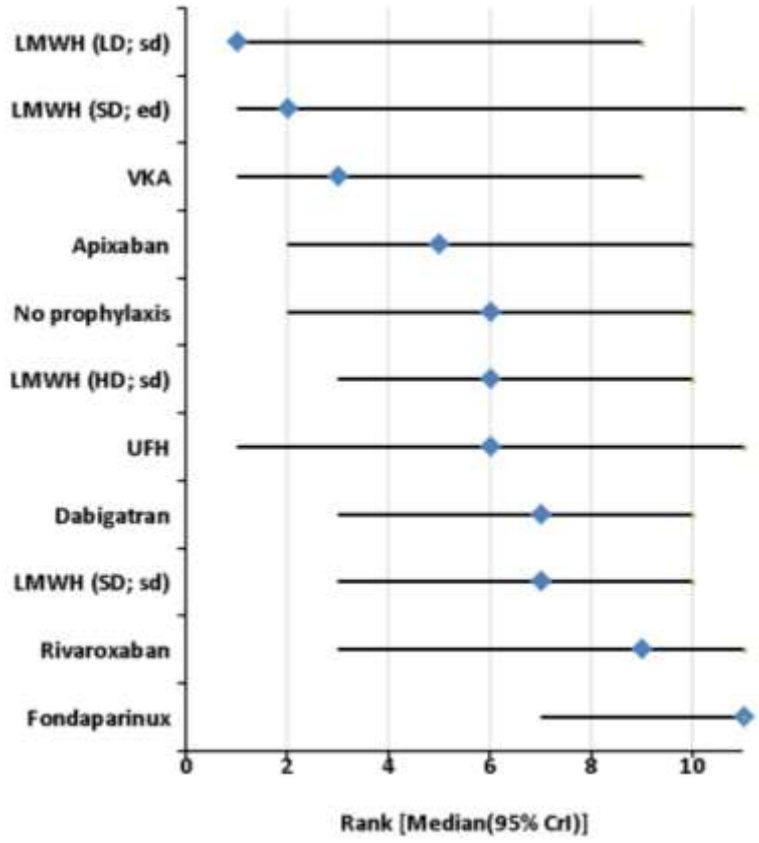
	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	Rivaroxaban	1.26 (0.66, 2.40)*	1.43 (0.41, 4.45)
	LMWH (standard dose; extended duration)	0.34 (0.01, 8.34)	0.19 (0.00, 7.62)
	UFH	-	0.95 (0.07, 10.30)
	VKA	-	0.48 (0.09, 2.05)
Versus LMWH (high dose; standard duration)	Fondaparinux	11.22 (1.44, 87.20)*	6.57 (1.07, 62.67)
	LMWH (low dose; standard duration)	-	0.08 (0.00, 2.09)
	Apixaban	0.61 (0.31, 1.19)*	0.77 (0.30, 2.70)
	Dabigatran	0.42 (0.15, 1.19)*	1.05 (0.35, 3.99)
	Rivaroxaban	1.68 (0.90, 3.13)*	1.50 (0.49, 5.32)
	LMWH (standard dose; extended duration)	-	0.20 (0.00, 10.27)
	UFH	1.01 (0.20, 5.08)*	1.01 (0.11, 8.95)
	VKA	0.61 (0.28, 1.37)*	0.51 (0.15, 1.57)
Versus Fondaparinux	LMWH (low dose; standard duration)	-	0.01 (0.00, 0.48)
	Apixaban	-	0.12 (0.01, 1.08)
	Dabigatran	-	0.16 (0.01, 1.44)
	Rivaroxaban	-	0.23 (0.02, 2.05)
	LMWH (standard dose; extended duration)	-	0.03 (0.00, 2.25)
	UFH	-	0.15 (0.01, 2.68)
	VKA	-	0.08 (0.01, 0.65)
Versus LMWH (low dose; standard duration)	Apixaban	-	9.71 (0.37, 5795.00)
	Dabigatran	-	13.03 (0.54, 7827.00)
	Rivaroxaban	-	18.67 (0.71, 11130.00)
	LMWH (standard dose; extended duration)	-	2.64 (0.00, 3297.00)
	UFH	-	13.32 (0.24, 9936.00)
	VKA		6.30 (0.20, 3743.00)
Versus Apixaban	Dabigatran	-	1.36 (0.33, 5.46)
	Rivaroxaban	-	1.98 (0.41, 7.59)
	LMWH (standard dose; extended duration)	-	0.26 (0.00, 12.79)
	UFH	-	1.31 (0.10, 13.72)
	VKA	0.22 (0.01, 4.13)*	0.66 (0.12, 2.53)
Versus Dabigatran	Rivaroxaban	-	1.45 (0.32, 5.66)
	LMWH (standard dose; extended duration)	-	0.19 (0.00, 9.01)
	UFH	-	0.96 (0.07, 10.66)
	VKA		0.48 (0.08, 2.24)
Versus Rivaroxaban	LMWH (standard dose; extended duration)	-	0.13 (0.00, 6.77)

	Intervention	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
	UFH	-	0.67 (0.05, 7.67)
	VKA		0.33 (0.06, 1.59)
Versus LMWH (standard dose; extended duration)	UFH	-	5.25 (0.05, 3299.00)
	VKA		2.51 (0.04, 1310.00)
Versus UFH	VKA		0.50 (0.04, 5.92)

** Intervention and comparison have been switched in Review Manager*

Figure 838 shows the rank of each intervention compared to the others. The rank indicates the probability of being the best treatment, second best, third best and so on among the 11 different interventions being evaluated.

Figure 838: Rank order for interventions based on the relative risk of experiencing major bleeding



SD = standard dose; HD = high dose; sd = standard duration; ed = extended duration

Goodness of fit and inconsistency

Both fixed effects and random effects models were fitted to the data. The random effects model had a DIC of 196 compared with 197 for the fixed effects model. The random effects model used for the NMA is a good fit, with a residual deviance of 41 reported. This corresponds well to the total number of trial arms, 40. The between trial standard deviation in the random effects analysis was 0.54 (95% CI 0.19 to 1.28). No inconsistency was identified between the direct RR and NMA results. The DIC statistics were as follows in **Table 256**.

Table 256: Posterior mean of the residual deviance (resdev) and DIC for the RE network meta-analysis and inconsistency models – Major bleeding

	DIC	TotResDev
Consistency model	196.222	42
Inconsistency model	199.124	42

M.2.4 Discussion

Based on the results of conventional meta-analyses of direct evidence, as has been previously presented in Chapter 26 and appendix H, deciding upon the most clinical and cost effective prophylaxis intervention in patients undergoing elective knee replacement surgery is challenging. In order to overcome the difficulty of interpreting the conclusions from numerous separate comparisons, network meta-analysis of the direct evidence was performed. The findings of the NMA were used to facilitate the committee in decision-making when developing recommendations.

Our analyses were divided into three critical outcomes. 23 studies informed the DVT network where 19 different individual or combination treatments were evaluated including three mechanical interventions, nine pharmacological interventions, and six interventions that combined both mechanical and pharmacological prophylaxis. 12 studies informed the PE network of 13 different treatments, including two mechanical interventions, seven pharmacological interventions, and two interventions that combined both mechanical and pharmacological prophylaxis. The major bleeding network included 19 studies evaluating 11 treatments, nine of which were pharmacological as for this outcome any mechanical prophylaxis measures were combined with the no prophylaxis intervention as it is believed that mechanical prophylaxis has no associated bleeding risk.

In the DVT network, the top three interventions were rivaroxaban, apixaban and LMWH at a high dose for a standard duration. The bottom three interventions were no prophylaxis, AES (length unspecified) and LMWH at a high dose for a standard duration plus AES. The highest ranked combination of mechanical and pharmacological prophylaxis was fondaparinux plus AES in tenth place. The four other combination interventions of mechanical plus pharmacological interventions ranked from 15 to 17. There was considerable uncertainty about the estimates with the credible intervals for some of the interventions being quite wide. The top three interventions spanned up to 7 rankings.

In the PE network, the top three interventions were LMWH at a standard dose for an extended duration, rivaroxaban, and IPCD (length unspecified). The bottom three interventions were UFH, LMWH at a standard dose for a standard duration plus AES andno prophylaxis. There was also considerable uncertainty in the PE network with wide credible intervals for a majority of the interventions, for example for LMWH at a low dose for a standard duration plus AES and LMWH at a standard dose for a standard duration plus AES spanning all 13 ranking positions.

In the major bleeding network the highest ranked intervention was LMWH at a low dose for a standard duration, followed LMWH at a standard dose for an extended duration then VKA. The bottom three interventions were fondaparinux, rivaroxaban and LMWH at a standard dose for a standard duration. There was a lot of uncertainty within the major bleeding network with very wide credible intervals for all of the interventions spanning almost all ranking positions.

In summary, the three outcomes chosen for analyses were considered to be among the most critical for assessing clinical effectiveness of different VTE prophylaxis strategies. All three networks seemed to fit well, as demonstrated by residual deviance and no obvious inconsistency found in the networks. However the credible intervals around the ranking of treatments in all three networks were wide suggesting considerable uncertainty about these results.

M.2.5 Conclusion

This analysis allowed us to combine findings from many different comparisons presented in the review even when direct comparative data was lacking.

The committee and orthopaedic subgroup noted the wide credible intervals particularly for the PE and major bleeding network meta-analyses. They both also noted that even with the high levels of uncertainty, interventions such as rivaroxaban and LMWH present possible clinical effectiveness in terms of the outcomes of DVT (symptomatic and asymptomatic) and PE.

For details of the rationale and discussion leading to recommendations, please refer to the section linking the evidence to the recommendations (section 27.6, chapter 27).

M.2.6 WinBUGS codes

M.2.6.1 WinBUGS code for number of patients with DVT (symptomatic and asymptomatic)

```
#Random effects model for multi-arm trials (any number of arms)

model{

for(i in 1:NS){

  w[i,1] <-0

  delta[i,t[i,1]]<-0

  mu[i] ~ dnorm(0,.0001) # vague priors for trial baselines

  for (k in 1:na[i]){

    r[i,k] ~ dbin(p[i,t[i,k]],n[i,k]) # binomial likelihood

    logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]  # model

#Deviance residuals for data i

  rhat[i,k] <- p[i,t[i,k]] * n[i,k]                                    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))

   }

  sdev[i]<- sum(dev[i,1:na[i]])

  for (k in 2:na[i]){

# trial-specific LOR distributions

    delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])

    md[i,t[i,k]] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions

    taud[i,t[i,k]] <- tau *2*(k-1)/k     #precision of LOR distributions

#adjustment, multi-arm RCTs

    w[i,k] <- (delta[i,t[i,k]]  - d[t[i,k]] + d[t[i,1]])

# cumulative adjustment for multi-arm trials
```

```
   sw[i,k] <-sum(w[i,1:k-1])/(k-1)
  }
 }
d[1]<-0
for (k in 2:NT){d[k] ~ dnorm(0,.0001) } # vague priors for basic parameters
#sd ~ dunif(0,5)        # vague prior for random effects standard deviation
#tau <- 1/pow(sd,2)
sd.sq ~ dlnorm(m.tau,prec.tau)  # empirical prior for between-trial Var
prec.tau <- pow(sd.tau,-2)
tau <- pow(sd.sq,-1)   # between-trial precision = (1/between-trial variance)
sd <- sqrt(sd.sq)

#A ~ dnorm(meanA, precA)  # A is on log-odds scale
#precA <- pow(sdA,-2)     # turn st dev into precision

v[16] ~ dbeta(a, b)    # distribution for prob event on LMWH (std/std)+AES
b <- N-a
N <- 120639
a <- 16891
for (k in 1:15){       # treatments below 16
  logit(v[k]) <- logit(v[16]) - lor[k,16]       # note change in sign
  rr[k] <- v[k]/v[1]     # calculate relative risk
 }

for (k in 17:NT){    # treatments above 16
  logit(v[k]) <- logit(v[16]) + lor[16,k]
  rr[k] <- v[k]/v[1]     # calculate relative risk
 }

rr[16] <- v[16]/v[1]
sumdev <- sum(sdev[])    # Calculate residual deviance
# Ranking and prob{treatment k is best}
```

```
for (k in 1:NT){
  rk[k] <- rank(rr[],k)
  best[k] <- equals(rank(rr[],k),1)
 }
# pairwise ORs and RRs
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]
    lrr[c,k] <- log(rr[k]) - log(rr[c])
    log(rrisk[c,k]) <- lrr[c,k]
   }
 }
}
# NT=no. treatments, NS=no. studies;
# NB : set up M vectors each r[,]. n[,] and t[,],  where M is the Maximum number of treatments
#         per trial in the dataset. In this dataset M is 3.


list(NT=19, NS=23,
# meanA and sdA are the  posterior mean and sd of log-odds of event
#meanA=-1.673, sdA=0.2529,
#Empirical prior Table IV (Turner et al) intervention: Non-Pharma v Pharma;
# outcome type: general physical health indicators
m.tau= -1.26, sd.tau=1.25 )

 r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1]  t[,2]  t[,3]     t[,4]     t[,5]    na[]
 24 110 6 110 14 110 9 110 NA NA 1 2 4 6 NA 4
 37 64 11 65 NA NA NA NA NA NA 1 3 NA NA NA 2
 57 101 23 96 NA NA NA NA NA NA 1 5 NA NA NA 2
 19 32 5 28 NA NA NA NA NA NA 1 7 NA NA NA 2
 192 685 182 675 NA NA NA NA NA NA 2 5 NA NA NA 2
```

16 67 34 63 NA NA NA NA NA NA 2 6 NA NA NA 2

0.5 15 4.5 16 NA NA NA NA NA NA 2 8 NA NA NA 2

14 112 3 102 18 110 NA NA NA NA 2 9 10 NA NA 3

160 878 79 824 NA NA NA NA NA NA 2 9 NA NA NA 2

37 144 33 155 NA NA NA NA NA NA 2 11 NA NA NA 2

243 997 142 971 NA NA NA NA NA NA 2 12 NA NA NA 2

158 643 181 604 NA NA NA NA NA NA 3 5 NA NA NA 2

86 959 61 965 NA NA NA NA NA NA 3 9 NA NA NA 2

15 109 21 208 29 109 NA NA NA NA 3 12 15 NA NA 3

92 1122 89 1142 NA NA NA NA NA NA 3 12 NA NA NA 2

44 173 79 176 NA NA NA NA NA NA 3 13 NA NA NA 2

76 206 109 211 NA NA NA NA NA NA 3 13 NA NA NA 2

56 145 77 143 NA NA NA NA NA NA 3 14 NA NA NA 2

19 74 5 74 NA NA NA NA NA NA 4 15 NA NA NA 2

48 79 25 74 34 78 NA NA NA NA 4 16 17 NA NA 3

57 99 48 89 NA NA NA NA NA NA 8 16 NA NA NA 2

45 361 98 361 NA NA NA NA NA NA 15 18 NA NA NA 2

21 91 25 93 NA NA NA NA NA NA 16 19 NA NA NA 2

END

list(
d=c(NA,0,0,0,0,0,0,0,1,2,3,4,2,3,1,0,2,1,-2), # one for each treatment
sd.sq=1,
mu=c(0,0,3,0,0, 0,2,0,-1,0, 4,0,3,1,0, 0, 2,1,3, 2,0, 1, 2))

list(
d=c(NA,1,0,2,0,3,0,0,1,2,3,4,2,3,1,0,1,3,-3), # one for each treatment
sd.sq=0.1,
mu=c(0,2,1,0,-2, 0,3,0,4,0, 2,0,1,3,0, 0, 2,1,3,1,0, 0, -1))

list(

```
d=c(NA,0,0,0,0,0,0,0,1,2,3,4,2,3,1,0,0,1,2), # one for each treatment
sd.sq=2,
mu=c(0,3,3,0,4, 0,1,0,-2,0, 1,2,0,2,0, 0, 2,1,3,-3,4, 2, 1) )
```

M.2.6.2 WinBUGS code for inconsistency model for number of patients with DVT

```
VTE - inconsistency model - Elective knee DVT
==============================
23 trials
19 treaments
==============================
# Binomial likelihood, logit link, inconsistency model
# Random effects model
model{                  # *** PROGRAM STARTS
for(i in 1:ns){          # LOOP THROUGH STUDIES
   delta[i,1]<-0         # treatment effect is zero in control arm
   mu[i] ~ dnorm(0,.0001)  # vague priors for trial baselines
   for (k in 1:na[i])  {   # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
        +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
    }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {  # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
    }
 }
totresdev <- sum(resdev[])   # Total Residual Deviance
```

```
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
   for (k in (c+1):nt)  { d[c,k] ~ dnorm(0,.0001) }
 }
#sd ~ dunif(0,5)  # vague prior for between-trial standard deviation
#var <- pow(sd,2) # between-trial variance
#tau <- 1/var     # between-trial precision
sd.sq ~ dlnorm(m.tau,prec.tau)  # empirical prior for between-trial Var
prec.tau <- pow(sd.tau,-2)
tau <- pow(sd.sq,-1)   # between-trial precision = (1/between-trial variance)
sd <- sqrt(sd.sq)

} # *** PROGRAM ENDS

 Data
# DVT
# nt=no. treatments, ns=no. studies
list(nt=19,ns=23, m.tau= -1.26, sd.tau=1.25)

 r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1]  t[,2]  t[,3]     t[,4]     t[,5]    na[]
 24 110 6 110 14 110 9 110 NA NA 1 2 4 6 NA 4
 37 64 11 65 NA NA NA NA NA NA 1 3 NA NA NA 2
 57 101 23 96 NA NA NA NA NA NA 1 5 NA NA NA 2
 19 32 5 28 NA NA NA NA NA NA 1 7 NA NA NA 2
 192 685 182 675 NA NA NA NA NA NA 2 5 NA NA NA 2
 16 67 34 63 NA NA NA NA NA NA 2 6 NA NA NA 2
 0.5 15 4.5 16 NA NA NA NA NA NA 2 8 NA NA NA 2
 14 112 3 102 18 110 NA NA NA NA 2 9 10 NA NA 3
 160 878 79 824 NA NA NA NA NA NA 2 9 NA NA NA 2
 37 144 33 155 NA NA NA NA NA NA 2 11 NA NA NA 2
 243 997 142 971 NA NA NA NA NA NA 2 12 NA NA NA 2
 158 643 181 604 NA NA NA NA NA NA 3 5 NA NA NA 2
 86 959 61 965 NA NA NA NA NA NA 3 9 NA NA NA 2
```

15 109 21 208 29 109 NA NA NA NA 3 12 15 NA NA 3

92 1122 89 1142 NA NA NA NA NA NA 3 12 NA NA NA 2

44 173 79 176 NA NA NA NA NA NA 3 13 NA NA NA 2

76 206 109 211 NA NA NA NA NA NA 3 13 NA NA NA 2

56 145 77 143 NA NA NA NA NA NA 3 14 NA NA NA 2

19 74 5 74 NA NA NA NA NA NA 4 15 NA NA NA 2

48 79 25 74 34 78 NA NA NA NA 4 16 17 NA NA 3

57 99 48 89 NA NA NA NA NA NA 8 16 NA NA NA 2

45 361 98 361 NA NA NA NA NA NA 15 18 NA NA NA 2

21 91 25 93 NA NA NA NA NA NA 16 19 NA NA NA 2

END

INITS

#chain 1

list(sd.sq=1, mu=c(2,0,3,0,2, -2,2,-2,-1,3, 2,-2,1,3,1, 1,2,-3,2,-2, -2,1,1),

d = structure(.Data = c(

NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,0,

NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,0,

NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,0,

NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,0,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,0,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,0,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,0,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,0,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,

NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,

```
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0  ),
.Dim = c(18,19))   )

# chain 2
list(sd.sq=1.5,  mu=c(2,1,3,1,2,   0,2,0,-1,3,   2,0,1,3,1,   1,2,-3,2,0,   0,0,-1),
d = structure(.Data = c(
        NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5  ),
.Dim = c(18,19))  )

# chain 3
list(sd.sq=3,  mu=c(2,0.5,3,0.5,2,   -2,2,1,-1,3,    2,1,1,3,1,    1,2,-3,2,1,    1,2,2),
d = structure(.Data = c(
        NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
```

```
        NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3  ),
.Dim = c(18,19))  )
```

M.2.6.3 WinBUGS code for number of patients with pulmonary embolism (PE)

```
#Random effects model for multi-arm trials (any number of arms)
model{
for(i in 1:NS){
  w[i,1] <-0
  delta[i,t[i,1]]<-0
  mu[i] ~ dnorm(0,.0001) # vague priors for trial baselines
  for (k in 1:na[i]){
    r[i,k] ~ dbin(p[i,t[i,k]],n[i,k]) # binomial likelihood
    logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]  # model
#Deviance residuals for data i
  rhat[i,k] <- p[i,t[i,k]] * n[i,k]                                    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
   }
```

```
 sdev[i]<- sum(dev[i,1:na[i]])
 for (k in 2:na[i]){
# trial-specific LOR distributions
   delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])
   md[i,t[i,k]] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions
   taud[i,t[i,k]] <- tau *2*(k-1)/k     #precision of LOR distributions
#adjustment, multi-arm RCTs
   w[i,k] <- (delta[i,t[i,k]]  - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
   sw[i,k] <-sum(w[i,1:k-1])/(k-1)
  }
 }
d[1]<-0
for (k in 2:NT){d[k] ~ dnorm(0,.0001) } # vague priors for basic parameters
#sd ~ dunif(0,5)        # vague prior for random effects standard deviation
#tau <- 1/pow(sd,2)
sd.sq ~ dlnorm(m.tau,prec.tau)  # empirical prior for between-trial Var
prec.tau <- pow(sd.tau,-2)
tau <- pow(sd.sq,-1)   # between-trial precision = (1/between-trial variance)
sd <- sqrt(sd.sq)

#A ~ dnorm(meanA, precA)  # A is on log-odds scale
#precA <- pow(sdA,-2)     # turn st dev into precision

v[9] ~ dbeta(a, b)    # distribution for prob event on LMWH (std/std)+AES
b <- N-a
N <- 120639
a <- 539
for (k in 1:8){       # treatments below 8
 logit(v[k]) <- logit(v[9]) - lor[k,9]       # note change in sign
 rr[k] <- v[k]/v[1]     # calculate relative risk
 }
```

```
for (k in 10:NT){    # treatments above 9
  logit(v[k]) <- logit(v[9]) + lor[9,k]
  rr[k] <- v[k]/v[1]     # calculate relative risk
 }

rr[9] <- v[9]/v[1]
sumdev <- sum(sdev[])    # Calculate residual deviance
# Ranking and prob{treatment k is best}
for (k in 1:NT){
  rk[k] <- rank(rr[],k)
  best[k] <- equals(rank(rr[],k),1)
 }
# pairwise ORs and RRs
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]
    lrr[c,k] <- log(rr[k]) - log(rr[c])
    log(rrisk[c,k]) <- lrr[c,k]
   }
 }
}
# NT=no. treatments, NS=no. studies;
# NB : set up M vectors each r[,]. n[,] and t[,],  where M is the Maximum number of treatments
#         per trial in the dataset. In this dataset M is 4.

list(NT=13, NS=12,
# meanA and sdA are the  posterior mean and sd of log-odds of event
#meanA=-1.673, sdA=0.2529,
#Empirical prior Table IV (Turner et al) intervention: Non-Pharma v Pharma;
# outcome type: general physical health indicators
```

m.tau= -1.26, sd.tau=1.25)

r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1] t[,2] t[,3] t[,4] t[,5] na[]

1.5 111 0.5 111 1.5 111 0.5 111 NA NA 1 2 3 4 NA 4

4.5 1218 0.5 1202 NA NA NA NA NA NA 2 6 NA NA NA 2

1 1529 7 1528 NA NA NA NA NA NA 2 7 NA NA NA 2

2.5 222 0.5 218 NA NA NA NA NA NA 2 8 NA NA NA 2

1 79 1 74 1 78 NA NA NA NA 3 9 10 NA NA 3

6 604 5 643 NA NA NA NA NA NA 5 11 NA NA NA 2

4 1526 8 1508 NA NA NA NA NA NA 6 11 NA NA NA 2

15 1599 10 1596 NA NA NA NA NA NA 7 11 NA NA NA 2

0.5 209 2.5 110 0.5 110 NA NA NA NA 7 11 12 NA NA 3

0.5 174 1.5 177 NA NA NA NA NA NA 11 12 NA NA NA 2

1 206 3 211 NA NA NA NA NA NA 11 12 NA NA NA 2

0.5 146 1.5 144 NA NA NA NA NA NA 11 13 NA NA NA 2

END

list(
d=c(NA,0,0,0,0,0,0,0,1,2,3,4,2), # one for each treatment
sd.sq=1,
mu=c(0,0,3,0,0, 0,2,0,-1,0, 4,1))

list(
d=c(NA,1,0,2,0,3,0,0,1,2,3,4,2), # one for each treatment
sd.sq=0.1,
mu=c(0,2,1,0,-2, 0,3,0,4,0, 2,-1))

list(
d=c(NA,0,0,0,0,0,0,0,1,2,3,4,2), # one for each treatment
sd.sq=2,
mu=c(0,3,3,0,4, 0,1,0,-2,0, 1,0))

M.2.6.4 WinBUGS code for inconsistency model for number of patients with PE

```
VTE - inconsistency model - Elective knee PE
==============================
12 studies
13 treaments
==============================
# Binomial likelihood, logit link, inconsistency model
# Random effects model
model{                  # *** PROGRAM STARTS
for(i in 1:ns){          # LOOP THROUGH STUDIES
   delta[i,1]<-0         # treatment effect is zero in control arm
   mu[i] ~ dnorm(0,.0001)  # vague priors for trial baselines
   for (k in 1:na[i])  {   # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
        +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
     }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {  # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
     }
 }
totresdev <- sum(resdev[])   # Total Residual Deviance
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
   for (k in (c+1):nt)  { d[c,k] ~ dnorm(0,.0001) }
```

```
 }
#sd ~ dunif(0,5)  # vague prior for between-trial standard deviation
#var <- pow(sd,2) # between-trial variance
#tau <- 1/var     # between-trial precision
sd.sq ~ dlnorm(m.tau,prec.tau)  # empirical prior for between-trial Var
prec.tau <- pow(sd.tau,-2)
tau <- pow(sd.sq,-1)   # between-trial precision = (1/between-trial variance)
sd <- sqrt(sd.sq)

} # *** PROGRAM ENDS

 Data
# DVT
# nt=no. treatments, ns=no. studies
list(nt=13,ns=12, m.tau= -1.26, sd.tau=1.25)

 r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1]  t[,2]  t[,3]     t[,4]     t[,5]    na[]
 1.5 111 0.5 111 1.5 111 0.5 111 NA NA 1 2 3 4 NA 4
 4.5 1218 0.5 1202 NA NA NA NA NA NA 2 6 NA NA NA 2
 1 1529 7 1528 NA NA NA NA NA NA 2 7 NA NA NA 2
 2.5 222 0.5 218 NA NA NA NA NA NA 2 8 NA NA NA 2
 1 79 1 74 1 78 NA NA NA NA 3 9 10 NA NA 3
 6 604 5 643 NA NA NA NA NA NA 5 11 NA NA NA 2
 4 1526 8 1508 NA NA NA NA NA NA 6 11 NA NA NA 2
 15 1599 10 1596 NA NA NA NA NA NA 7 11 NA NA NA 2
 0.5 209 2.5 110 0.5 110 NA NA NA NA 7 11 12 NA NA 3
 0.5 174 1.5 177 NA NA NA NA NA NA 11 12 NA NA NA 2
 1 206 3 211 NA NA NA NA NA NA 11 12 NA NA NA 2
 0.5 146 1.5 144 NA NA NA NA NA NA 11 13 NA NA NA 2

END
```

```
 INITS
#chain 1
list(sd.sq=1,  mu=c(2,0,3,0,2,   -2,2,-2,-1,3,   2,-2),
d = structure(.Data = c(
        NA,0,0,0,0,0,0,0,0,0,0,0,
        NA,NA,0,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,0,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,0,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,0,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,0,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,0,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0,0,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,0  ),
.Dim = c(12,13))   )

# chain 2
list(sd.sq=1.5,  mu=c(2,1,3,1,2,   0,2,0,-1,3,   2,0),
d = structure(.Data = c(
        NA,5,5,5,5,5,5,5,5,5,5,5,
        NA,NA,5,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,
```

```
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5),
.Dim = c(12,13))  )

# chain 3
list(sd.sq=3,  mu=c(2,0.5,3,0.5,2,   -2,2,1,-1,3,    2,1),
d = structure(.Data = c(
        NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3  ),
.Dim = c(12,13))  )
```

M.2.6.5 WinBUGS code for number of patients with major bleeding

```
#Random effects model for multi-arm trials (any number of arms)
model{
for(i in 1:NS){
  w[i,1] <-0
  delta[i,t[i,1]]<-0
  mu[i] ~ dnorm(0,.0001) # vague priors for trial baselines
  for (k in 1:na[i]){
    r[i,k] ~ dbin(p[i,t[i,k]],n[i,k]) # binomial likelihood
    logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]  # model
#Deviance residuals for data i
  rhat[i,k] <- p[i,t[i,k]] * n[i,k]                                    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
```

```
  }
 sdev[i]<- sum(dev[i,1:na[i]])
 for (k in 2:na[i]){
# trial-specific LOR distributions
   delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])
   md[i,t[i,k]] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions
   taud[i,t[i,k]] <- tau *2*(k-1)/k     #precision of LOR distributions
#adjustment, multi-arm RCTs
   w[i,k] <- (delta[i,t[i,k]]  - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
   sw[i,k] <-sum(w[i,1:k-1])/(k-1)
  }
 }
d[1]<-0
for (k in 2:NT){d[k] ~ dnorm(0,.0001) } # vague priors for basic parameters
#sd ~ dunif(0,5)        # vague prior for random effects standard deviation
#tau <- 1/pow(sd,2)
sd.sq ~ dlnorm(m.tau,prec.tau)  # empirical prior for between-trial Var
prec.tau <- pow(sd.tau,-2)
tau <- pow(sd.sq,-1)   # between-trial precision = (1/between-trial variance)
sd <- sqrt(sd.sq)

#A ~ dnorm(meanA, precA)  # A is on log-odds scale
#precA <- pow(sdA,-2)     # turn st dev into precision

v[2] ~ dbeta(a, b)    # distribution for prob event on LMWH (std/std)+AES
b <- N-a
N <- 120639
a <- 465
for (k in 1:1){       # treatments below 2
  logit(v[k]) <- logit(v[2]) - lor[k,2]       # note change in sign
  rr[k] <- v[k]/v[1]     # calculate relative risk
```

```
 }

for (k in 3:NT){    # treatments above 2
  logit(v[k]) <- logit(v[2]) + lor[2,k]
  rr[k] <- v[k]/v[1]     # calculate relative risk
 }

rr[2] <- v[2]/v[1]
sumdev <- sum(sdev[])    # Calculate residual deviance
# Ranking and prob{treatment k is best}
for (k in 1:NT){
  rk[k] <- rank(rr[],k)
  best[k] <- equals(rank(rr[],k),1)
 }
# pairwise ORs and RRs
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]
    lrr[c,k] <- log(rr[k]) - log(rr[c])
    log(rrisk[c,k]) <- lrr[c,k]
   }
 }
}
# NT=no. treatments, NS=no. studies;
# NB : set up M vectors each r[,]. n[,] and t[,],  where M is the Maximum number of treatments
#         per trial in the dataset. In this dataset M is 3.


list(NT=11, NS=19,
# meanA and sdA are the  posterior mean and sd of log-odds of event
#meanA=-1.673, sdA=0.2529,
```

#Empirical prior Table IV (Turner et al) intervention: Non-Pharma v Pharma;

outcome type: adverse events

m.tau= -0.84, sd.tau=1.24)

r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1] t[,2] t[,3] t[,4] t[,5] na[]

4.5 90 1.5 92 0.5 90 NA NA NA NA 1 2 5 NA NA 3

0.5 111 2.5 111 NA NA NA NA NA NA 1 2 NA NA NA 2

0.5 64 1.5 68 NA NA NA NA NA NA 1 2 NA NA NA 2

1.5 66 0.5 67 NA NA NA NA NA NA 1 3 NA NA NA 2

1 87 1 84 NA NA NA NA NA NA 1 4 NA NA NA 2

1 124 4 129 NA NA NA NA NA NA 1 7 NA NA NA 2

14 1508 9 1501 NA NA NA NA NA NA 2 6 NA NA NA 2

9 694 10 679 NA NA NA NA NA NA 2 7 NA NA NA 2

2 45 3 45 NA NA NA NA NA NA 2 7 NA NA NA 2

17 1277 21 1254 NA NA NA NA NA NA 2 8 NA NA NA 2

1.5 222 0.5 218 NA NA NA NA NA NA 2 9 NA NA NA 2

1 517 11 517 NA NA NA NA NA NA 3 4 NA NA NA 2

22 1588 11 1596 NA NA NA NA NA NA 3 6 NA NA NA 2

0.5 150 4.5 306 0.5 152 NA NA NA NA 3 6 11 NA NA 3

12 868 5 857 NA NA NA NA NA NA 3 7 NA NA NA 2

16 1564 27 1584 NA NA NA NA NA NA 3 8 NA NA NA 2

3 228 3 225 NA NA NA NA NA NA 3 10 NA NA NA 2

9 173 4 176 NA NA NA NA NA NA 3 11 NA NA NA 2

6 336 5 334 NA NA NA NA NA NA 3 11 NA NA NA 2

END

list(

d=c(NA,0,0,0,0,0,0,0,1,2,0), # one for each treatment

sd.sq=1,

mu=c(0,0,3,0,0, 0,2,0,-1,0, 4,0,3,1,0,1,3, 2, 1))

```
list(
d=c(NA,1,0,2,0,3,0,0,1,2,-2), # one for each treatment
sd.sq=0.1,
mu=c(0,2,1,0,-2, 0,3,0,4,0, 2,0,1,3,0,0,1,0,0) )

list(
d=c(NA,0,0,0,0,0,0,0,1,2,2), # one for each treatment
sd.sq=2,
mu=c(0,3,3,0,4, 0,1,0,-2,0, 1,2,0,2,0,-3,1,2, -1) )
```

M.2.6.6 WinBUGS code for inconsistency model for number of patients with major bleeding

```
VTE - inconsistency model - Elective knee MB
==============================
19 trials
11 treaments
==============================
# Binomial likelihood, logit link, inconsistency model
# Random effects model
model{                  # *** PROGRAM STARTS
for(i in 1:ns){          # LOOP THROUGH STUDIES
   delta[i,1]<-0         # treatment effect is zero in control arm
   mu[i] ~ dnorm(0,.0001)  # vague priors for trial baselines
   for (k in 1:na[i])  {   # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
        +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
    }
# summed residual deviance contribution for this trial
```

```
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {  # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
    }
 }
totresdev <- sum(resdev[])   # Total Residual Deviance
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
   for (k in (c+1):nt)  { d[c,k] ~ dnorm(0,.0001) }
 }
#sd ~ dunif(0,5)  # vague prior for between-trial standard deviation
#var <- pow(sd,2) # between-trial variance
#tau <- 1/var     # between-trial precision
sd.sq ~ dlnorm(m.tau,prec.tau)  # empirical prior for between-trial Var
prec.tau <- pow(sd.tau,-2)
tau <- pow(sd.sq,-1)   # between-trial precision = (1/between-trial variance)
sd <- sqrt(sd.sq)

} # *** PROGRAM ENDS


 Data
# DVT
# nt=no. treatments, ns=no. studies
list(nt=11,ns=19, m.tau= -0.84, sd.tau=1.24)


 r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1]  t[,2]  t[,3]     t[,4]     t[,5]    na[]
 4.5 90 1.5 92 0.5 90 NA NA NA NA 1 2 5 NA NA 3
 0.5 111 2.5 111 NA NA NA NA NA NA 1 2 NA NA NA 2
 0.5 64 1.5 68 NA NA NA NA NA NA 1 2 NA NA NA 2
 1.5 66 0.5 67 NA NA NA NA NA NA 1 3 NA NA NA 2
 1 87 1 84 NA NA NA NA NA NA 1 4 NA NA NA 2
 1 124 4 129 NA NA NA NA NA NA 1 7 NA NA NA 2
```

```
14 1508 9 1501 NA NA NA NA NA NA 2 6 NA NA NA 2

9 694 10 679 NA NA NA NA NA NA 2 7 NA NA NA 2

2 45 3 45 NA NA NA NA NA NA 2 7 NA NA NA 2

17 1277 21 1254 NA NA NA NA NA NA 2 8 NA NA NA 2

1.5 222 0.5 218 NA NA NA NA NA NA 2 9 NA NA NA 2

1 517 11 517 NA NA NA NA NA NA 3 4 NA NA NA 2

22 1588 11 1596 NA NA NA NA NA NA 3 6 NA NA NA 2

0.5 150 4.5 306 0.5 152 NA NA NA NA 3 6 11 NA NA 3

12 868 5 857 NA NA NA NA NA NA 3 7 NA NA NA 2

16 1564 27 1584 NA NA NA NA NA NA 3 8 NA NA NA 2

3 228 3 225 NA NA NA NA NA NA 3 10 NA NA NA 2

9 173 4 176 NA NA NA NA NA NA 3 11 NA NA NA 2

6 336 5 334 NA NA NA NA NA NA 3 11 NA NA NA 2

END



 INITS

#chain 1

list(sd.sq=1,  mu=c(2,0,3,0,2,   -2,2,-2,-1,3,   2,-2,1,3,1,     1,1,0,-1),

d = structure(.Data = c(

          NA,0,0,0,0,0,0,0,0,0,

          NA,NA,0,0,0,0,0,0,0,0,

          NA,NA,NA,0,0,0,0,0,0,0,

          NA,NA,NA,NA,0,0,0,0,0,0,

          NA,NA,NA,NA,NA,0,0,0,0,0,

          NA,NA,NA,NA,NA,NA,0,0,0,0,

          NA,NA,NA,NA,NA,NA,NA,0,0,0,

          NA,NA,NA,NA,NA,NA,NA,NA,0,0,

          NA,NA,NA,NA,NA,NA,NA,NA,NA,0 ),

.Dim = c(10,11))   )
```

```
# chain 2
list(sd.sq=1.5,  mu=c(2,1,3,1,2,   0,2,0,-1,3,   2,0,1,3,1,   1,2,0,0),
d = structure(.Data = c(
        NA,5,5,5,5,5,5,5,5,5,5,
        NA,NA,5,5,5,5,5,5,5,5,5,
        NA,NA,NA,5,5,5,5,5,5,5,5,
        NA,NA,NA,NA,5,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,5,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,5,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,5,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,5,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,5,5,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,5 ),
.Dim = c(10,11))  )


# chain 3
list(sd.sq=3,  mu=c(2,0.5,3,0.5,2,   -2,2,1,-1,3,    2,1,1,3,1,     0,1,-1,-3),
d = structure(.Data = c(
        NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,-3,-3,
        NA,NA,NA,NA,NA,NA,NA,NA,NA,NA,-3  ),
.Dim = c(10,11))  )
```

M.3 Network meta-analysis for VTE prophylaxis in those undergoing abdominal surgery

M.3.1 Introduction

The results of conventional meta-analyses of direct evidence alone (as presented in the GRADE profiles in Chapter 35 and forest plots in appendix L) does not help inform which intervention is most effective as VTE prophylaxis in patients undergoing abdominal surgery. The challenge of interpretation has arisen for two reasons:

- In isolation, each pair-wise comparison does not inform the choice among the different treatments; in addition direct evidence is not available for some pair-wise comparisons in a randomised controlled trial.
- There are frequently multiple overlapping comparisons, which could potentially give inconsistent estimates of effect.

