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Clinical Practice Guideline

For the Prevention of Venous Thromboembolism in Patients Admitted to Australian Hospitals

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Disclaimer

This document is a general guide to appropriate practice, to be followed subject to the clinician's judgment and patient's preference in each individual case. The guideline is designed to provide information to assist decision-making and is based on the best evidence available at the time of development of this publication.

Contents

ExecutAve su\ \ ary

Although effective pharmacological and mechanical preventive options have existed for decades,

u ary of reco endat ns

This summary section provides a list of the evidence-based recommendations detailed in the text of Section 5. Each of the recommendations is given an overall grading based on the NHMRC additional levels of evidence and grades of recommendation (2008-2010).[1] When no Level I or II evidence was available but there was consensus among the Committee, recommended best practice points have been provided, and can be identified throughout the guideline with the following:

Good practice point (GPP)

Consensus recommendations and recommendations for further research have not been graded.

Grade of recommendation	Description
A	Body of ev dence can be trusted to gu de pract e
B	Body of ev dence can be trusted to gu de pract e A ost s uat ns
C	Body of ev dence prov des so e support for reco endat n s but care s ou d be

urgAa patAnts

RECOMMENDATIONS BY CLINICAL PROCEDURE	GRADE	EVIDENCE IN SECTION
Urological surgery		
– Consider t roi boprop yaxA for patAnts adi Ated to ospAa for uro ogAa surgery based on an assessi ent of t e patAnts rA of E and b eedAg–	**GPP**	7
Gynaecological surgery		
– se t roi boprop yaxA for a patAnts adi Ated to ospAa for i a'or gynaeco ogAa surgery–	**GPP**	
– In t e absence of contraAdAatAns use p ani aco ogAa t roi boprop yaxA and contAue for up to one wee or untAt e patAnt As fu yi obAe fo owAg i a'or gynaeco ogAa surgery– se one of t e fo owAg • ow i decu ar weAg t epar A • unfractAnated epar A–	 **B** **B**	
– Consider t e addAAna use of graduated coi pressAn stoc Ags or ot er i ec anAa t roi boprop yaxA fo owAg i a'or gynaeco ogAa surgery especA y A p ani aco ogAa t roi boprop yaxA As contraAdAated–	**GPP**	
– arfarA As not recoi i'ended for t roi boprop yaxA fo owAg i a'or gynaeco ogAa surgery–	**C**	
Abdominal surgery		
– se t roi boprop yaxA for a patAnts adi Ated to ospAa for i a'or abdoi Aa surgery–	**GPP**	
– In t e absence of contraAdAatAns use p ani aco ogAa t roi boprop yaxA for i a'or abdoi Aa surgery patAnts and contAue for at east ve to nAe days wA ow i decu ar weAg t epar A–	**B**	
– FondaparAux As not recoi i'ended for t roi boprop yaxA fo owAg i a'or abdoi Aa surgery–	**C**	
– se graduated coi pressAn stoc Ags for a patAnts fo owAg abdoi Aa surgery w et er or not p ani aco ogAa t roi boprop yaxA As used untAt e patAnt As fu yi obAe–	**B**	

RECOMMENDATIONS BY MEDICAL CONDITION	GRADE	EVIDENCE IN SECTION

¸– Purpose of t /S Gu de Ae

The purpose of this Guideline is to provide practical, evidence-based recommendations for the prevention of VTE in adult surgical and medical patients and pregnant women admitted to Australian metropolitan, regional and rural hospitals. The recommendations should be followed subject to the judgement of clinicians caring for individual patients and patients' own preferences.

¸– Intended users

This Guideline is intended for doctors, nurses, pharmacists and allied health professionals. It also provides useful information for consumers and those responsible for the quality and safety of healthcare.

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This Guideline provides recommendations for prevention of VTE in adult patients admitted to Australian hospitals in the following categories:

- **patients undergoing surgery including orthopaedic, major general, major gynaecological, urological, cardiothoracic, vascular and neurosurgery**
- **patients with acute medical illnesses, including myocardial infarction, stroke, and other medical conditions**
- **trauma patients**
- **patients admitted to intensive care units**
- **cancer patients (with or without cancer treatment)**
- **patients admitted during pregnancy and the puerperium.**

This Guideline does not provide recommendations for prevention of VTE in:

- **patients under the age of 18 years**
- **patients attending hospital as outpatients**
- **patients who present to emergency departments but are not admitted**
- **elderly or immobile patients cared for at home or in external residential accommodation (unless admitted to hospital)**
- **patients in long-term hospital rehabilitation**
- **patients who have not been hospitalised**
- **those at risk of developing travel-related VTE.**

¸– Met ods used to deve op t /S Gu de Ae

The National Institute of Clinical Studies (NICS), an institute of the NHMRC, developed this Guideline in accordance with NHMRC guideline development processes.[20-22]

In July 2008, NICS convened a multidisciplinary committee comprising professional group members with specific expertise in VTE prevention and a consumer representative. Details of the membership of the VTE Prevention Guideline Adaptation Committee (the Committee) are provided in Appendix A.1 and the process for their appointment can be found in Appendix B.1. The terms of reference for the Committee are provided in Appendix A.3.

