37 Cardiac surgery

37.1 Introduction

This section covers patients undergoing cardiac surgery.

Factors that may alter the risk of VTE in cardiac surgery:

- Pacing wires and implantable cardioverter-defibrillator devices may lead to an increase in upper limb deep vein thrombosis

Factors that increase the risk of bleeding or hazard associated with it:

- Many patients will be receiving antiplatelet medication, heparin or warfarin and will therefore have an increased risk of bleeding.

Other special factors that would affect the choice of, and use of, specific methods of prophylaxis:

- Several procedures in cardiac surgery involve the use of anticoagulation or antiplatelet therapy:
  - Full heparin anticoagulation is used during cardiopulmonary bypass which is typically 1-2 hours of a 2-5 hour surgery.
  - Surgeries performed "off pump" (without the use of heart lung machines) are also covered by heparin anticoagulation.
  - Most patients with coronary artery disease are given antiplatelet therapy up to shortly prior to surgery and it is recommenced soon after.
  - Many patients with valve disease have warfarin anticoagulation.
  - Patients in atrial fibrillation will generally have warfarin or other anticoagulants.
- Many cardiac surgery patients have leg veins removed for use as grafts. This would preclude the use of both AES and IPCD during the surgery but they could be used afterwards.

37.2 Review question: What is the effectiveness of different pharmacological and mechanical prophylaxis strategies (alone or in combination) for people undergoing cardiac surgery?

For full details see the review protocol in appendix C.

Table 217: PICO characteristics of review question

Population	Adults and young people (16 years and older) undergoing cardiac surgery who are: • Admitted to hospital • Discharged from hospital • Outpatients
Interventions	Mechanical: • Anti-embolism stockings (AES) (above or below knee) • Intermittent pneumatic compression (IPCD) devices (full leg or below knee) • Foot pumps or foot impulse devices (FID) • Electrical stimulation (including Geko devices) • Continuous passive motion Pharmacological: • Unfractionated heparin (UFH) (low dose, administered subcutaneously)

	• Low molecular weight heparin (LMWH), licensed in UK:
	  ○ enoxaparin (standard prophylactic dose 40 mg daily; minimum 20 mg daily* to maximum 60mg twice daily*)
	  ○ dalteparin (standard prophylactic dose 5000 units once daily; minimum 1250 units once daily* to maximum 5000 units twice daily*; obese patients – maximum 7500 twice units daily*)
	  ○ tinzaparin (standard prophylactic dose 4500 units once daily; minimum 2500 units once daily* to maximum 4500 units twice daily*; obese patients – maximum 6750 twice daily*)
	• LMWH, licensed in countries other than UK:
	  ○ bemiparin (standard 2500 units daily; minimum 2500 units daily to maximum 3500 units daily)
	  ○ certoparin (3000 units daily)
	  ○ nadroparin (standard 2850 units once daily; minimum 2850 units once daily to maximum up to 57 units/kg once daily)
	  ○ parnaparin (standard 3200 units once daily; minimum 3200 units once daily to maximum 4250 units once daily)
	  ○ reviparin (minimum 1750 units once daily to maximum 4200 units once daily)
	• Vitamin K Antagonists:
	  ○ warfarin (variable dose only)
	  ○ acenocoumarol (all doses)
	  ○ phenindione (all doses)
	• Fondaparinux (all doses)*
	• Apixaban (all doses)*
	• Dabigatran (all doses)*
	• Rivaroxaban (all doses)*
	• Aspirin (up to 300 mg)*
	
	*off-label

Comparisons	Compared to: • Other VTE prophylaxis treatment, including monotherapy and combination treatments (between class comparisons for pharmacological treatments only) • No VTE prophylaxis treatment (no treatment, usual care, placebo) Within intervention (including same drug) comparisons, including: • Above versus below knee stockings • Full leg versus below knee IPC devices • Standard versus extended duration prophylaxis • Low versus high dose for LMWH • Preoperative versus post-operative initiation of LMWH
Outcomes	**Critical outcomes:** • All-cause mortality (up to 90 days from hospital discharge) • Deep vein thrombosis (symptomatic and asymptomatic) (up to 90 days from hospital discharge). Confirmed by: radioiodine fibrinogen uptake test; venography; Duplex (Doppler) ultrasound; MRI; Impedance Plethysmography (used as rule out tool) • Pulmonary embolism (symptomatic and asymptomatic) (up to 90 days from hospital discharge) (NMA outcome). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE • Major bleeding (up to 45 days from hospital discharge). A major bleeding event meets one or more of the following criteria: results in death; occurs at a critical site