To overcome these problems, a hierarchical Bayesian network meta-analysis (NMA) was performed. This type of analysis allows for the synthesis of data from direct and indirect comparisons without breaking randomisation and allows for the ranking of different interventions. In this case the outcomes were defined as:

- Deep vein thrombosis (DVT; symptomatic and asymptomatic)
- Pulmonary embolism (PE)
- Major bleeding

The analysis also provided estimates of effect (with 95% credible intervals) for each intervention compared to one another and compared to a single baseline risk (in this case the baseline treatment was no prophylaxis or in the case of the major bleeding outcome a combination of no prophylaxis and mechanical prophylaxis). These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on the best available evidence.

Conventional fixed effects meta-analysis assumes that the relative effect of one treatment compared to another is the same across an entire set of trials. In a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials.

Network meta-analysis requires an additional assumption over conventional meta-analysis. The additional assumption is that intervention A has the same effect on people in trials of intervention A compared to intervention B as it does for people in trials of intervention A versus intervention C, and so on. Thus, in a random effects network meta-analysis, the assumption is that intervention A has the same effect distribution across trials of A versus B, A versus C and so on.

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.

M.3.2 Methods

M.3.2.1 Study selection

To estimate the relative risks, we performed an NMA that simultaneously used all the relevant RCT evidence from the clinical evidence review. As with conventional meta-analyses, this type of analysis does not break the randomisation of the evidence, nor does it make any assumptions about adding the effects of different interventions. The effectiveness of a particular treatment strategy

combination will be derived only from randomised controlled trials that had that particular combination in a trial arm.

M.3.2.2 Outcome measures

The NMA evidence reviews for interventions considered three clinical efficacy outcomes identified from the clinical evidence review; number of people with DVT, number of people with PE and number of people with major bleeding. Other outcomes were not considered for the NMA as they were infrequently reported across the studies. The committee considered that these outcomes were the most critical clinical outcomes for testing effectiveness of VTE prophylaxis.

M.3.2.3 Comparability of interventions

The interventions compared in the model were those found in the randomised controlled trials and included in the clinical evidence review already presented in Chapter 35 of the full guideline and in appendix H. If an intervention was evaluated in a study that met the inclusion criteria for the network (that is if it reported at least one of the outcomes of interest and matched the inclusion criteria for the meta-analysis) then it was included in the network meta-analysis, otherwise it was excluded.

The treatments included in each network are shown in Table 257**.**

Table 257: Treatments included in network meta-analysis

Network 1: Number of people with DVT	**Network 2: Number of people with PE**	**Network 3: Number of people with major bleeding.**
Electrical stimulation	Fondaparinux standard duration	Fondaparinux standard duration
Fondaparinux standard duration	IPCD below knee	No/mechanical prophylaxis
Fondaparinux standard duration + IPCD any location	IPCD full leg	Post-operative LMWH standard duration, standard dose
Foot pump	No prophylaxis	Pre-operative LMWH extended duration, standard dose
IPCD below knee	Post-operative LMWH standard duration, standard dose	Pre-operative LMWH standard duration, high dose
IPCD full leg	Pre-operative LMWH extended duration, standard dose	Pre-operative LMWH standard duration, low dose
IPCD undefined	Pre-operative LMWH standard duration, low dose	Pre-operative LMWH standard duration, standard dose
No prophylaxis	Pre-operative LMWH standard duration, standard dose	UFH standard duration
Post-operative LMWH standard duration, standard dose	AES above knee	-
Post-operative LMWH standard duration, standard dose + IPCD undefined	AES above knee + IPCD full leg	-
Pre-operative LMWH extended duration, standard dose	AES above knee + UFH standard	-
Pre-operative LMWH standard duration, high dose	UFH standard duration	-
Pre-operative LMWH standard duration, low dose	VKA standard duration	-
Pre-operative LMWH standard duration, standard dose	-	-
AES above knee	-	-
AES above knee + IPCD full leg	-	-

AES above knee + UFH standard	-	-
AES below knee	-	-
AES combination + IPCD full leg	-	-
AES undefined	-	-
UFH standard duration	-	-
VKA standard duration	-	-

The details of these interventions can be found in the clinical evidence review in Chapter 35 of the full guideline and evidence tables in appendix H.

M.3.2.4 Baseline risk

The baseline risk is defined here as the risk of achieving the outcome of interest in the no prophylaxis group. This figure is useful because it allows us to convert the results of the NMA from odds ratios to relative risks.

Baseline odds were derived by the logistic regression in WinBUGS. This approach has the advantage that baseline and relative effects are both modelled on the same log odds scale, and also ensures that the uncertainty in the estimation of baseline and relative effects is accounted for in the model. This method produced baseline odds [mean (SD)] as follows:

- -1.372 (1.174) for number of patients with DVT in the no prophylaxis group
- -3.939 (2.201) for number of patients with PE in the no prophylaxis group
- -5.331 (3.482) for the number of patients with major bleeding in the no/mechanical prophylaxis group.

For details of data informing these models, please refer to the full analyses in sections M.3.6.1, M.3.6.4 and M.3.6.6.

M.3.2.5 Statistical analysis

A hierarchical Bayesian network meta-analysis (NMA) was performed using the software WinBUGS. We adapted a three-arm random effects model template for the networks, from the University of Bristol website (https://www.bris.ac.uk/cobm/research/mpes/mtc.html). This model accounts for the correlation between study level effects induced by multi-arm trials.

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 outcome subgroup, a diagram of the evidence network is presented in section M.3.3.

The model used was a random effects logistic regression model, with parameters estimated by Markov chain Monte Carlo simulation. As it was a Bayesian analysis, for each parameter the evidence distribution is weighted by a distribution of prior beliefs. These were estimated from the baseline models for the dichotomous outcomes using the following equations.

Predictive probability of response (MeanA) =mean of mu.new

Precision (PrecA)=1/(standard deviation of mu.new)^2

A non-informative prior distribution was used to maximise the weighting given to the data for continuous outcomes. These priors were normally distributed with a mean of 0 and standard deviation of 10,000.

For the analyses, a series of 60,000 burn-in simulations were run to allow convergence and then a further 600,000 simulations were run to produce the outputs. For the baseline analyses, a series of 100,000 burn-in simulations were run to allow convergence and then a further 100,000 simulations

were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots.

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.

The results, in terms of relative risk, of pair-wise meta-analyses are presented in the clinical evidence review (Chapter 35, and appendix H).

The aim of the NMA was to calculate treatment specific log odds ratios and relative risks for response to be consistent with the comparative effectiveness results presented elsewhere in the clinical evidence review and for ease of interpretation. Let BO, $\tilde{\theta}$, $\widetilde{\mathrm{OR}}$ and p denote the baseline odds, treatment specific odds, treatment specific log odds ratio and absolute probability respectively. Then:

$$\widetilde{\boldsymbol{\theta}} = \boldsymbol{Ln}\left(\widetilde{\boldsymbol{OR}}\right) + \boldsymbol{Ln}(\boldsymbol{BO})$$

And:

$$\boldsymbol{p} = \frac{\boldsymbol{e}^{\widetilde{\boldsymbol{\theta}}}}{\mathbf{1} + \boldsymbol{e}^{\widetilde{\boldsymbol{\theta}}}}$$

Once the treatment specific probabilities for response are calculated, we divide them by the baseline probability ($\boldsymbol{p_b}$) to get treatment specific relative risks ($\boldsymbol{rr_b}$):

$$\boldsymbol{p_b} = \frac{\boldsymbol{e}^{\boldsymbol{BO}}}{\mathbf{1} + \boldsymbol{e}^{\boldsymbol{BO}}}$$

$$\boldsymbol{rr_b} = \frac{\boldsymbol{p}}{\boldsymbol{p_b}}$$

This approach has the advantage that baseline and relative effects are both modelled on the same log odds scale, and also ensures that the uncertainty in the estimation of both baseline and relative effects is accounted for in the model.

We also calculated the overall ranking of interventions according to their relative risk compared to control group. Due to the skewness of the data, the NMA relative risks and rank results are reported as medians rather than means (as in the direct comparisons) to give a more accurate representation of the 'most likely' value. The median rank for each intervention was derived from the resulting distribution and these are presented on a rank plot with the associated 95% credible intervals.

A key assumption behind NMA is that the network is consistent. In other words, it is assumed that the direct and indirect treatment effect estimates do not disagree with one another. Discrepancies between direct and indirect estimates of effect may result from several possible causes. First, there is chance and if this is the case then the network meta-analysis results are likely to be more precise as they pool together more data than conventional meta-analysis estimates alone. Second, there could be differences between the trials included in terms of their clinical or methodological characteristics.

This heterogeneity is a problem for network meta-analysis but may be dealt with by subgroup analysis, meta-regression or by carefully defining inclusion criteria. Inconsistency, caused by heterogeneity, was assessed subjectively by comparing the relative risks from the direct evidence (from pair-wise meta-analysis) to the relative risks from the combined direct and indirect evidence (from NMA). We assumed the evidence to be inconsistent where the relative risk from the NMA did not fit within the confidence interval of the relative risk from the direct comparison. We further tested for inconsistency by developing inconsistency models for networks of binary outcomes using the TSD 4 template from the University of Bristol website

(https://www.bris.ac.uk/cobm/research/mpes/mtc.html). We compared the posterior mean of the residual deviance between the consistency and inconsistency models to see which was a better fit to the data (closest to the number of trial arms in each network) and checked the difference in deviance information criterion (DIC) values between the two models was small (less than 3-5) or if it was larger, that the smaller DIC and hence better fitting model was the consistency model. No inconsistency was identified.

M.3.3 Results

M.3.3.1 Deep vein thrombosis (symptomatic and asymptomatic)

Included studies

66 studies were identified as reporting on DVT outcomes. After excluding papers that reported zero events in each arm and papers reporting on combinations that did not connect to any other intervention in the network, 48 studies involving 22 treatments were included in the network for DVT (symptomatic and asymptomatic). The network can be seen in **Figure 839** and the trial data for each of the studies included in the NMA are presented in **Table 258**.

Figure 839: Network diagram for DVT

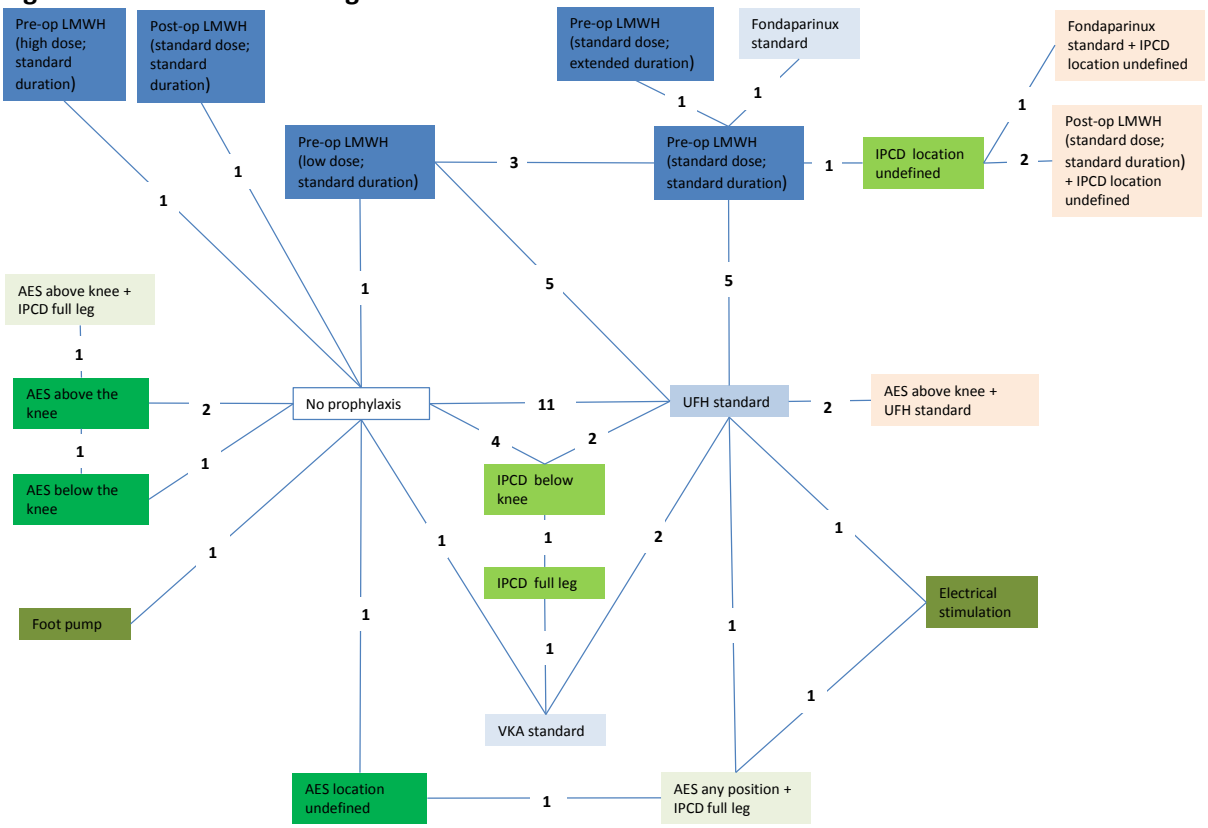


Table 258: Study data for DVT network meta-analysis

Study	Intervention 1	Intervention 2	Intervention 3	Intervention 1		Intervention 2		Intervention 3	
				Events	N	Events	N	Events	N
Coe 1978	No prophylaxis	UFH standard	IPCD below knee	6	24	6	28	2	29

Study	Intervention 1	Intervention 2	Intervention 3	Intervention 1		Intervention 2		Intervention 3	
Tabemer 1978	No prophylaxis	UFH standard	VKA standard	11	48	3	49	3	48
Bergqvist 1980	No prophylaxis	UFH standard	NA	14	51	6	46	NA	NA
Clarke-Pearson 1983	No prophylaxis	UFH standard	NA	11	97	11	88	NA	NA
Gallus 1973	No prophylaxis	UFH standard	NA	4	118	1	108	NA	NA
Gallus 1976	No prophylaxis	UFH standard	NA	12	412	4	408	NA	NA
Gordon-Smith 1972	No prophylaxis	UFH standard	NA	21	50	4	48	NA	NA
Kakkar 1972	No prophylaxis	UFH standard	NA	17	39	3	39	NA	NA
Strand 1925	No prophylaxis	UFH standard	NA	10	50	3	50	NA	NA
Tomgren 1978	No prophylaxis	UFH standard	NA	20	61	10	63	NA	NA
Vandendris 1980	No prophylaxis	UFH standard	NA	13	33	3	31	NA	NA
Buston 1981	No prophylaxis	IPCD below knee	NA	4	57	6	62	NA	NA
Clarke-Pearson 1984A	No prophylaxis	IPCD below knee	NA	11	97	14	97	NA	NA
Clarke-Pearson 1984B	No prophylaxis	IPCD below knee	NA	17	52	5	55	NA	NA
Allan 1983	No prophylaxis	AES position not reported	NA	37	103	15	97	NA	NA
Tsapogas 1971	No prophylaxis	AES below knee	NA	6	44	2	51	NA	NA
Halford 1976	No prophylaxis	AES above knee	NA	23	47	11	48	NA	NA
Turner 1984	No prophylaxis	AES above knee	NA	4.5	93	0.5	105	NA	NA
Scurr 1981	No prophylaxis	Foot pump	NA	15	33	6	33	NA	NA
Marassi 1993	No prophylaxis	Pre-operative LMWH standard high	NA	11	31	2	30	NA	NA
Bergqvist 1996	No prophylaxis	Post-operative LMWH standard standard	NA	9	41	3	39	NA	NA
Ockelford 1989	No prophylaxis	Pre-operative LMWH	NA	14	88	4	95	NA	NA

Study	Intervention 1	Intervention 2	Intervention 3	Intervention 1		Intervention 2		Intervention 3	
		standard low							
Clarke-Pearson 1993	UFH standard	IPCD below knee	NA	6	107	3	101	NA	NA
van Vroonhoven 1974	UFH standard	VKA standard	NA	1	50	9	50	NA	NA
Leizorovicz 1991	UFH standard	Pre-operative LMWH standard low	Pre-operative LMWH standard standard	7	429	16	431	7	430
Caen 1988	UFH standard	Pre-operative LMWH standard low	NA	7	190	6	195	NA	NA
Hartl 1990	UFH standard	Pre-operative LMWH standard low	NA	5	115	5	112	NA	NA
Koller 1986B	UFH standard	Pre-operative LMWH standard low	NA	1	72	2	74	NA	NA
Nurmohamed 1995	UFH standard	Pre-operative LMWH standard low	NA	8	709	25	718	NA	NA
Bergqvist 1988	UFH standard	Pre-operative LMWH standard standard	NA	41	497	28	505	NA	NA
Onarheim 1986	UFH standard	Pre-operative LMWH standard standard	NA	0.5	28	1.5	26	NA	NA
Bergqvist 1986	UFH standard	Pre-operative LMWH standard standard	NA	9	217	13	215	NA	NA
Wille-Jorgensen 1991	UFH standard	AES above knee + UFH standard	NA	12	81	2	79	NA	NA
Wille-Jorgensen 1985	UFH standard	AES above knee + UFH standard	NA	7	90	1	86	NA	NA
Nicolaides 1983	UFH standard	Electrical stimulation	AES combination + IPCD full leg	7	50	12	50	3	50
Soderdahl 1997	IPCD below knee	IPCD full leg	NA	1.5	44	0.5	48	NA	NA
Chandhoke 1992	VKA standard	IPCD full leg	NA	0.5	54	2.5	48	NA	NA
Gao	AES position	AES	NA	14	56	5	52	NA	NA

Study	Intervention 1	Intervention 2	Intervention 3	Intervention 1		Intervention 2		Interventi on 3	
2012	not reported	combination + IPCD full leg							
Porteou s 1989	AES below knee	AES above knee	NA	1	58	3	56	NA	NA
Caprini 1983	AES above knee	AES above knee + IPCD full leg	NA	5	39	1	38	NA	NA
Harch 1988	Pre-operative LMWH standard low	Pre-operative LMWH standard standard	NA	2.5	17	0.5	20	NA	NA
Bergqvis t 1995	Pre-operative LMWH standard low	Pre-operative LMWH standard standard	NA	124	976	65	981	NA	NA
Bergqvis t 2002	Pre-operative LMWH standard standard	Pre-operative LMWH extended standard	NA	20	167	8	165	NA	NA
Agnelli 2005	Pre-operative LMWH standard standard	Fondaparinux standard	NA	59	1018	43	102 4	NA	NA
Maxwell 2001	Pre-operative LMWH standard standard	IPCD location un-defined	NA	2	105	1	106	NA	NA
Turpie 2007	IPCD location un-defined	Fondaparinux standard + IPCD any location	NA	22	418	7	424	NA	NA
Sakon 2010	IPCD location un-defined	IPCD undefined + Post-operative LMWH standard standard	NA	6	31	1	78	NA	NA
Song 2014	IPCD location un-defined	IPCD undefined + Post-operative LMWH standard standard	NA	3.5	113	0.5	109	NA	NA

NMA results

Table 259 summarises the results of the conventional meta-analyses in terms of risk ratios generated from studies directly comparing different interventions, together with the results of the NMA in terms of risk ratios for every possible treatment comparison.