	(intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood ; leads to a drop in haemoglobin of ≥2 g/dl; a serious or life threatening clinical event. Includes unplanned visit to theatre for control of bleeding • Fatal PE (up to 90 days from hospital discharge). Confirmed by: CT scan with spiral or contrast; pulmonary angiogram; ventilation/ perfusion scan including VQSpect; autopsy; echocardiography; clinical diagnosis with the presence of proven VTE **Important outcomes:** • Clinically relevant non-major bleeding (up to 45 days from hospital discharge): bleeding that does not meet the criteria for major bleed but requires medical attention and/or a change in antithrombotic therapy. • Health-related quality of life (validated scores only)(up to 90 days from hospital discharge) • Heparin-induced thrombocytopaenia (HIT) (duration of study) • Technical complications of mechanical interventions (duration of study) • Major adverse cardiac events (MACE) (duration of study): death, Q-wave myocardial infarction (MI) and the need for repeat revascularization by redo-CABG or repeat percutaneous intervention
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs

37.3 Clinical evidence

A search was conducted for randomised trials comparing the effectiveness of mechanical and pharmacological prophylaxis strategies (alone or in combination) in people undergoing cardiac surgery. Two new studies were identified (Kolluri 2016[171]; Myles 2016[222]). Of the three studies included in the previous guideline (CG92), one study was included[116,249], and two studies were excluded (Beghi 1993[18]; Ramos 1996[249]). The included study is summarised in Table 218 below. See also the study selection flow chart in appendix E, forest plots in appendix L, study evidence tables in appendix H, GRADE tables in appendix K and excluded studies list in appendix N.

Summary of included studies

Table 218: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Goldhaber 1995[116]	Intervention (n = 172) Thigh-length IPCD + AES (unknown length) + aspirin 325 mg/day. Started post-operatively Comparison (n=172) AES (unknown length) + aspirin 325 mg/day. Started post-operatively	n=344 People having coronary artery bypass Adults (mean age 63.2±9.7 years) Male to female ratio 229:112 USA	All-cause mortality (until discharge) DVT (≥4 days post-op until discharge): confirmed by bilateral Doppler ultrasound PE (until discharge): confirmed by high probability V/Q scan Fatal PE: confirmed by: assumed clinical evaluation (pulmonary emobolectomy procedure)	First 98 patients enrolled had delayed initiation of prophylaxis with IPCD Significantly greater proportion of people in the comparison group had cancer (numbers not reported in CG92)

Study	Intervention and comparison	Population	Outcomes	Comments
Kolluri 2016[171]	Intervention (n = 41) Fondapainux (2.5mg subcutaneously, once daily) starting at a mean of 12 hours after wound closure or in the morning of the first postoperative day. Administered for 9 days or until discharge. Comparison (n=37) No VTE prophylaxis (subcutaneous injections of saline) Both groups routinely received AES and/or IPCD	n=78 People having coronary artery bypass graft surgery Adults (mean age: intervention 64.4±8.9; comparison 62±8.9) Male to female ratio 57:21 USA	DVT (9-11 days): confirmed by duplex ultrasound	
Myles 2016[222]	Intervention (n=1059): Aspirin (100mg) starting 1-2 hours before surgery, with or without anxiolytic premedication Comparison (n=1068): No VTE prophylaxis (matched placebo tablets 1 to 2 hours before surgery, with or without anxiolytic premedication)	n=2127 People having coronary artery surgery who are at increased risk for complications Adults (mean age: intervention 66.5±9.7; comparison 66.2±10.2) Male to female ratio 1730:370 Australia	All-cause mortality (30 days) PE (30 days): method of confirmation not reported Major bleeding (30 days): defined as any excessive bleeding leading to surgical re-exploration	There was no limitation to the use or postoperative aspirin or other antiplatelet therapy, and such therapy was administered in accordance with local practices