Table 259: Risk ratios for DVT (symptomatic and asymptomatic)

Comparisons		Risk ratio	
		Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)
Versus no prophylaxis	UFH standard	0.36 (0.10, 1.27)	0.35 (0.221, 0.62)
	IPCD below knee	0.64 (0.26, 1.59)	0.53 (0.22, 0.95)
	VKA standard	0.27 (0.08, 0.92)	0.58 (0.17, 1.44)
	AES position not reported	0.43 (0.25, 0.73)	0.40 (0.12, 1.07)
	AES below knee	0.29 (0.06, 1.35)	0.18 (0.03, 0.82)
	AES above knee	0.41 (0.23, 0.73)	0.34 (0.10, 0.91)
	Foot pump	0.40 (0.18, 0.90)	0.32 (0.06, 1.20)
	Pre-operative LMWH standard duration, high dose	0.19 (0.05, 0.78)	0.14 (0.01, 0.83)
	Post-operative LMWH standard duration, standard dose	0.35 (0.10, 1.20)	0.34 (0.05, 1.41)
	Pre-operative LMWH standard duration, low dose	0.26 (0.09, 0.77)	0.57 (0.27, 1.01)
	Pre-operative LMWH standard duration, standard dose	-	0.31 (0.13, 0.69)
	AES above knee + UFH standard	-	0.05 (0.01, 0.24)
	Electrical stimulation	-	0.65 (0.15, 2.00)
	AES combination + IPCD full leg	-	0.13 (0.03, 0.54)
	IPCD full leg	-	0.85 (0.10, 3.90)
	AES above knee + IPCD full leg	-	0.05 (0.00, 0.63)
	Pre-operative LMWH extended duration, standard dose	-	0.12 (0.02, 0.60)
	Fondaparinux standard	-	0.23 (0.05, 0.87)
	IPCD location un-defined	-	0.14 (0.00, 1.63)
	Fondaparinux standard + IPCD any location	-	0.04 (0.00, 0.91)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.01 (0.00, 0.28)
Versus UFH standard duration	IPCD below knee	0.42 (0.16, 1.15)	1.46 (0.72, 3.01)
	VKA standard	3.03 (1.00, 9.18)	1.57 (0.53, 4.38)
	AES position not reported	-	1.11 (0.34, 3.30)
	AES below knee	-	0.52 (0.08, 2.44)
	AES above knee	-	0.94 (0.27, 2.87)
	Foot pump	-	0.89 (0.17, 3.80)
	Pre-operative LMWH standard duration, high dose	-	0.40 (0.04, 2.43)
	Post-operative LMWH standard duration, standard dose	-	0.93 (0.13, 4.49)
	Pre-operative LMWH standard duration, low dose	1.27 (0.93, 1.73)	1.57 (0.91, 2.76)
	Pre-operative LMWH standard duration,	0.85 (0.59, 1.24)	0.88 (0.46, 1.63)

		Risk ratio	
	standard dose		
	AES above knee + UFH standard	0.16 (0.05, 0.54)	0.14 (0.02, 0.57)
	Electrical stimulation	1.71 (0.74, 3.99)	1.75 (0.46, 6.06)
	AES combination + IPCD full leg	0.43 (0.12, 1.56)	0.38 (0.09, 1.38)
	IPCD full leg	-	2.24 (0.30, 12.75)
	AES above knee + IPCD full leg	-	0.13 (0.00, 1.76)
	Pre-operative LMWH extended duration, standard dose	-	0.34 (0.07, 1.52)
	Fondaparinux standard	-	0.64 (0.16, 2.32)
	IPCD location un-defined	-	0.38 (0.01, 4.66)
	Fondaparinux standard + IPCD any location	-	0.11 (0.00, 2.43)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.02 (0.00, 0.74)
Versus IPCD below knee	VKA standard	-	1.09 (0.32, 3.45)
	AES position not reported	-	0.76 (0.21, 2.56)
	AES below knee	-	0.36 (0.05, 1.79)
	AES above knee	-	0.65 (0.17, 2.15)
	Foot pump	-	0.61 (0.11, 2.80)
	Pre-operative LMWH standard duration, high dose	-	0.28 (0.02, 1.76)
	Post-operative LMWH standard duration, standard dose	-	0.64 (0.08, 3.27)
	Pre-operative LMWH standard duration, low dose	-	1.07 (0.46, 2.60)
	Pre-operative LMWH standard duration, standard dose	-	0.60 (0.23, 1.52)
	AES above knee + UFH standard	-	0.09 (0.01, 0.47)
	Electrical stimulation	-	1.20 (0.27, 4.83)
	AES combination + IPCD full leg	-	0.26 (0.05, 1.10)
	IPCD full leg	0.31 (0.01, 7.31)	1.54 (0.21, 8.61)
	AES above knee + IPCD full leg	-	0.09 (0.00, 1.28)
	Pre-operative LMWH extended duration, standard dose	-	0.23 (0.04, 1.22)
	Fondaparinux standard	-	0.44 (0.09, 1.88)
	IPCD location un-defined	-	0.26 (0.01, 3.42)
	Fondaparinux standard + IPCD any location	-	0.08 (0.00, 1.78)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.01 (0.00, 0.54)
Versus VKA standard duration	AES position not reported	-	0.71 (0.16, 3.10)
	AES below knee	-	0.33 (0.04, 2.08)
	AES above knee	-	0.60 (0.13, 2.64)
	Foot pump	-	0.56 (0.08, 3.25)
	Pre-operative LMWH standard duration, high dose	-	0.26 (0.02, 2.01)
	Post-operative LMWH standard duration, standard dose	-	0.59 (0.07, 3.77)

		Risk ratio	
	Pre-operative LMWH standard duration, low dose	-	0.99 (0.32, 3.34)
	Pre-operative LMWH standard duration, standard dose	-	0.56 (0.17, 1.93)
	AES above knee + UFH standard	-	0.09 (0.01, 0.52)
	Electrical stimulation	-	1.11 (0.21, 5.54)
	AES combination + IPCD full leg	-	0.24 (0.04, 1.25)
	IPCD full leg	0.18 (0.01, 3.60)	1.41 (0.21, 8.02)
	AES above knee + IPCD full leg	-	0.08 (0.00, 1.37)
	Pre-operative LMWH extended duration, standard dose	-	0.22 (0.03, 1.37)
	Fondaparinux standard	-	0.41 (0.07, 2.14)
	IPCD location un-defined	-	0.24 (0.01, 3.62)
	Fondaparinux standard + IPCD any location	-	0.07 (0.00, 1.83)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.01 (0.00, 0.56)
Versus AES position not reported	AES below knee	-	0.47 (0.06, 3.03)
	AES above knee	-	0.85 (0.18, 3.87)
	Foot pump	-	0.80 (0.12, 4.79)
	Pre-operative LMWH standard duration, high dose	-	0.36 (0.03, 2.92)
	Post-operative LMWH standard duration, standard dose	-	0.84 (0.10, 5.62)
	Pre-operative LMWH standard duration, low dose	-	1.41 (0.44, 5.16)
	Pre-operative LMWH standard duration, standard dose	-	0.79 (0.22, 2.97)
	AES above knee + UFH standard	-	0.12 (0.02, 0.77)
	Electrical stimulation	-	1.57 (0.33, 7.46)
	AES combination + IPCD full leg	0.38 (0.15, 0.99)	0.34 (0.09, 1.17)
	IPCD full leg	-	2.01 (0.22, 15.68)
	AES above knee + IPCD full leg	-	0.12 (0.00, 1.97)
	Pre-operative LMWH extended duration, standard dose	-	0.31 (0.04, 2.06)
	Fondaparinux standard	-	0.58 (0.10, 3.25)
	IPCD location un-defined	-	0.34 (0.01, 5.60)
	Fondaparinux standard + IPCD any location	-	0.10 (0.00, 2.73)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.02 (0.00, 0.81)
Versus AES below the knee	AES above knee	3.11 (0.33, 28.99)	1.78 (0.37, 11.60)
	Foot pump	-	1.69 (0.19, 17.66)
	Pre-operative LMWH standard duration, high dose	-	0.78 (0.05, 10.05)
	Post-operative LMWH standard duration, standard dose	-	1.76 (0.16, 19.83)
	Pre-operative LMWH standard duration, low dose	-	3.00 (0.61, 22.24)

		Risk ratio	
	Pre-operative LMWH standard duration, standard dose	-	1.68 (0.31, 12.43)
	AES above knee + UFH standard	-	0.26 (0.02, 2.86)
	Electrical stimulation	-	3.36 (0.45, 32.66)
	AES combination + IPCD full leg	-	0.73 (0.09, 7.04)
	IPCD full leg	-	4.27 (0.36, 54.64)
	AES above knee + IPCD full leg	-	0.26 (0.01, 5.18)
	Pre-operative LMWH extended duration, standard dose	-	0.66 (0.07, 7.38)
	Fondaparinux standard	-	1.23 (0.15, 12.30)
	IPCD location un-defined	-	0.73 (0.02, 17.86)
	Fondaparinux standard + IPCD any location	-	0.22 (0.00, 8.27)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.04 (0.00, 2.35)
Versus AES above the knee	Foot pump	-	0.94 (0.14, 5.77)
	Pre-operative LMWH standard duration, high dose	-	0.43 (0.03, 3.56)
	Post-operative LMWH standard duration, standard dose	-	0.99 (0.12, 6.71)
	Pre-operative LMWH standard duration, low dose	-	1.66 (0.51, 6.36)
	Pre-operative LMWH standard duration, standard dose	-	0.93 (0.26, 3.69)
	AES above knee + UFH standard	-	0.15 (0.02, 0.96)
	Electrical stimulation	-	1.86 (0.34, 10.48)
	AES combination + IPCD full leg	-	0.40 (0.07, 2.30)
	IPCD full leg	-	2.36 (0.26, 19.24)
	AES above knee + IPCD full leg	0.21 (0.03, 1.68)	0.15 (0.00, 1.43)
	Pre-operative LMWH extended duration, standard dose	-	0.36 (0.05, 2.50)
	Fondaparinux standard	-	0.68 (0.11, 4.02)
	IPCD location un-defined	-	0.41 (0.01, 6.71)
	Fondaparinux standard + IPCD any location	-	0.12 (0.00, 3.29)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.02 (0.00, 0.98)
Versus foot pump	Pre-operative LMWH standard duration, high dose	-	0.46 (0.03, 4.87)
	Post-operative LMWH standard duration, standard dose	-	1.04 (0.10, 9.67)
	Pre-operative LMWH standard duration, low dose	-	1.77 (0.39, 10.02)
	Pre-operative LMWH standard duration, standard dose	-	0.99 (0.20, 5.73)
	AES above knee + UFH standard	-	0.16 (0.02, 1.36)
	Electrical stimulation	-	1.97 (0.28, 15.29)
	AES combination + IPCD full leg	-	0.43 (0.06, 3.34)
	IPCD full leg	-	2.50 (0.23, 26.76)

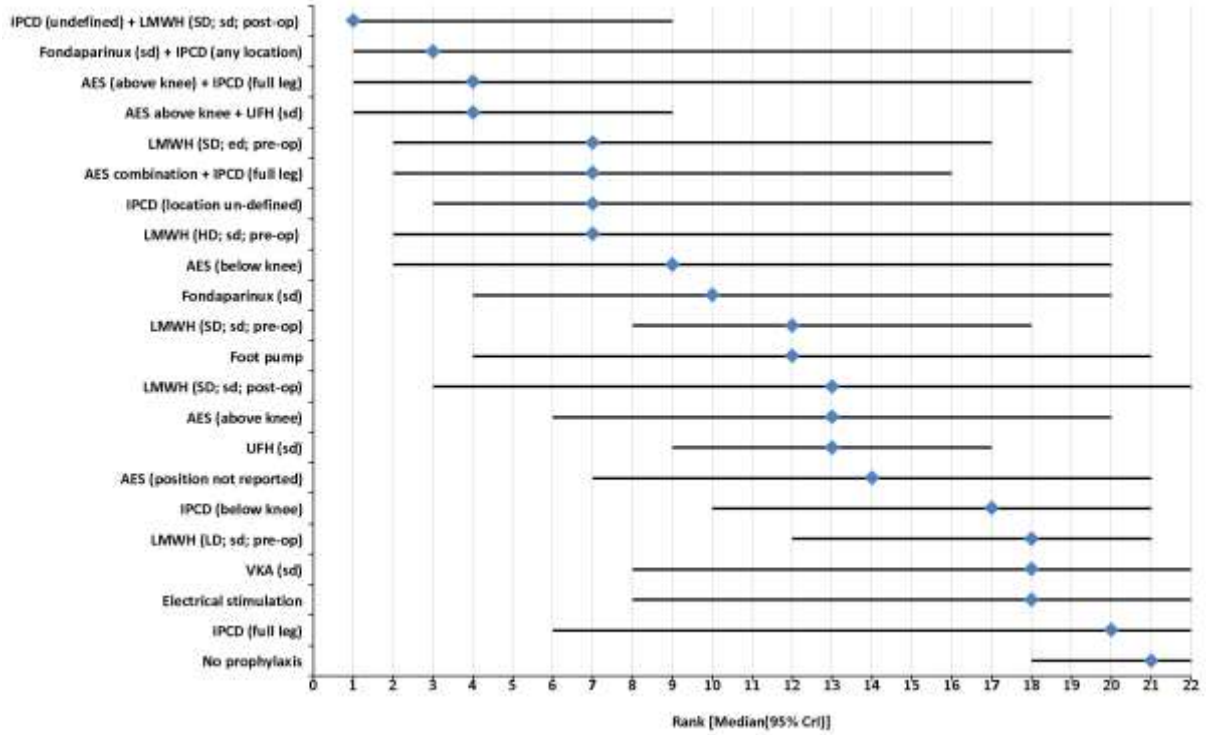
		Risk ratio	
	AES above knee + IPCD full leg	-	0.15 (0.00, 3.09)
	Pre-operative LMWH extended duration, standard dose	-	0.39 (0.04, 3.56)
	Fondaparinux standard	-	0.73 (0.09, 5.77)
	IPCD location un-defined	-	0.43 (0.01, 8.79)
	Fondaparinux standard + IPCD any location	-	0.13 (0.00, 4.15)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.02 (0.00, 1.19)
Versus pre-operative LMWH standard duration, high dose	Post-operative LMWH standard duration, standard dose	-	2.28 (0.17, 37.32)
	Pre-operative LMWH standard duration, low dose	-	3.89 (0.61, 44.72)
	Pre-operative LMWH standard duration, standard dose	-	2.17 (0.32, 25.28)
	AES above knee + UFH standard	-	0.34 (0.03, 5.45)
	Electrical stimulation	-	4.36 (0.47, 63.35)
	AES combination + IPCD full leg	-	0.94 (0.09, 13.53)
	IPCD full leg	-	5.54 (0.41, 99.61)
	AES above knee + IPCD full leg	-	0.33 (0.01, 10.68)
	Pre-operative LMWH extended duration, standard dose	-	0.85 (0.07, 13.89)
	Fondaparinux standard	-	1.60 (0.16, 23.52)
	IPCD location un-defined	-	0.95 (0.02, 30.24)
	Fondaparinux standard + IPCD any location	-	0.28 (0.00, 13.34)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.05 (0.00, 3.76)
Versus post-operative LMWH standard duration, standard dose	Pre-operative LMWH standard duration, low dose	-	1.68 (0.33, 12.74)
	Pre-operative LMWH standard duration, standard dose	-	0.94 (0.17, 7.14)
	AES above knee + UFH standard	-	0.15 (0.01, 1.61)
	Electrical stimulation	-	1.88 (0.25, 18.67)
	AES combination + IPCD full leg	-	0.41 (0.05, 4.02)
	IPCD full leg	-	2.41 (0.20, 31.62)
	AES above knee + IPCD full leg	-	0.15 (0.00, 3.45)
	Pre-operative LMWH extended duration, standard dose	-	0.37 (0.04, 4.13)
	Fondaparinux standard	-	0.70 (0.08, 6.91)
	IPCD location un-defined	-	0.42 (0.01, 9.72)
	Fondaparinux standard + IPCD any location	-	0.12 (0.00, 4.59)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.02 (0.00, 1.28)
Versus pre-operative LMWH standard duration, low	Pre-operative LMWH standard duration, standard dose	0.51 (0.39, 0.66)	0.56 (0.28,1.05)
	AES above knee + UFH standard	-	0.09 (0.01, 0.41)
	Electrical stimulation	-	1.13 (0.26, 4.17)
	AES combination + IPCD full leg	-	0.24 (0.05, 0.98)