Table 219: Clinical evidence summary: IPC + AES + aspirin compared to AES + aspirin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with AES + aspirin	Risk difference with IPCD + AES + aspirin (95% CI)
All-cause mortality	330 (1 study) until discharge	VERY LOW[b,c] due to risk of bias, imprecision	Peto OR 7.53 (0.47 to 120.83)	0 per 1000	Not estimable[a]
DVT	330 (1 study) ≥4 days post-op until discharge	VERY LOW[b,c] due to risk of bias, imprecision	RR 0.87 (0.57 to 1.34)	217 per 1000	28 fewer per 1000 (from 93 fewer to 74 more)
PE	330 (1 study) until discharge	VERY LOW[b,c] due to risk of bias, imprecision	RR 1.01 (0.06 to 16.05)	6 per 1000	0 more per 1000 (from 6 fewer to 91 more)
PE, fatal	329 (1 study) until discharge	VERY LOW[b,c] due to risk of bias, imprecision	Peto OR 1.01 (0.06 to 16.15)	6 per 1000	0 more per 1000 (from 6 fewer to 84 more)

a Zero events in control arm
b Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
c Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 220: Clinical evidence summary: Aspirin versus no prophylaxis

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Aspirin versus no prophylaxis (95% CI)
All-cause mortality	2100 (1 study)	LOW[a] due to	RR 1.56 (0.68 to 3.6)	9 per 1000	5 more per 1000 (from 3 fewer to 22 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Aspirin versus no prophylaxis (95% CI)
	30 days	imprecision			
PE	2100 (1 study) 30 days	LOW[a] due to imprecision	RR 0.8 (0.32 to 2.03)	9 per 1000	2 fewer per 1000 (from 7 fewer to 10 more)
Major bleeding	2100 (1 study) 30 days	LOW[a] due to imprecision	RR 0.87 (0.47 to 1.6)	21 per 1000	3 fewer per 1000 (from 11 fewer to 13 more)
a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 221: Clinical evidence summary: Fondaparinux + AES and/or IPCD versus AES and/or IPCD for VTE prophylaxis in people undergoing cardiac surgery

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Fonda + AES/IPCD versus AES/IPCD (95% CI)
DVT	67 (1 study) 9-11 days	LOW[a] due to imprecision	Peto OR 0.12 (0 to 6.23)	31 per 1000	27 fewer per 1000 (from 31 fewer to 136 more)
a Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

37.4 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

37.5 Evidence statements

Clinical

In one study of very low quality, a possible clinical benefit of IPCD + AES + aspirin was found for the outcome all-cause mortality, however there was very serious imprecision around the estimate, and therefore was also associated with no difference and clinical harm (n=330). For the DVT outcome, evidence from the same study showed a possible clinical harm of IPCD + AES + aspirin, however again there was very serious imprecision around the estimate. There was no clinical difference between the two interventions in terms of PE or fatal PE. The evidence for these outcomes also showed very serious imprecision and was associated with both clinical benefit and clinical harm.

One study compared aspirin to no VTE prophylaxis. There was a possible clinical harm of aspirin compared to no prophylaxis in terms of all-cause mortality, and no clinical difference between the two interventions for the PE and major bleeding outcomes (low quality; n=2100). For all outcomes there was very serious imprecision around the estimate.

One small study of 67 participants compared a combination of fondaparinux and mechanical prophylaxis with mechanical prophylaxis alone. The evidence demonstrated a possible clinical benefit for combined fondaparinux and mechanical prophylaxis in terms of DVT, however there was very serious imprecision around the estimate and therefore was also associated with no difference or clinical harm. No other outcomes were reported.

Economic

- No relevant economic evaluations were identified.