		Risk ratio	
dose	IPCD full leg	-	1.44 (0.18, 8.41)
	AES above knee + IPCD full leg	-	0.08 (0.00, 1.19)
	Pre-operative LMWH extended duration, standard dose	-	0.22 (0.04, 0.98)
	Fondaparinux standard	-	0.41 (0.10, 1.48)
	IPCD location un-defined	-	0.24 (0.01, 2.94)
	Fondaparinux standard + IPCD any location	-	0.07 (0.00, 1.54)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.01 (0.00, 0.48)
Versus pre-operative LMWH standard duration, standard dose	AES above knee + UFH standard	-	0.16 (0.02, 0.74)
	Electrical stimulation	-	1.99 (0.46, 8.11)
	AES combination + IPCD full leg	-	0.43 (0.09, 1.82)
	IPCD full leg	-	2.54 (0.32, 16.59)
	AES above knee + IPCD full leg	-	0.15 (0.00, 2.19)
	Pre-operative LMWH extended duration, standard dose	0.40 (0.18, 0.89)	0.39 (0.09, 1.51)
	Fondaparinux standard	0.72 (0.49, 1.06)	0.73 (0.21, 2.28)
	IPCD location un-defined	0.50 (0.05, 5.38)	0.44 (0.01, 5.03)
	Fondaparinux standard + IPCD any location	-	0.13 (0.00, 2.58)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.02 (0.00, 0.79)
Versus AES above knee + UFH standard duration	Electrical stimulation	-	12.82 (1.83, 112.70)
	AES combination + IPCD full leg	-	2.76 (0.37, 24.75)
	IPCD full leg	-	16.32 (1.43, 199.70)
	AES above knee + IPCD full leg	-	0.96 (0.02, 23.31)
	Pre-operative LMWH extended duration, standard dose	-	2.49 (0.29, 24.71)
	Fondaparinux standard	-	4.65 (0.65, 42.46)
	IPCD location un-defined	-	2.76 (0.06, 62.80)
	Fondaparinux standard + IPCD any location	-	0.83 (0.01, 28.66)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.16 (0.00, 8.15)
Versus electrical stimulation	AES combination + IPCD full leg	-	0.22 (0.04, 0.93)
	IPCD full leg	-	1.28 (0.13, 10.84)
	AES above knee + IPCD full leg	-	0.08 (0.00, 1.38)
	Pre-operative LMWH extended duration, standard dose	-	0.20 (0.02, 1.40)
	Fondaparinux standard	-	0.37 (0.06, 2.30)
	IPCD location un-defined	-	0.22 (0.01, 3.67)
	Fondaparinux standard + IPCD any location	-	0.06 (0.00, 1.83)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.01 (0.00, 0.55)
Versus AES combination +	IPCD full leg	-	5.85 (0.58, 56.54)
	AES above knee + IPCD full leg	-	0.35 (0.01, 6.88)

		Risk ratio	
IPCD full leg	Pre-operative LMWH extended duration, standard dose	-	0.90 (0.11, 7.21)
	Fondaparinux standard	-	1.69 (0.25, 11.55)
	IPCD location un-defined	-	1.00 (0.02, 19.07)
	Fondaparinux standard + IPCD any location	-	0.30 (0.01, 9.04)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.06 (0.00, 2.57)
Versus IPCD full leg	AES above knee + IPCD full leg	-	0.06 (0.00, 1.48)
	Pre-operative LMWH extended duration, standard dose	-	0.15 (0.01, 1.83)
	Fondaparinux standard	-	0.29 (0.03, 2.98)
	IPCD location un-defined	-	0.17 (0.00, 4.22)
	Fondaparinux standard + IPCD any location	-	0.05 (0.00, 1.96)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.01 (0.00, 0.56)
Versus AES above the knee + IPCD full leg	Pre-operative LMWH extended duration, standard dose	-	2.61 (0.12, 143.30)
	Fondaparinux standard	-	4.88 (0.25, 260.40)
	IPCD location un-defined	-	2.85 (0.04, 266.80)
	Fondaparinux standard + IPCD any location	-	0.87 (0.01, 106.20)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.17 (0.00, 28.67)
Versus pre-operative LMWH extended duration, standard dose	Fondaparinux standard	-	1.88 (0.30, 12.20)
	IPCD location un-defined	-	1.11 (0.03, 19.99)
	Fondaparinux standard + IPCD any location	-	0.33 (0.01, 9.53)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.06 (0.00, 2.69)
Versus fondaparinux standard duration	IPCD location un-defined	-	0.60 (0.02, 9.40)
	Fondaparinux standard + IPCD any location	-	0.18 (0.00, 4.57)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.03 (0.00, 1.31)
Versus IPCD location un-defined	Fondaparinux standard + IPCD any location	0.31 (0.14, 0.73)	0.31 (0.07, 1.23)
	IPCD undefined + Post-operative LMWH standard duration, standard dose	0.09 (0.02, 0.46)	0.06 (0.00, 0.42)
Versus fondaparinux standard duration + IPCD any location	IPCD undefined + Post-operative LMWH standard duration, standard dose	-	0.20 (0.01, 2.17)

Figure 840 shows the rank of each intervention compared to the others. The rank is based on the relative risk compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 22 different interventions being evaluated in comparison with no prophylaxis.

Figure 840: Rank order for interventions based the relative risk of experiencing DVT compared to baseline (no prophylaxis)



LD = low dose; SD = standard dose; HD = high dose; sd = standard duration; ed = extended duration

Goodness of fit and inconsistency

The random effects model used for the NMA is a relatively good fit, with a residual deviance of 101 reported. This corresponds fairly well to the total number of trial arms, 100. The between trial standard deviation in the random effects analysis was 0.57 (95% CI 0.23 to 0.96). On evaluating inconsistency by comparing risk ratios, the NMA estimated risk ratio for IPCD below the knee compared to UFH at a standard duration (1.46 [0.72, 3.01]) lay outside of the confidence interval of the risk ratio estimated for the direct comparison (0.42 [0.16, 1.15]). An inconsistency model was run and the DIC statistics were as follows in **Table 260**. The difference in the DIC is small (<3-5) with the consistency model having the lower DIC value. This suggests that it fits the data better than the inconsistency model.

Table 260: DIC for DVT (symptomatic and asymptomatic) – random effects

	DIC	TotResDev
Consistency model	530.880	101
Inconsistency model	532.606	100

M.3.3.2 Pulmonary embolism (PE)

Included studies

51 studies were identified as reporting on PE outcomes. After excluding papers that reported zero events in each arm and papers reporting on combinations that did not connect to any other

intervention in the network, 26 studies involving 13 treatments were included in the network for PE. The network can be seen in **Figure 841** and the trial data for each of the studies included in the NMA are presented in **Table 261**.

Figure 841: Network diagram for PE

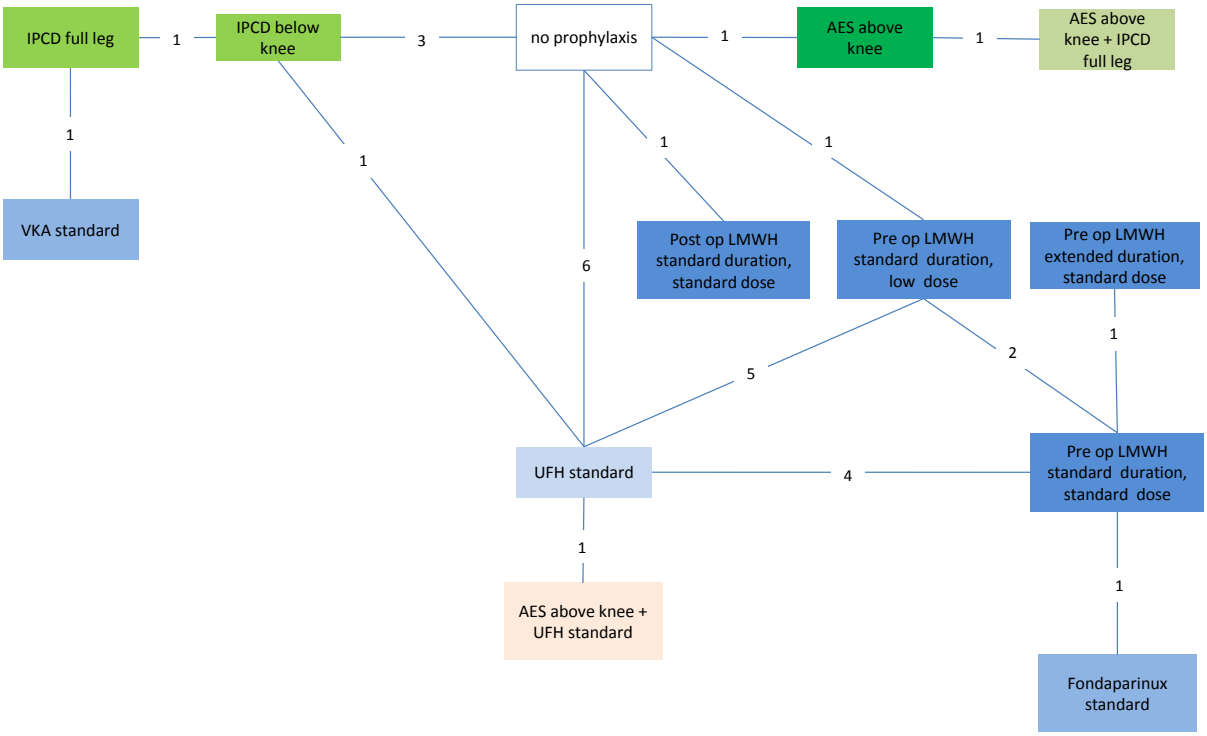


Table 261: Study data for PE network meta-analysis

Study	Intervention 1	Intervention 2	Intervention 3	Intervention 1		Intervention 2		Intervention 3	
				Events	N	Events	N	Events	N
Clarke-Pearson 1984A	no prophylaxis	IPCD below knee	NA	1	97	4	97	NA	NA
Clarke-Pearson 1984B	no prophylaxis	IPCD below knee	NA	1	52	2	55	NA	NA
Coe 1978	no prophylaxis	IPCD below knee	UFH standard	1	24	1	29	1	28
Gordon-Smith 1972	no prophylaxis	UFH standard	NA	0.5	51	2.5	49	NA	NA
Bejjani 1983	no prophylaxis	UFH standard	NA	1.5	18	0.5	18	NA	NA
Clarke-Pearson 1983	no prophylaxis	UFH standard	NA	0.5	98	4.5	89	NA	NA
Lahnborg 1975 + 1974	no prophylaxis	UFH standard	NA	24	54	9	58	NA	NA

Study	Intervention 1	Intervention 2	Intervention 3	Intervention 1		Intervention 2		Intervention 3	
Tongren 1978	no prophylaxis	UFH standard	NA	2	61	1	63	NA	NA
Bergqvist 1996	no prophylaxis	Post op LMWH standard standard	NA	1.5	42	0.5	40	NA	NA
Ockelford 1989	no prophylaxis	Pre op LMWH standard low	NA	2.5	89	0.5	96	NA	NA
Holford 1976	no prophylaxis	AES above knee	NA	1.5	48	0.5	49	NA	NA
Soderdahl 1997	IPCD below knee	IPCD full leg	NA	0.5	44	1.5	48	NA	NA
Borstad 1992	UFH standard	Pre op LMWH standard low	NA	0.5	71	1.5	72	NA	NA
Caen 1988	UFH standard	Pre op LMWH standard low	NA	1.5	191	0.5	196	NA	NA
Kakkar 1993	UFH standard	Pre op LMWH standard low	NA	11	1915	8	1894	NA	NA
Koller 1986	UFH standard	Pre op LMWH standard low	NA	1.5	73	0.5	75	NA	NA
Leizorovicz 1991	UFH standard	Pre op LMWH standard low	Pre op LMWH standard standard	2	429	4	431	1	430
Wille-Jorgensen 1985	UFH standard	AES above knee + UFH standard	NA	6	90	2	86	NA	NA
Bergqvist 1988	UFH standard	Pre op LMWH standard standard	NA	4.5	498	0.5	506	NA	NA
Fricker 1988	UFH standard	Pre op LMWH standard standard	NA	5.5	41	0.5	41	NA	NA
McLeod 2001	UFH standard	Pre op LMWH standard standard	NA	0.5	469	1.5	469	NA	NA
Bergqvist 1995	Pre op LMWH standard low	Pre op LMWH standard standard	NA	4	976	6	981	NA	NA
Caprini 1983	AES above knee	AES above knee + IPCD full leg	NA	1	39	1	38	NA	NA
Chandhoke 1992	IPCD full leg	VKA standard	NA	1.5	48	0.5	54	NA	NA
Bergqvist 2002	Pre op LMWH standard standard	Pre op LMWH extended standard	NA	2.5	168	0.5	166	NA	NA
Agnelli 2005	Pre op LMWH standard standard	Fondaparinux standard	NA	0.5	1463	2.5	1466	NA	NA

NMA results

Table 262 summarises the results of the conventional meta-analyses in terms of risk ratios generated from studies directly comparing different interventions, together with the results of the NMA in terms of risk ratios for every possible treatment comparison.

Table 262: Risk ratios for PE

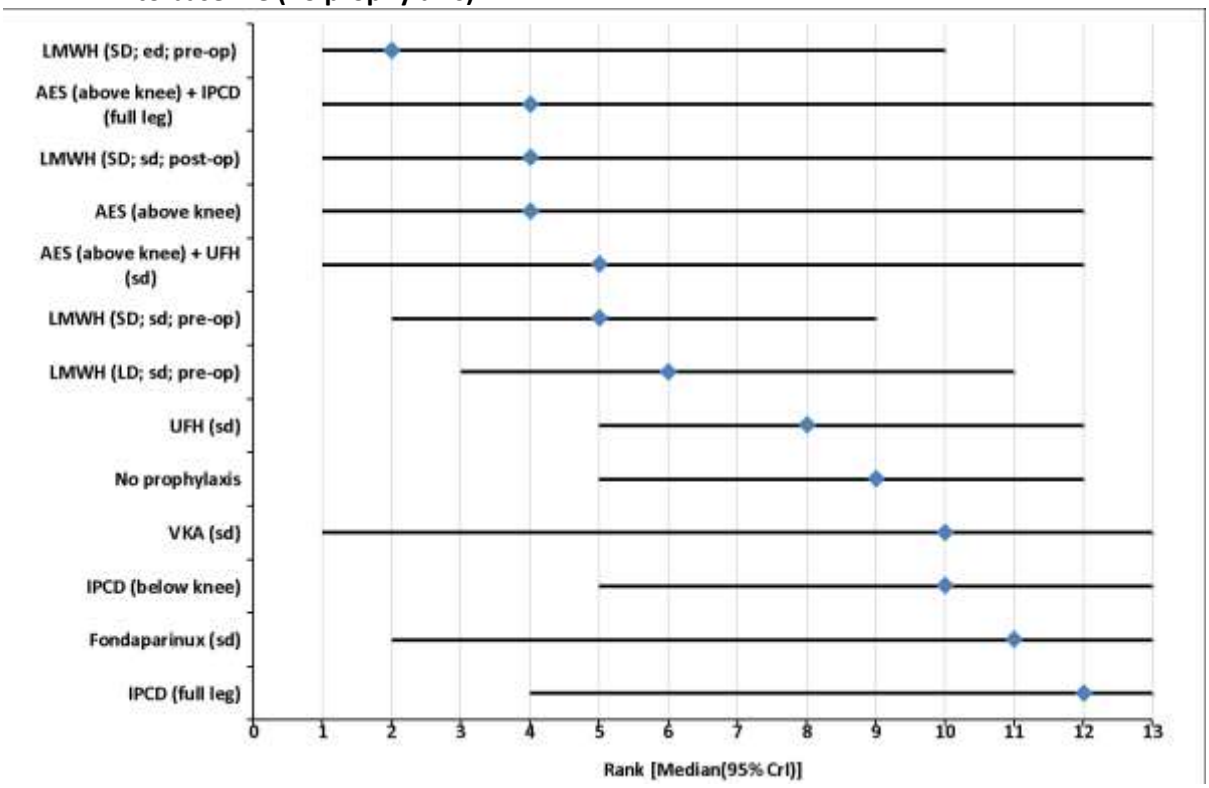
Comparisons		Risk ratio	
		Direct (mean with 95% confidence interval)	**NMA (median with 95% credible interval)**
Versus no prophylaxis	IPCD below the knee	2.19 (0.58, 8.24)	1.87 (0.34, 11.08)
	UFH standard duration	0.60 (0.36, (1.02)	0.81 (0.26, 2.75)
	Post-operative LMWH standard duration, standard dose	0.35 (0.01, 8.34)	0.20 (0.00, 8.38)
	Pre-operative LMWH standard duration, low dose	0.19 (0.01, 3.81)	0.50 (0.10, 2.32)
	AES above the knee	0.33 (0.01, 7.82)	0.20 (0.00, 8.23)
	IPCD full leg	-	5.32 (0.12, 238.70)
	AES above knee + UFH standard duration	-	0.24 (0.01, 4.41)
	Pre-operative LMWH standard duration, standard dose	-	0.29 (0.04, 1.70)
	AES above the knee + IPCD full leg	-	0.19 (0.00, 27.36)
	VKA standard duration	-	1.40 (0.00, 160.60)
	Pre-operative LMWH extended duration, standard dose	-	0.03 (0.00, 1.84)
	Fondaparinux standard duration	-	2.20 (0.04, 136.90)
Versus IPCD below the knee	UFH standard duration	1.04 (0.06, 17.00)	0.43 (0.06, 3.17)
	Post-operative LMWH standard duration, standard dose	-	0.10 (0.00, 6.18)
	Pre-operative LMWH standard duration, low dose	-	0.26 (0.03, 2.39)
	AES above the knee	-	0.10 (0.00, 6.02)
	IPCD full leg	2.75 (0.12, 65.76)	2.61 (0.09, 113.50)
	AES above knee + UFH standard duration	-	0.13 (0.00, 3.39)
	Pre-operative LMWH standard duration, standard dose	-	0.15 (0.01, 1.63)
	AES above the knee + IPCD full leg	-	0.10 (0.00, 18.30)
	VKA standard duration	-	0.81 (0.00, 74.14)
	Pre-operative LMWH extended duration, standard dose	-	0.01 (0.00, 1.31)
	Fondaparinux standard duration	-	1.21 (0.01, 93.75)
Versus UFH standard duration	Post-operative LMWH standard duration, standard dose	-	0.24 (0.00, 12.32)
	Pre-operative LMWH standard duration, low dose	0.88 (0.44, 1.78)	0.62 (0.17, 1.88)

		Risk ratio	
	AES above the knee	-	0.24 (0.00, 12.26)
	IPCD full leg	-	6.53 (0.13, 348.10)
	AES above knee + UFH standard duration	0.35 (0.07, 1.68)	0.31 (0.01, 3.98)
	Pre-operative LMWH standard duration, standard dose	0.24 (0.06, 0.93)	0.37 (0.07, 1.35)
	AES above the knee + IPCD full leg	-	0.24 (0.00, 39.87)
	VKA standard duration	-	1.66 (0.00, 226.70)
	Pre-operative LMWH extended duration, standard dose	-	0.04 (0.00, 1.85)
	Fondaparinux standard duration	-	2.63 (0.05, 167.50)
Versus post-operative LMWH standard duration, standard dose	Pre-operative LMWH standard duration, low dose	-	2.59 (0.04, 2169.00)
	AES above the knee	-	1.01 (0.00, 1859.00)
	IPCD full leg	-	30.87 (0.14, 52120.00)
	AES above knee + UFH standard duration	-	1.31 (0.01, 1562.00)
	Pre-operative LMWH standard duration, standard dose	-	1.54 (0.02, 1365.00)
	AES above the knee + IPCD full leg	-	1.06 (0.00, 3598.00)
	VKA standard duration	-	6.91 (0.00, 20470.00)
	Pre-operative LMWH extended duration, standard dose	-	0.16 (0.00, 316.50)
	Fondaparinux standard duration	-	12.75 (0.04, 23960.00)
Versus pre-operative LMWH standard duration, low dose	AES above the knee	-	0.40 (0.00, 24.51)
	IPCD full leg	-	10.89 (0.19, 678.30)
	AES above knee + UFH standard duration	-	0.50 (0.02, 9.11)
	Pre-operative LMWH standard duration, standard dose	0.87 (0.32, 2.40)	0.60 (0.12, 2.60)
	AES above the knee + IPCD full leg	-	0.39 (0.00, 77.56)
	VKA standard duration	-	2.60 (0.00, 435.90)
	Pre-operative LMWH extended duration, standard dose	-	0.06 (0.00, 3.30)
	Fondaparinux standard duration	-	4.27 (0.09, 313.00)
Versus AES above the knee	IPCD full leg	-	31.09 (0.14, 43070.00)
	AES above knee + UFH standard duration	-	1.28 (0.01, 1369.00)
	Pre-operative LMWH standard duration, standard dose	-	1.49 (0.02, 1131.00)
	AES above the knee + IPCD full leg	1.03 (0.07, 15.82)	1.05 (0.02. 45.55)

		Risk ratio	
	VKA standard duration	-	6.81 (0.00, 18380.00)
	Pre-operative LMWH extended duration, standard dose	-	0.16 (0.00, 279.10)
	Fondaparinux standard duration	-	12.43 (0.05, 21680.00)
Versus IPCD full leg	AES above knee + UFH standard duration	-	0.04 (0.00, 4.81)
	Pre-operative LMWH standard duration, standard dose	-	0.05 (0.00, 3.41)
	AES above the knee + IPCD full leg	-	0.03 (0.00, 16.57)
	VKA standard duration	0.30 (0.01, 7.10)	0.30 (0.00, 4.49)
	Pre-operative LMWH extended duration, standard dose	-	0.00 (0.00, 1.35)
	Fondaparinux standard duration	-	0.50 (0.00, 101.50)
Versus AES above the knee + UFH standard duration	Pre-operative LMWH standard duration, standard dose	-	1.20 (0.06, 31.58)
	AES above the knee + IPCD full leg	-	0.78 (0.00, 316.10)
	VKA standard duration	-	5.00 (0.00, 1871.00)
	Pre-operative LMWH extended duration, standard dose	-	0.12 (0.00, 17.72)
	Fondaparinux standard duration	-	8.99 (0.09, 1518.00)
Versus pre-operative LMWH standard duration, standard dose	AES above the knee + IPCD full leg	-	0.65 (0.00, 147.90)
	VKA standard duration	-	4.32 (0.00, 830.30)
	Pre-operative LMWH extended duration, standard dose	0.20 (0.01, 4.18)	0.11 (0.00, 4.23)
	Fondaparinux standard duration	4.99 (0.24, 103.84)	6.99 (0.22, 484.90)
Versus AES above the knee + IPCD full leg	VKA standard duration	-	6.39 (0.00, 46310.00)
	Pre-operative LMWH extended duration, standard dose	-	0.15 (0.00, 724.50)
	Fondaparinux standard duration	-	12.24 (0.02, 57240.00)
Versus VKA standard duration	Pre-operative LMWH extended duration, standard dose	-	0.02 (0.00, 121.10)
	Fondaparinux standard duration	-	1.55 (0.00, 9161.00)
Versus pre-operative LMWH extended duration, standard dose	Fondaparinux standard duration	-	80.07 (0.41, 134600.00)

Figure 842 shows the rank of each intervention compared to the others. The rank is based on the relative risk compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 13 different interventions being evaluated.

Figure 842: Rank order for interventions based the relative risk of experiencing PE compared to baseline (no prophylaxis)



LD = low dose; SD = standard dose; HD = high dose; sd = standard duration; ed = extended duration

Goodness of fit and inconsistency

The random effects model used for the NMA is a relatively good fit, with a residual deviance of 55 reported. This corresponds well to the total number of trial arms, 54. The between trial standard deviation in the random effects analysis was 1.01 (95% CI 0.30 to 2.11). No inconsistency was identified between the direct RR and NMA results. An inconsistency model was run and the DIC statistics were as follows in **Table 263**. The difference in the DIC is small (<3-5) with the consistency model having the lower DIC value. This suggests that it fits the data better than the inconsistency model.

Table 263: DIC for PE – random effects

	DIC	TotResDev
Consistency model	224.072	55
Inconsistency model	225.681	56

M.3.3.3 Major bleeding

Included studies

33 studies were identified as reporting on major bleeding outcomes. After excluding papers that reported zero events in each arm and papers reporting on combinations that did not connect to any other intervention in the network, 29 studies involving 8 treatments were included in the network for major bleeding. The network can be seen in **Figure 843** and the trial data for each of the studies included in the NMA are presented in **Table 264**.

Figure 843: Network diagram for major bleeding

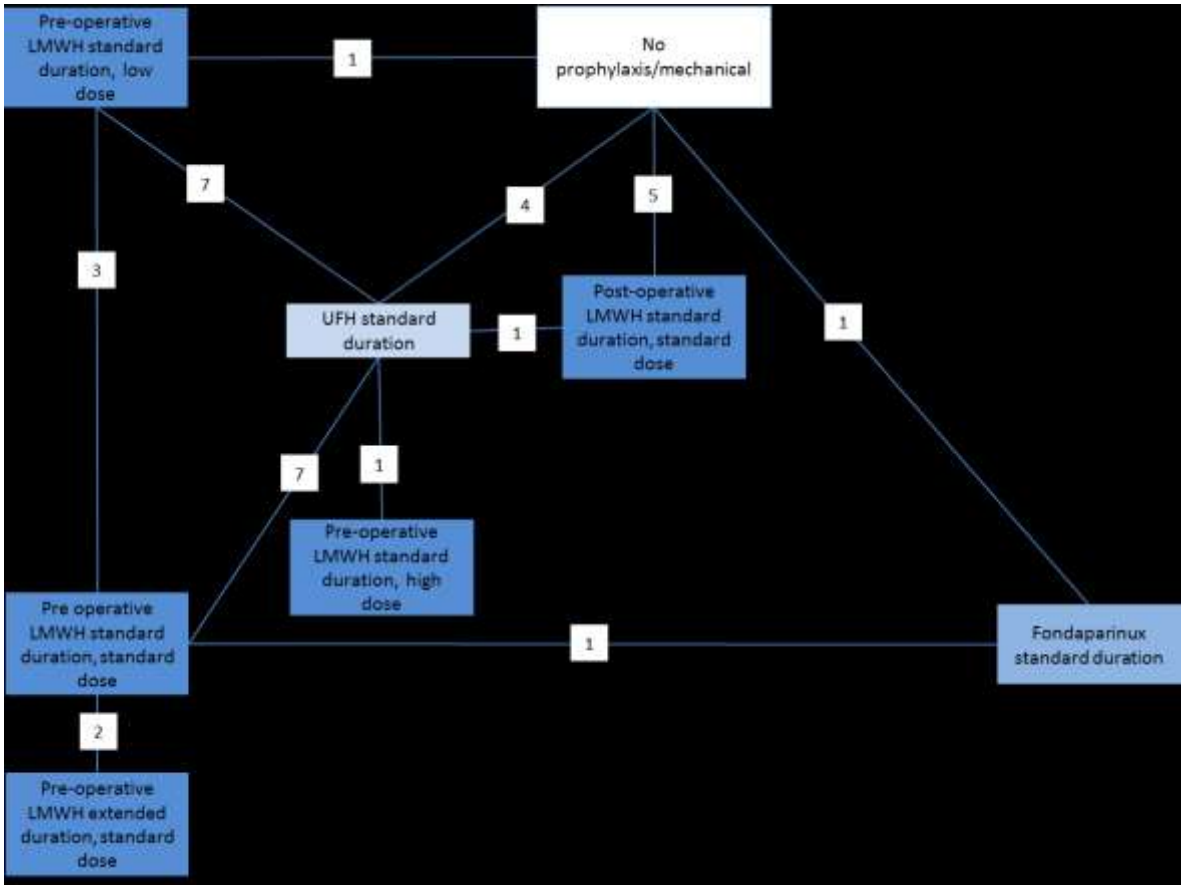


Table 264: Study data for major bleeding network meta-analysis

Study	Intervention 1	Intervention 2	Intervention 3	Intervention 1		Intervention 2		Intervention 3	
				Events	N	Events	N	Events	N
Ockelford 1989	no prophylaxis/mechanical	pre op LMWH standard duration, low dose	NA	4	88	4	95	NA	NA
Osman 2007	no prophylaxis/mechanical	UFH standard duration	Post op LMWH standard duration, standard dose	0	25	0	25	1	25
Allen 1978	no prophylaxis/mechanical	UFH standard duration	NA	0	30	6	30	NA	NA

Study	Intervention 1	Intervention 2	Intervention 3	Intervention 1		Intervention 2		Intervention 3	
Bejjani 1983	no prophylaxis/mechanical	UFH standard duration	NA	0	17	1	17	NA	NA
Tongren 1978	no prophylaxis/mechanical	UFH standard duration	NA	23	61	24	63	NA	NA
Bergqvist 1996	no prophylaxis/mechanical	Post op LMWH standard duration, standard dose	NA	0	41	1	39	NA	NA
Nagata 2015	no prophylaxis/mechanical	Post op LMWH standard duration, standard dose	NA	1	14	2	16	NA	NA
Sakon 2010	no prophylaxis/mechanical	Post op LMWH standard duration, standard dose	NA	1	38	5	109	NA	NA
Song 2014	no prophylaxis/mechanical	Post op LMWH standard duration, standard dose	NA	0	112	2	108	NA	NA
Turpie 2007	no prophylaxis/mechanical	Fondaparinux standard duration	NA	1	650	10	635	NA	NA
Borstad 1992	pre op LMWH standard duration, low dose	UFH standard duration	NA	14	71	9	70	NA	NA
Kaaja 1992	pre op LMWH standard duration, low dose	UFH standard duration	NA	0	37	6	31	NA	NA
Kakkar 1993	pre op LMWH standard duration, low dose	UFH standard duration	NA	69	1894	91	1915	NA	NA
Koller 1986B	pre op LMWH standard duration, low dose	UFH standard duration	NA	17	74	23	72	NA	NA
Leizorovicz 1991	pre op LMWH standard duration, low dose	UFH standard duration	pre op LMWH standard duration, standard dose	14	431	12	429	10	430
Hartl 1990	pre op LMWH standard duration, low dose	UFH standard duration	NA	2	112	15	115	NA	NA
Nurmohamed 1995	pre op LMWH standard duration, low dose	UFH standard duration	NA	11	725	18	719	NA	NA
Bergqvist	pre op LMWH standard	pre op LMWH standard duration,	NA	3	1034	13	1036	NA	NA

Study	Intervention 1	Intervention 2	Intervention 3	Intervention 1		Intervention 2		Intervention 3	
1995	duration, low dose	standard dose							
Hauch 1988	pre op LMWH standard duration, low dose	pre op LMWH standard duration, standard dose	NA	0	16	1	19	NA	NA
Bergqvist 1986	UFH standard duration	pre op LMWH standard duration, standard dose	NA	2	217	10	215	NA	NA
Borstad 1988	UFH standard duration	pre op LMWH standard duration, standard dose	NA	13	110	32	105	NA	NA
Fricker 1988	UFH standard duration	pre op LMWH standard duration, standard dose	NA	1	40	2	40	NA	NA
Gonzalez 1996	UFH standard duration	pre op LMWH standard duration, standard dose	NA	5	82	0	84	NA	NA
McLeod 2001	UFH standard duration	pre op LMWH standard duration, standard dose	NA	10	643	18	653	NA	NA
Onarheim 1986	UFH standard duration	pre op LMWH standard duration, standard dose	NA	1	27	1	25	NA	NA
Koller 1986 A	UFH standard duration	pre op LMWH standard duration, high dose	NA	1	20	6	23	NA	NA
Agnelli 2005	Fondaparinux standard duration	pre op LMWH standard duration, standard dose	NA	49	1433	34	1425	NA	NA
Bergqvist 2002	pre op LMWH standard duration, standard dose	pre op LMWH extended duration, standard dose	NA	1	248	3	253	NA	NA
Rasmussen 2006	pre op LMWH standard duration, standard dose	pre op LMWH extended duration, standard dose	NA	4	222	1	205	NA	NA

NMA results

Table 265 summarises the results of the conventional meta-analyses in terms of risk ratios generated from studies directly comparing different interventions, together with the results of the NMA in terms of risk ratios for every possible treatment comparison.

Table 265: Risk ratios for major bleeding

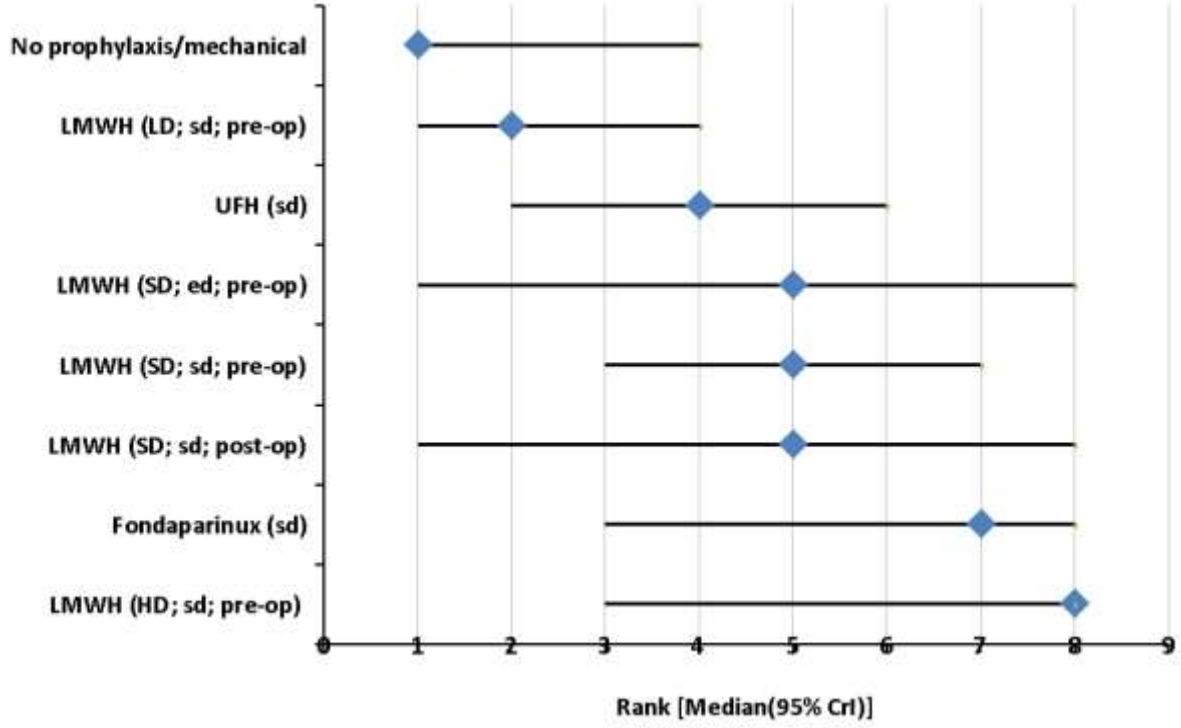
Comparisons	Risk ratio	
	Direct (mean with 95% confidence interval)	NMA (median with 95% credible interval)

		Risk ratio	
Versus no prophylaxis (or mechanical prophylaxis)	Pre-operative LMWH standard duration, low dose	0.93 (0.24, 3.59)	1.21 (0.41, 3.95)
	UFH standard duration	1.30 (0.84, 2.00)	2.01 (0.81, 6.52)
	Post-operative LMWH standard duration, standard dose	2.49 (0.78, 7.91)	2.98 (0.88, 14.80)
	Fondaparinux standard duration	10.24 (1.31, 79.73)	4.98 (1.05, 31.16)
	Pre-operative LMWH standard duration, standard dose	-	2.96 (1.00, 11.16)
	Pre-operative LMWH standard duration, high dose	-	11.26 (1.02, 349.30)
	Pre-operative LMWH extended duration, standard dose	-	2.39 (0.32, 22.51)
Versus pre-operative LMWH standard duration, low dose	UFH standard duration	1.36 (0.9, 2.05)	1.64 (0.94, 3.53)
	Post-operative LMWH standard duration, standard dose	-	2.35 (0.50, 16.10)
	Fondaparinux standard duration	-	4.01 (1.00, 24.20)
	Pre-operative LMWH standard duration, standard dose	1.73 (0.42, 7.19)	2.41 (1.02, 6.33)
	Pre-operative LMWH standard duration, high dose	-	8.95 (0.99, 265.00)
	Pre-operative LMWH extended duration, standard dose	-	1.92 (0.29, 15.24)
Versus UFH standard duration	Post-operative LMWH standard duration, standard dose	0.33 (0.01, 7.81)	1.40 (0.31, 8.28)
	Fondaparinux standard duration	-	2.36 (0.62, 12.34)
	Pre-operative LMWH standard duration, standard dose	1.67 (1.17, 2.39)	1.43 (0.74, 3.04)
	Pre-operative LMWH standard duration, high dose	5.22 (0.68, 39.74)	5.17 (0.64, 138.20)
	Pre-operative LMWH extended duration, standard dose	-	1.18 (0.17, 7.89)
Versus post-operative LMWH standard duration, standard dose	Fondaparinux standard duration	-	1.50 (0.24, 13.47)
	Pre-operative LMWH standard duration, standard dose	-	0.99 (0.17, 5.35)
	Pre-operative LMWH standard duration, high dose	-	3.32 (0.26, 122.30)
	Pre-operative LMWH extended duration, standard dose	-	0.89 (0.07, 8.93)
Versus fondaparinux standard duration	Pre-operative LMWH standard duration, standard dose	0.70 (0.45, 1.07)	0.63 (0.13, 2.18)
	Pre-operative LMWH standard duration, high dose	-	1.96 (0.16, 65.24)
	Pre-operative LMWH extended duration, standard dose	-	0.55 (0.05, 4.00)
Versus pre-operative LMWH standard duration,	Pre-operative LMWH standard duration, high dose	-	3.46 (0.39, 97.05)
	Pre-operative LMWH extended duration, standard dose	0.83 (0.22, 3.12)	0.90 (0.13, 4.66)

		Risk ratio	
standard dose			
Versus pre-operative LMWH standard duration, high dose	Pre-operative LMWH extended duration, standard dose	-	0.25 (0.01, 3.49)

Figure 844 shows the rank of each intervention compared to the others. The rank is based on the relative risk compared to baseline and indicates the probability of being the best treatment, second best, third best and so on among the 8 different interventions being evaluated.