37.6 Recommendations and link to evidence

Recommendations	**1.5.44 Consider mechanical VTE prophylaxis on admission for people who are undergoing cardiac surgery who are at increased risk of VTE. Choose either:** • **anti-embolism stockings or** • **intermittent pneumatic compression.** **Continue until the person no longer has significantly reduced mobility relative to their normal or anticipated mobility. [2018]** **1.5.45 Consider adding pharmacological VTE prophylaxis for a minimum of 7 days for people who are undergoing cardiac surgery and are not**

	having other anticoagulation therapy: • **Use LMWH[ee] as first-line treatment.** • **If LMWH[ff] is contraindicated use fondaparinux sodium[gg]. [2018]**
Research recommendation	**None**
Relative values of different outcomes	The committee considered all-cause mortality (up to 90 days from hospital discharge), deep vein thrombosis (symptomatic and asymptomatic) (up to 90 days from hospital discharge), pulmonary embolism (symptomatic and asymptomatic) (up to 90 days from hospital discharge), fatal PE (up to 90 days from hospital discharge), and major bleeding (up to 45 days from hospital discharge) as critical outcomes. The committee considered clinically relevant non-major bleeding (up to 45 days from hospital discharge), health-related quality of life (up to 90 days from hospital discharge), heparin-induced thrombocytopaenia (duration of study), and technical complications of mechanical interventions (duration of study) as important outcomes. Please see section 4.4.3 in the methods chapter for further detail on prioritisation of the critical outcomes.
Quality of the clinical evidence	The committee noted that there was little RCT evidence covering cardiac surgery. The included studies were generally well conducted methodologically with down-grading occurring predominantly due to imprecision.
Trade-off between clinical benefits and harms	The key risks in this patient group are risk of bleeding as they are likely to already be receiving antiplatelet medication. Additionally, this patient group has a high average age, and are likely to have undergone a long operation and a period of immobilisation. Cardiac surgery patients receive a large dose of heparin/anticoagulant during the surgery at the time of clamping, so any pharmacological VTE prophylaxis would not be initiated until after surgery. The committee noted the relatively small amount of evidence in this particular population. The committee pre-specified that if this was the case they would consider the evidence for the abdominal surgery population as indirect evidence. Both cardiac and abdominal surgery involves operations potentially lasting several hours and significant potential for post-operative immobility partly due to the presence of a large incision. The committee discussed the current evidence, considered the previous CG92 recommendations for the cardiac surgery population, as well as the recommendations for the abdominal surgery population. The committee considered that similar pharmacological VTE prophylaxis recommendations could be made for this population as for abdominal surgery patients (LMWH and fondaparinux). The committee considered that the small amount of evidence for fondaparinux identified in the cardiac population suggested a benefit for reducing DVT and that this was a reasonable addition to the

[ee] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[ff] At the time of publication (March 2018), LMWH did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[gg] At the time of publication (March 2018), fondaparinux sodium did not have a UK marketing authorisation for use in young people under 18 for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

	recommended options from CG92. However, the use of fondaparinux sodium in the cardiac surgery population is off-label as fondaparinux sodium did not have a UK marketing authorisation for this indication at the time of consultation (October 2017). Therefore the committee recommend LMWH in the first instance and fondaparinux sodium only if LMWH is contraindicated. Mechanical prophylaxis is recommended until the patient is back to normal mobility as the committee believe that mechanical prophylaxis offers little benefit once a patient is mobile. Pharmacological prophylaxis is recommended for a minimum of 7 days because the average duration of trials extrapolated from the abdominal surgery was between 7 and 10 days.
Trade-off between net clinical effects and costs	No economic studies were identified for this review. Unit costs were presented. The committee highlighted that the VTE risk in people undergoing cardiac surgery is high. They discussed that current practice follows the recommendation of CG92, where combined prophylaxis (pharmacological and mechanical) was considered to be cost effective for this population. The clinical evidence presented limited their ability to draw a conclusion specific for this population and that extrapolation from the abdominal surgery population for which combined prophylaxis was recommended would be acceptable. Given the high baseline risk of VTE in this population, it was considered that the additional cost of combined prophylaxis would be off-set by the savings from the averted VTE events. The choice of the mechanical and pharmacological prophylaxis options was considered. It was determined that the options given for the abdominal surgery population should be recommended for the cardiac surgery population to allow for tailored prophylaxis prescribing, accommodating licence restrictions, the presence of contraindications and patient preferences.
Other considerations	The committee noted that current practice is to use AES as opposed to graduated compression stockings. In terms of pharmacological prophylaxis, current practice is to give a large dose of heparin pre-operatively which is then reversed post-operatively and a lower dose is then offered. Therefore there is a different risk of VTE in these two distinct stages.