Figure 844: Rank order for interventions based the relative risk of major bleeding compared to baseline (no prophylaxis/mechanical prophylaxis)



LD = low dose; SD = standard dose; HD = high dose; sd = standard duration

Goodness of fit and inconsistency

The random effects model used for the NMA is a relatively good fit, with a residual deviance of 59 reported. This corresponds fairly well to the total number of trial arms, 60. The between trial standard deviation in the random effects analysis was 0.82 (95% CI 0.40 to 1.44). On evaluating inconsistency by comparing risk ratios, the NMA estimated risk ratio for UFH at a standard duration compared to no prophylaxis (2.01 [0.81, 6.52]) lay outside of the confidence interval of the risk ratio estimated for the direct comparison (1.30 [0.84, 2.00]). Therefore an inconsistency model was run

and the DIC statistics were as follows in Table 266. The difference in the DIC is small (<3-5) which suggests that there is no obvious inconsistency in the network.

Table 266: DIC for major bleeding – random effects

	DIC	TotResDev
Consistency model	299.227	59
Inconsistency model	302.084	60

M.3.4 Discussion

Based on the results of conventional meta-analyses of direct evidence, as has been previously presented in Chapter 35 and appendix H, deciding upon the most clinical and cost effective prophylaxis intervention in patients undergoing abdominal surgery is challenging. In order to overcome the difficulty of interpreting the conclusions from numerous separate comparisons, network meta-analysis of the direct evidence was performed. The findings of the NMA were used to facilitate the committee in decision-making when developing recommendations.

Our analyses were divided into three critical outcomes. 48 studies informed the DVT network where 22 different individual or combination treatments were evaluated including 10 mechanical interventions, eight pharmacological interventions, and three interventions that combined both mechanical and pharmacological prophylaxis. 26 studies informed the PE network of 13 different treatments, including four mechanical interventions, seven pharmacological interventions, and one intervention that combined both mechanical and pharmacological prophylaxis. The major bleeding network included 29 studies evaluating eight treatments, seven of which were pharmacological as for this outcome any mechanical prophylaxis measures were combined with the no prophylaxis intervention as it is believed that mechanical prophylaxis has no associated bleeding risk.

In the DVT network, the three interventions that represented a combination of mechanical and pharmacological prophylaxis featured in the top four best ranked treatments. IPCD (undefined location) plus post-operative LMWH at a standard duration and standard dose was ranked first, IPCD (any location) plus fondaparinux for a standard duration was ranked second, and AES above the knee plus unfractionated heparin for a standard duration was ranked fourth. The treatment in the third spot was a combination of two forms of mechanical prophylaxis (AES above the knee plus IPCD full leg). There is considerable uncertainty about these estimates as the credible intervals are quite wide (with the top intervention spanning nine ranking positions, and the second and third spanning 19 and 18 respectively).

In the PE network the only combination intervention evaluated (AES above the knee plus unfractionated heparin standard duration) came in fifth, and was outranked by pre-operative LMWH extended duration and standard dose, AES above the knee plus IPCD full leg, post-operative LMWH standard duration and standard dose, and AES above the knee alone. However the credible intervals were very wide, with the top ranked treatment spanning 10 rankings, the second and third treatments spanning all 13 rankings, and the fourth and fifth treatments spanning 12 rankings.

In the major bleeding network the highest ranked intervention was no prophylaxis/mechanical prophylaxis. This was followed by the low dose of pre-operative LMWH for a standard duration (with a credible interval spanning four ranking positions). This was followed by unfractionated heparin for a standard duration, then the three standard doses of LMWH preoperatively for either an extended or standard duration, or post-operatively for a standard duration. Fondaparinux for a standard duration came in seventh, and last was the high dose of pre-operative LMWH for a standard duration.

In summary, the three outcomes chosen for analyses were considered to be among the most critical for assessing clinical effectiveness of different VTE prophylaxis strategies. All three networks seemed to fit well, as demonstrated by residual deviance and no obvious inconsistency found in the networks. However the credible intervals around the ranking of treatments in all three networks were wide suggesting considerable uncertainty about these results.

M.3.5 Conclusion

This analysis allowed us to combine findings from many different comparisons presented in the review even when direct comparative data was lacking.

Overall the committee agreed that the results for the three networks were not conclusive. It was acknowledged that a combination of mechanical and pharmacological prophylaxis were likely to be the most effective prophylaxis and therefore may be appropriate to offer those people undergoing abdominal surgery who have been assessed as having a low risk of bleeding. For details of the rationale and discussion leading to recommendations, please refer to the section linking the evidence to the recommendations (section 35.6, chapter 35).

M.3.6 WinBUGS code

M.3.6.1 WinBUGS code for assessment of baseline risk of DVT

```
# Binomial likelihood, logit link
# Baseline random effects model
model{                    # *** PROGRAM STARTS
for (i in 1:ns){            # LOOP THROUGH STUDIES
   r[i] ~ dbin(p[i],n[i])                  # Likelihood
   logit(p[i]) <- mu[i]                              # Log-odds of response
   mu[i] ~ dnorm(m,tau.m)     # Random effects model
 }
mu.new ~ dnorm(m,tau.m)              # predictive dist. (log-odds)
m ~ dnorm(0,.0001)            # vague prior for mean
var.m <- 1/tau.m              # between-trial variance
tau.m <- pow(sd.m,-2)   # between-trial precision = (1/between-trial variance)
sd.m ~ dunif(0,5)             # vague prior for between-trial SD
#tau.m ~ dgamma(0.001,0.001)
#sd.m <- sqrt(var.m)
logit(R) <- m                 # posterior probability of response
logit(R.new) <- mu.new        # predictive probability of response
}
```

Data

list(ns=22) # ns=number of studies

r[]	n[]

6	24

11	48

14	51

11	97

4	118

12	412

21	50

17	39

10	50

20	61

13	33

4	57

11	97

17	52

37	103

6	44

23	47

4	92

15	33

11	31

9	41

14	88

END

Inits

list(mu=c(0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0), sd.m=1, m=0)

list(mu = c(-1,-1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1), sd.m=2, m= -1)

list(mu = c(1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,1,1,1,1, 1,1), sd.m = 0.5, m = 1)

M.3.6.2 WinBUGS code for number of patients with DVT

```
#Random effects model for multi-arm trials (any number of arms)
model{
for(i in 1:NS){
  w[i,1] <-0
  delta[i,t[i,1]]<-0
  mu[i] ~ dnorm(0,.0001) # vague priors for trial baselines
  for (k in 1:na[i]){
    r[i,k] ~ dbin(p[i,t[i,k]],n[i,k]) # binomial likelihood
    logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]  # model
#Deviance residuals for data i
  rhat[i,k] <- p[i,t[i,k]] * n[i,k]                                    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
   }
  sdev[i]<- sum(dev[i,1:na[i]])
  for (k in 2:na[i]){
# trial-specific LOR distributions
    delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])
    md[i,t[i,k]] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions
    taud[i,t[i,k]] <- tau *2*(k-1)/k     #precision of LOR distributions
#adjustment, multi-arm RCTs
    w[i,k] <- (delta[i,t[i,k]]  - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
    sw[i,k] <-sum(w[i,1:k-1])/(k-1)
   }
 }
d[1]<-0
for (k in 2:NT){d[k] ~ dnorm(0,.0001) } # vague priors for basic parameters
sd ~ dunif(0,5)        # vague prior for random effects standard deviation
tau <- 1/pow(sd,2)

A ~ dnorm(meanA, precA)  # A is on log-odds scale
```

```
precA <- pow(sdA,-2)    # turn st dev into precision


for (k in 1:NT){        # v[1] will give prob of event on treat 1
  logit(v[k]) <- A + d[k]
  rr[k] <- v[k]/v[1]    # calculate relative risk
 }
sumdev <- sum(sdev[])   # Calculate residual deviance
# Ranking and prob{treatment k is best}
for (k in 1:NT){
  rk[k] <- rank(rr[],k)
  best[k] <- equals(rank(rr[],k),1)
 }
# pairwise ORs and RRs
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]
    lrr[c,k] <- log(rr[k]) - log(rr[c])
    log(rrisk[c,k]) <- lrr[c,k]
   }
 }
}


# NT=no. treatments, NS=no. studies;
# NB : set up M vectors each r[,]. n[,] and t[,],  where M is the Maximum number of treatments
#         per trial in the dataset. In this dataset M is 3.


list(NS=48, NT=22, meanA=-1.371, sdA=1.105)


r[,1]     n[,1]     r[,2]     n[,2]     r[,3]     n[,3]     t[,1]      t[,2]      t[,3]     na[]
6         24        6         28        2         29        1         2         3         3
11        48        3         49        3         48        1         2         4         3
```

14	51	6	46	NA	NA	1	2	NA	2
11	97	11	88	NA	NA	1	2	NA	2
4	118	1	108	NA	NA	1	2	NA	2
12	412	4	408	NA	NA	1	2	NA	2
21	50	4	48	NA	NA	1	2	NA	2
17	39	3	39	NA	NA	1	2	NA	2
10	50	3	50	NA	NA	1	2	NA	2
20	61	10	63	NA	NA	1	2	NA	2
13	33	3	31	NA	NA	1	2	NA	2
4	57	6	62	NA	NA	1	3	NA	2
11	97	14	97	NA	NA	1	3	NA	2
17	52	5	55	NA	NA	1	3	NA	2
37	103	15	97	NA	NA	1	5	NA	2
6	44	2	51	NA	NA	1	6	NA	2
23	47	11	48	NA	NA	1	7	NA	2
4.5	93	0.5	105	NA	NA	1	7	NA	2
15	33	6	33	NA	NA	1	8	NA	2
11	31	2	30	NA	NA	1	9	NA	2
9	41	3	39	NA	NA	1	10	NA	2
14	88	4	95	NA	NA	1	11	NA	2
6	107	3	101	NA	NA	2	3	NA	2
1	50	9	50	NA	NA	2	4	NA	2
7	429	16	431	7	430	2	11	12	3
7	190	6	195	NA	NA	2	11	NA	2
5	115	5	112	NA	NA	2	11	NA	2
1	72	2	74	NA	NA	2	11	NA	2
8	709	25	718	NA	NA	2	11	NA	2
41	497	28	505	NA	NA	2	12	NA	2
0.5	28	1.5	26	NA	NA	2	12	NA	2
9	217	13	215	NA	NA	2	12	NA	2
12	81	2	79	NA	NA	2	13	NA	2
7	90	1	86	NA	NA	2	13	NA	2

7	50	12	50	3	50	2	14	15	3
1.5	44	0.5	48	NA	NA	3	16	NA	2
0.5	54	2.5	48	NA	NA	4	16	NA	2
14	56	5	52	NA	NA	5	15	NA	2
1	58	3	56	NA	NA	6	7	NA	2
5	39	1	38	NA	NA	7	17	NA	2
2.5	17	0.5	20	NA	NA	11	12	NA	2
124	976	65	981	NA	NA	11	12	NA	2
20	167	8	165	NA	NA	12	18	NA	2
59	1018	43	1024	NA	NA	12	19	NA	2
2	105	1	106	NA	NA	12	20	NA	2
22	418	7	424	NA	NA	20	21	NA	2
6	31	1	78	NA	NA	20	22	NA	2
3.5	113	0.5	109	NA	NA	20	22	NA	2

END

Inits

#chain 1

list(

d=c(NA,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0), # one for each treatment

sd=1,

mu=c(3,2,-3,1,0,3,-2,-1,2,-2, -1,3,1,3,-2,-1,2,-2,3,-1, 1,-1,-2,-3,-1,-3,0,2,-1,-3, -2,1,1,3,-1,1,-2,-1,3,-2, -2,-3,1,-2,0,0,2,2))

#chain 2

list(

d=c(NA,-3,1,-1,-3, -1,-3,1,-1,-3, 1,-1,-2,-3,-1, -2,-1,2,-2,3, 0,0), # one for each treatment

sd=0.1,

mu=c(3,2,-3,1,0,3,-2,-1,2,-2, -1,3,1,3,-2,-1,2,-2,3,-1, 1,-1,-2,-3,-1,-3,0,2,-1,-3, -2,1,1,3,-1,1,-2,-1,3,-2, -2,-3,1,-2,0,0,3,-2))

#chain 3

list(

```
d=c(NA,0,1,1,0,  0,0,0,1,2,  3,4,2,0,0,  -2,-1,2,-2,3,  0,0), # one for each treatment
sd=2,
mu=c(3,2,-3,1,0,3,-2,-1,2,-2,  -1,3,1,3,-2,-1,2,-2,3,-1,  1,-1,-2,-3,-1,-3,0,2,-1,-3,  -2,1,1,3,-1,1,-2,-1,3,-2,  -2,-3,1,-2,0,0,1,-1) )
```

M.3.6.3 WinBUGS code for inconsistency model for number of patients with DVT

```
# Binomial likelihood, logit link, inconsistency model
# Random effects model
model{                  # *** PROGRAM STARTS
for(i in 1:ns){          # LOOP THROUGH STUDIES
   delta[i,1]<-0         # treatment effect is zero in control arm
   mu[i] ~ dnorm(0,.0001)  # vague priors for trial baselines
   for (k in 1:na[i])  {   # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
        +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
     }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {  # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
     }
 }
totresdev <- sum(resdev[])   # Total Residual Deviance
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
   for (k in (c+1):nt)  { d[c,k] ~ dnorm(0,.0001) }
 }
```

```
sd ~ dunif(0,5)  # vague prior for between-trial standard deviation
var <- pow(sd,2) # between-trial variance
tau <- 1/var     # between-trial precision
} # *** PROGRAM ENDS

 Data
# DVT
# nt=no. treatments, ns=no. studies
list(nt=22,ns=48)
```

r[,1]	n[,1]	r[,2]	n[,2]	r[,3]	n[,3]	t[,1]	t[,2]	t[,3]	na[]
6	24	6	28	2	29	1	2	3	3
11	48	3	49	3	48	1	2	4	3
14	51	6	46	NA	NA	1	2	NA	2
11	97	11	88	NA	NA	1	2	NA	2
4	118	1	108	NA	NA	1	2	NA	2
12	412	4	408	NA	NA	1	2	NA	2
21	50	4	48	NA	NA	1	2	NA	2
17	39	3	39	NA	NA	1	2	NA	2
10	50	3	50	NA	NA	1	2	NA	2
20	61	10	63	NA	NA	1	2	NA	2
13	33	3	31	NA	NA	1	2	NA	2
4	57	6	62	NA	NA	1	3	NA	2
11	97	14	97	NA	NA	1	3	NA	2
17	52	5	55	NA	NA	1	3	NA	2
37	103	15	97	NA	NA	1	5	NA	2
6	44	2	51	NA	NA	1	6	NA	2
23	47	11	48	NA	NA	1	7	NA	2
4.5	93	0.5	105	NA	NA	1	7	NA	2
15	33	6	33	NA	NA	1	8	NA	2
11	31	2	30	NA	NA	1	9	NA	2
9	41	3	39	NA	NA	1	10	NA	2

14	88	4	95	NA	NA	1	11	NA	2
6	107	3	101	NA	NA	2	3	NA	2
1	50	9	50	NA	NA	2	4	NA	2
7	429	16	431	7	430	2	11	12	3
7	190	6	195	NA	NA	2	11	NA	2
5	115	5	112	NA	NA	2	11	NA	2
1	72	2	74	NA	NA	2	11	NA	2
8	709	25	718	NA	NA	2	11	NA	2
41	497	28	505	NA	NA	2	12	NA	2
0.5	28	1.5	26	NA	NA	2	12	NA	2
9	217	13	215	NA	NA	2	12	NA	2
12	81	2	79	NA	NA	2	13	NA	2
7	90	1	86	NA	NA	2	13	NA	2
7	50	12	50	3	50	2	14	15	3
1.5	44	0.5	48	NA	NA	3	16	NA	2
0.5	54	2.5	48	NA	NA	4	16	NA	2
14	56	5	52	NA	NA	5	15	NA	2
1	58	3	56	NA	NA	6	7	NA	2
5	39	1	38	NA	NA	7	17	NA	2
2.5	17	0.5	20	NA	NA	11	12	NA	2
124	976	65	981	NA	NA	11	12	NA	2
20	167	8	165	NA	NA	12	18	NA	2
59	1018	43	1024	NA	NA	12	19	NA	2
2	105	1	106	NA	NA	12	20	NA	2
22	418	7	424	NA	NA	20	21	NA	2
6	31	1	78	NA	NA	20	22	NA	2
3.5	113	0.5	109	NA	NA	20	22	NA	2

END

INITS

#chain 1

list(sd=1, mu=c(2,0,3,0,2, -2,2,-2,-1,3, 2,-2,1,3,1, 1,2,-3,2,-2, -2,1,0,-3,3, 0,-3,-2,-3,-2, 3,-3,0,-1,-3, 2,1,3,-2,2, 2,0,1,2,0, 0,-2,0))

chain 2

list(sd=1.5, mu=c(2,1,3,1,2, 0,2,0,-1,3, 2,0,1,3,1, 1,2,-3,2,0, 0,1,1,-3,3, 1,-3,0,-3,0, 3,-3,1,-1,-3, 2,1,3,0,2, 2,1,1,2,1, 1,0,1))

chain 3

list(sd=3, mu=c(2,0.5,3,0.5,2, -2,2,1,-1,3, 2,1,1,3,1, 1,2,-3,2,1, 1,1,0.5,-3,3, 0.5,-3,1,-3,1, 3,-3,0.5,-1,-3, 2,1,3,1,2, 2,0.5,1,2,0.5, 0.5,0,1))

M.3.6.4 WinBUGS code for assessment of baseline risk of PE

```
# Binomial likelihood, logit link

# Baseline random effects model

model{                    # *** PROGRAM STARTS

for (i in 1:ns){          # LOOP THROUGH STUDIES

   r[i] ~ dbin(p[i],n[i])              # Likelihood

   logit(p[i]) <- mu[i]                        # Log-odds of response

   mu[i] ~ dnorm(m,tau.m)     # Random effects model

 }

mu.new ~ dnorm(m,tau.m)           # predictive dist. (log-odds)

m ~ dnorm(0,.0001)          # vague prior for mean

var.m <- 1/tau.m            # between-trial variance

tau.m <- pow(sd.m,-2)   # between-trial precision = (1/between-trial variance)

sd.m ~ dunif(0,5)           # vague prior for between-trial SD

#tau.m ~ dgamma(0.001,0.001)

#sd.m <- sqrt(var.m)

logit(R) <- m               # posterior probability of response

logit(R.new) <- mu.new      # predictive probability of response

}

Data

list(ns=11)  # ns=number of studies

r[]      n[]

1        97

1        52
```

```
1	24
0	50
1	17
0	97
24	54
2	61
1	41
2	88
1	47
END
 Inits
list(mu=c(0,0,0,0,0,   0,0,0,0,0,   0), sd.m=1, m=0)
list(mu = c(-1,-1,-1,-1,-1,   -1,-1,-1,-1,-1,   -1), sd.m=2, m= -1)
list(mu = c(1,1,1,1,1,   1,1,1,1,1,   1), sd.m = 0.5, m = 1)
```

M.3.6.5 WinBUGS code for number of patients with PE

```
#Random effects model for multi-arm trials (any number of arms)
model{
for(i in 1:NS){
  w[i,1] <-0
  delta[i,t[i,1]]<-0
  mu[i] ~ dnorm(0,.0001) # vague priors for trial baselines
  for (k in 1:na[i]){
    r[i,k] ~ dbin(p[i,t[i,k]],n[i,k]) # binomial likelihood
    logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]  # model
#Deviance residuals for data i
  rhat[i,k] <- p[i,t[i,k]] * n[i,k]                                    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
   }
  sdev[i]<- sum(dev[i,1:na[i]])
  for (k in 2:na[i]){
# trial-specific LOR distributions
    delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])
```

```
   md[i,t[i,k]] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions
   taud[i,t[i,k]] <- tau *2*(k-1)/k     #precision of LOR distributions
#adjustment, multi-arm RCTs
   w[i,k] <- (delta[i,t[i,k]]  - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
   sw[i,k] <-sum(w[i,1:k-1])/(k-1)
  }
 }
d[1]<-0
for (k in 2:NT){d[k] ~ dnorm(0,.0001) } # vague priors for basic parameters
sd ~ dunif(0,5)       # vague prior for random effects standard deviation
tau <- 1/pow(sd,2)

A ~ dnorm(meanA, precA)  # A is on log-odds scale
precA <- pow(sdA,-2)     # turn st dev into precision

for (k in 1:NT){        # v[1] will give prob of event on treat 1
  logit(v[k]) <- A + d[k]
  rr[k] <- v[k]/v[1]     # calculate relative risk
 }
sumdev <- sum(sdev[])    # Calculate residual deviance
# Ranking and prob{treatment k is best}
for (k in 1:NT){
  rk[k] <- rank(rr[],k)
  best[k] <- equals(rank(rr[],k),1)
 }
# pairwise ORs and RRs
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]
    lrr[c,k] <- log(rr[k]) - log(rr[c])
```

```
   log(rrisk[c,k]) <- lrr[c,k]
  }
 }
}
```

Data

```
# NT=no. treatments, NS=no. studies;
# NB : set up M vectors each r[,]. n[,] and t[,],  where M is the Maximum number of treatments
#        per trial in the dataset. In this dataset M is 3.
list(NS=26, NT=13, meanA=-3.939, sdA=2.201)
```

r[,1]	n[,1]	r[,2]	n[,2]	r[,3]	n[,3]	t[,1]	t[,2]	t[,3]	na[]
1	97	4	97	NA	NA	1	2	NA	2
1	52	2	55	NA	NA	1	2	NA	2
1	24	1	29	1	28	1	2	3	3
0.5	51	2.5	49	NA	NA	1	3	NA	2
1.5	18	0.5	18	NA	NA	1	3	NA	2
0.5	98	4.5	89	NA	NA	1	3	NA	2
24	54	9	58	NA	NA	1	3	NA	2
2	61	1	63	NA	NA	1	3	NA	2
1.5	42	0.5	40	NA	NA	1	4	NA	2
2.5	89	0.5	96	NA	NA	1	5	NA	2
1.5	48	0.5	49	NA	NA	1	6	NA	2
0.5	44	1.5	48	NA	NA	2	7	NA	2
0.5	71	1.5	72	NA	NA	3	5	NA	2
1.5	191	0.5	196	NA	NA	3	5	NA	2
11	1915	8	1894	NA	NA	3	5	NA	2
1.5	73	0.5	75	NA	NA	3	5	NA	2
2	429	4	431	1	430	3	5	9	3
6	90	2	86	NA	NA	3	8	NA	2
4.5	498	0.5	506	NA	NA	3	9	NA	2
5.5	41	0.5	41	NA	NA	3	9	NA	2
0.5	469	1.5	469	NA	NA	3	9	NA	2
4	976	6	981	NA	NA	5	9	NA	2

1	39	1	38	NA	NA	6	10	NA	2
1.5	48	0.5	54	NA	NA	7	11	NA	2
2.5	168	0.5	166	NA	NA	9	12	NA	2
0.5	1463	2.5	1466	NA	NA	9	13	NA	2

END

Inits

#chain 1

list(

d=c(NA,0,0,0,0, 0,0,0,0,0, 0,0,0), # one for each treatment

sd=1,

mu=c(3,2,-3,1,0,3,-2,-1,2,-2, -1,3,1,3,-2,-1,2,-2,3,-1, 1,-1,-2,-3,-1,-3))

#chain 2

list(

d=c(NA,-3,1,-1,-3, -1,-3,1,-1,-3, 1,-1,-2), # one for each treatment

sd=0.1,

mu=c(3,2,-3,1,0,3,-2,-1,2,-2, -1,3,1,3,-2,-1,2,-2,3,-1, 1,-1,-2,-3,-1,-3))

#chain 3

list(

d=c(NA,0,1,1,0, 0,0,0,1,2, 3,4,2), # one for each treatment

sd=2,

mu=c(3,2,-3,1,0,3,-2,-1,2,-2, -1,3,1,3,-2,-1,2,-2,3,-1, 1,-1,-2,-3,-1,-3))

M.3.6.6 WinBUGS code for inconsistency model for number of patients with PE

```
# Binomial likelihood, logit link, inconsistency model
# Random effects model
model{                  # *** PROGRAM STARTS
for(i in 1:ns){          # LOOP THROUGH STUDIES
   delta[i,1]<-0         # treatment effect is zero in control arm
   mu[i] ~ dnorm(0,.0001)  # vague priors for trial baselines
   for (k in 1:na[i])  {   # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
```

```
      logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
        +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
    }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {  # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
    }
 }
totresdev <- sum(resdev[])   # Total Residual Deviance
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
   for (k in (c+1):nt)  { d[c,k] ~ dnorm(0,.0001) }
 }
sd ~ dunif(0,5)  # vague prior for between-trial standard deviation
var <- pow(sd,2) # between-trial variance
tau <- 1/var     # between-trial precision
} # *** PROGRAM ENDS
```

Data

```
# DVT
# nt=no. treatments, ns=no. studies
list(nt=13,ns=26)
```

r[,1]	n[,1]	r[,2]	n[,2]	r[,3]	n[,3]	t[,1]	t[,2]	t[,3]	na[]
1	97	4	97	NA	NA	1	2	NA	2
1	52	2	55	NA	NA	1	2	NA	2
1	24	1	29	1	28	1	2	3	3
0.5	51	2.5	49	NA	NA	1	3	NA	2
1.5	18	0.5	18	NA	NA	1	3	NA	2

0.5	98	4.5	89	NA	NA	1	3	NA	2
24	54	9	58	NA	NA	1	3	NA	2
2	61	1	63	NA	NA	1	3	NA	2
1.5	42	0.5	40	NA	NA	1	4	NA	2
2.5	89	0.5	96	NA	NA	1	5	NA	2
1.5	48	0.5	49	NA	NA	1	6	NA	2
0.5	44	1.5	48	NA	NA	2	7	NA	2
0.5	71	1.5	72	NA	NA	3	5	NA	2
1.5	191	0.5	196	NA	NA	3	5	NA	2
11	1915	8	1894	NA	NA	3	5	NA	2
1.5	73	0.5	75	NA	NA	3	5	NA	2
2	429	4	431	1	430	3	5	9	3
6	90	2	86	NA	NA	3	8	NA	2
4.5	498	0.5	506	NA	NA	3	9	NA	2
5.5	41	0.5	41	NA	NA	3	9	NA	2
0.5	469	1.5	469	NA	NA	3	9	NA	2
4	976	6	981	NA	NA	5	9	NA	2
1	39	1	38	NA	NA	6	10	NA	2
1.5	48	0.5	54	NA	NA	7	11	NA	2
2.5	168	0.5	166	NA	NA	9	12	NA	2
0.5	1463	2.5	1466	NA	NA	9	13	NA	2

END

INITS

#chain 1

list(sd=1, mu=c(2,0,3,0,2, -2,2,-2,-1,3, 2,-2,1,3,1, 1,2,-3,2,-2, -2,1,0,-3,3, 0))

chain 2

list(sd=1.5, mu=c(2,1,3,1,2, 0,2,0,-1,3, 2,0,1,3,1, 1,2,-3,2,0, 0,1,1,-3,3, 1))

chain 3

list(sd=3, mu=c(2,0.5,3,0.5,2, -2,2,1,-1,3, 2,1,1,3,1, 1,2,-3,2,1, 1,1,0.5,-3,3, 0.5))

M.3.6.7 WinBUGS code for assessment of baseline risk of major bleeding

```
# Binomial likelihood, logit link
# Baseline random effects model
model{                    # *** PROGRAM STARTS
for (i in 1:ns){          # LOOP THROUGH STUDIES
   r[i] ~ dbin(p[i],n[i])              # Likelihood
   logit(p[i]) <- mu[i]                        # Log-odds of response
   mu[i] ~ dnorm(m,tau.m)     # Random effects model
 }
mu.new ~ dnorm(m,tau.m)           # predictive dist. (log-odds)
m ~ dnorm(0,.0001)          # vague prior for mean
var.m <- 1/tau.m            # between-trial variance
tau.m <- pow(sd.m,-2)   # between-trial precision = (1/between-trial variance)
sd.m ~ dunif(0,5)           # vague prior for between-trial SD
#tau.m ~ dgamma(0.001,0.001)
#sd.m <- sqrt(var.m)
logit(R) <- m               # posterior probability of response
logit(R.new) <- mu.new      # predictive probability of response
}
 Data

list(ns=10)  # ns=number of studies
r[]     n[]
4       88
0       25
0       30
0       17
23      61
0       41
1       14
1       38
0       112
```

```
1          650

END

 Inits

list(mu=c(0,0,0,0,0,   0,0,0,0,0), sd.m=1, m=0)

list(mu = c(-1,-1,-1,-1,-1,   -1,-1,-1,-1,-1), sd.m=2, m= -1)

list(mu = c(1,1,1,1,1,   1,1,1,1,1), sd.m = 0.5, m = 1)
```

M.3.6.8 WinBUGS code for number of patients with major bleeding

```
#Random effects model for multi-arm trials (any number of arms)

model{

for(i in 1:NS){

  w[i,1] <-0

  delta[i,t[i,1]]<-0

  mu[i] ~ dnorm(0,.0001) # vague priors for trial baselines

  for (k in 1:na[i]){

    r[i,k] ~ dbin(p[i,t[i,k]],n[i,k]) # binomial likelihood

    logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]  # model

#Deviance residuals for data i

  rhat[i,k] <- p[i,t[i,k]] * n[i,k]                                    dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))

   }

  sdev[i]<- sum(dev[i,1:na[i]])

  for (k in 2:na[i]){

# trial-specific LOR distributions

    delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])

    md[i,t[i,k]] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions

    taud[i,t[i,k]] <- tau *2*(k-1)/k     #precision of LOR distributions

#adjustment, multi-arm RCTs

    w[i,k] <- (delta[i,t[i,k]]  - d[t[i,k]] + d[t[i,1]])

# cumulative adjustment for multi-arm trials

    sw[i,k] <-sum(w[i,1:k-1])/(k-1)

   }

 }
```

```
d[1]<-0
for (k in 2:NT){d[k] ~ dnorm(0,.0001) } # vague priors for basic parameters
sd ~ dunif(0,5)       # vague prior for random effects standard deviation
tau <- 1/pow(sd,2)

A ~ dnorm(meanA, precA)  # A is on log-odds scale
precA <- pow(sdA,-2)     # turn st dev into precision

for (k in 1:NT){        # v[1] will give prob of event on treat 1
  logit(v[k]) <- A + d[k]
  rr[k] <- v[k]/v[1]     # calculate relative risk
 }
sumdev <- sum(sdev[])    # Calculate residual deviance
# Ranking and prob{treatment k is best}
for (k in 1:NT){
  rk[k] <- rank(rr[],k)
  best[k] <- equals(rank(rr[],k),1)
 }
# pairwise ORs and RRs
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]
    lrr[c,k] <- log(rr[k]) - log(rr[c])
    log(rrisk[c,k]) <- lrr[c,k]
   }
 }
}
```

Data

```
# NT=no. treatments, NS=no. studies;
# NB : set up M vectors each r[,]. n[,] and t[,],  where M is the Maximum number of treatments
#         per trial in the dataset. In this dataset M is 3.
```

list(NS=29, NT=8, meanA=-5.331 sdA=3.482)

r[,1]	n[,1]	r[,2]	n[,2]	r[,3]	n[,3]	t[,1]	t[,2]	t[,3]	na[]
4	88	4	95	NA	NA	1	2	NA	2
0.5	26	0.5	26	1.5	26	1	3	4	3
0.5	31	6.5	31	NA	NA	1	3	NA	2
0.5	18	1.5	18	NA	NA	1	3	NA	2
23	61	24	63	NA	NA	1	3	NA	2
0.5	42	1.5	40	NA	NA	1	4	NA	2
1	14	2	16	NA	NA	1	4	NA	2
1	38	5	109	NA	NA	1	4	NA	2
0.5	113	2.5	109	NA	NA	1	4	NA	2
1	650	10	635	NA	NA	1	5	NA	2
14	71	9	70	NA	NA	2	3	NA	2
0.5	38	6.5	32	NA	NA	2	3	NA	2
69	1894	91	1915	NA	NA	2	3	NA	2
17	74	23	72	NA	NA	2	3	NA	2
14	431	12	429	10	430	2	3	6	3
2	112	15	115	NA	NA	2	3	NA	2
11	725	18	719	NA	NA	2	3	NA	2
3	1034	13	1036	NA	NA	2	6	NA	2
0.5	17	1.5	20	NA	NA	2	6	NA	2
2	217	10	215	NA	NA	3	6	NA	2
13	110	32	105	NA	NA	3	6	NA	2
1	40	2	40	NA	NA	3	6	NA	2
5.5	83	0.5	85	NA	NA	3	6	NA	2
10	643	18	653	NA	NA	3	6	NA	2
1	27	1	25	NA	NA	3	6	NA	2
1	20	6	23	NA	NA	3	7	NA	2
49	1433	34	1425	NA	NA	5	6	NA	2
1	248	3	253	NA	NA	6	8	NA	2
4	222	1	205	NA	NA	6	8	NA	2

END

```
 Inits
#chain 1
list(
d=c(NA,0,0,0,0,   0,0,0), # one for each treatment
sd=1,
mu=c(3,2,-3,1,0,3,-2,-1,2,-2,    -1,3,1,3,-2,-1,2,-2,3,-1,   1,-1,-2,-3,-1,-3,0,2,1) )
#chain 2
list(
d=c(NA,-3,1,-1,-3,   -1,-3,1), # one for each treatment
sd=0.1,
mu=c(3,2,-3,1,0,3,-2,-1,2,-2,    -1,3,1,3,-2,-1,2,-2,3,-1,   1,-1,-2,-3,-1,-3,0,2,3) )
#chain 3
list(
d=c(NA,0,1,1,0,   0,0,0), # one for each treatment
sd=2,
mu=c(3,2,-3,1,0,3,-2,-1,2,-2,    -1,3,1,3,-2,-1,2,-2,3,-1,   1,-1,-2,-3,-1,-3,0,2,0) )
```

M.3.6.9 WinBUGS code for inconsistency model for number of patients with major bleeding

```
# Binomial likelihood, logit link, inconsistency model
# Random effects model
model{                    # *** PROGRAM STARTS
for(i in 1:ns){           # LOOP THROUGH STUDIES
   delta[i,1]<-0          # treatment effect is zero in control arm
   mu[i] ~ dnorm(0,.0001)  # vague priors for trial baselines
   for (k in 1:na[i])  {   # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
       +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
```

```
    }
# summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
  for (k in 2:na[i]) {  # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
    }
 }
totresdev <- sum(resdev[])   # Total Residual Deviance
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
   for (k in (c+1):nt)  { d[c,k] ~ dnorm(0,.0001) }
 }
sd ~ dunif(0,5)  # vague prior for between-trial standard deviation
var <- pow(sd,2) # between-trial variance
tau <- 1/var     # between-trial precision
} # *** PROGRAM ENDS
```

Data

```
# Major bleeding
# nt=no. treatments, ns=no. studies
list(nt=8,ns=29)
```

r[,1]	n[,1]	r[,2]	n[,2]	r[,3]	n[,3]	t[,1]	t[,2]	t[,3]	na[]
4	88	4	95	NA	NA	1	2	NA	2
0.5	26	0.5	26	1.5	26	1	3	4	3
0.5	31	6.5	31	NA	NA	1	3	NA	2
0.5	18	1.5	18	NA	NA	1	3	NA	2
23	61	24	63	NA	NA	1	3	NA	2
0.5	42	1.5	40	NA	NA	1	4	NA	2
1	14	2	16	NA	NA	1	4	NA	2
1	38	5	109	NA	NA	1	4	NA	2
0.5	113	2.5	109	NA	NA	1	4	NA	2

1	650	10	635	NA	NA	1	5	NA	2
14	71	9	70	NA	NA	2	3	NA	2
0.5	38	6.5	32	NA	NA	2	3	NA	2
69	1894	91	1915	NA	NA	2	3	NA	2
17	74	23	72	NA	NA	2	3	NA	2
14	431	12	429	10	430	2	3	6	3
2	112	15	115	NA	NA	2	3	NA	2
11	725	18	719	NA	NA	2	3	NA	2
3	1034	13	1036	NA	NA	2	6	NA	2
0.5	17	1.5	20	NA	NA	2	6	NA	2
2	217	10	215	NA	NA	3	6	NA	2
13	110	32	105	NA	NA	3	6	NA	2
1	40	2	40	NA	NA	3	6	NA	2
5.5	83	0.5	85	NA	NA	3	6	NA	2
10	643	18	653	NA	NA	3	6	NA	2
1	27	1	25	NA	NA	3	6	NA	2
1	20	6	23	NA	NA	3	7	NA	2
49	1433	34	1425	NA	NA	5	6	NA	2
1	248	3	253	NA	NA	6	8	NA	2
4	222	1	205	NA	NA	6	8	NA	2

END

INITS

#chain 1

list(sd=1, mu=c(2,0,3,0,2, -2,2,-2,-1,3, 2,-2,1,3,1, 1,2,-3,2,-2, -2,1,0,-3,3, 0,-3,-2,-3))

chain 2

list(sd=1.5, mu=c(2,1,3,1,2, 0,2,0,-1,3, 2,0,1,3,1, 1,2,-3,2,0, 0,1,1,-3,3, 1,-3,0,-3))

chain 3

list(sd=3, mu=c(2,0.5,3,0.5,2, -2,2,1,-1,3, 2,1,1,3,1, 1,2,-3,2,1, 1,1,0.5,-3,3, 0.5,-3,1,-3))