As a number of high quality international VTE prevention guidelines were already available, NICS developed this Guideline using an established guideline adaptation methodology (ADAPTE) rather than developing a new guideline *de novo*.[23] ADAPTE seeks to reduce duplication in guideline development by using existing high-quality guidelines as the basis for a local guideline.

Following the ADAPTE process, the Committee considered that the 2007 publication from the UK's National Institute for Health and Clinical Excellence (NICE)[11] best met the criteria for a high quality source guideline. This guideline was selected using the Appraisal of Guidelines Research and Evaluation instrument (AGREE),[24] which measures the extent to which the potential biases of guideline development have been adequately addressed, internal and external validity of the recommendations, and feasibility for practice, but does not assess the content of the guideline.

Although the 2007 NICE VTE prevention guideline was considered the most comprehensive review of available evidence, its structure was unsuitable for direct adaptation into an Australian guideline. The NICE guideline grouped all surgical procedures together, and the Committee considered that this would not be clinically meaningful in the Australian context. The Committee also considered that the evidence for individual surgical procedures needed to be examined separately, as the patient risk profile for each procedure differed and overall recommendations for practice were not expected to be clinically relevant to practitioners from different surgical and medical specialties.

The American College of Chest Physicians (ACCP) guidelines were used by the Committee to help provide a broad structure by indication for the guidelines; and to crosscheck that relevant studies had been included in this guideline.[10]

As the adaptation process progressed, the Committee found that evidence and recommendations could not be taken from existing guidelines (i.e. the ADAPTE process could not be followed entirely). Therefore, the Committee resolved to use a modified guideline adaptation process based in principle on ADAPTE but incorporating elements of *de novo* guideline development. The literature searches undertaken for the 2007 NICE guideline "Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery"[11] were used as the primary source of evidence, with top-up searches undertaken (from April 2006 to January 2009) to ensure currency and completeness and new meta-analysis undertaken. No other guidelines were used as a source of evidence for adaptation. The format of this Guideline considers evidence for each clinical indication separately. However, many of the source documents used in developing this Guideline have synthesised studies of different clinical indications together in meta-analyses comparing the same intervention. In order for these existing meta-analyses to be used in this Guideline, the component studies needed to be extracted and grouped according to clinical indication. Therefore, the original systematic review or meta-analysis may not be cited as an evidence source in the guideline but all of its component studies will have been included in the relevant clinical indications. For further details on the inclusion and exclusion criteria and source documents, refer to Appendix B.3v.

All the recommendations within this Guideline were developed by the Committee using procedures outlined in the "NHMRC additional levels of evidence and grades for recommendations for developers of guidelines: Stage 2 consultation 2008-2010".[1] Each recommendation was assigned a grade by the Committee, taking into account the volume, consistency, generalisability, applicability and clinical impact of the body of evidence supporting each recommendation. The table in Appendix B.3viii sets out the evidence gradings.[1] A standardised evidence statement form used to formulate and grade the recommendations can be found in Appendix E.[1] Good practice points were used when the conventional grading of evidence was not possible. These points represent consensus views of the Committee and are identified throughout by the abbreviation GPP (in place of a recommendation grading).

A detailed report on the modified ADAPTE process used to develop this Guideline is provided in Appendix B.

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NHMRC recommends that guidelines be reviewed and revised no more than five years after initial publication. However, the evidence base on which this Guideline was developed is likely to change sooner. Therefore, the Committee will be re-convened to review relevant sections of the Guideline if any of the following occur within five years:

- **registration by the Australian Therapeutic Goods Administration of any new drugs for the prevention of VTE in hospitalised patients**
- **a change in the indications registered by the Therapeutic Goods Administration for any drug included in this Guideline**
- **publication of any new major randomised controlled trials or systematic reviews that potentially have a bearing on the recommendations in this Guideline**
- **emergence of any major safety concerns relevant to this Guideline.**

7 – Fund Ag

The development of this Guideline was funded by the National Health and Medical Research Council (NHMRC).

2 Options for thromboprophylaxis in Australia

Adequate hydration and early mobilisation are simple measures that should be applied as standard practice to prevent VTE. Other important options for VTE prophylaxis include pharmacological or mechanical methods. Their effectiveness varies depending upon the clinical procedure and patient-related risk factors.

The pharmacological options considered for this Guideline were:

- **subcutaneously administered unfractionated heparin (UFH) or low molecular weight heparins (LMWH)**
- **subcutaneously administered fondaparinux, a selective inhibitor of activated Factor X (Xa)**
- **subcutaneously administered danaparoid, a heparinoid**
- **orally administered rivaroxaban, a direct factor Xa inhibitor**
- **orally administered dabigatran etexilate, a direct thrombin inhibitor**
- **orally administered aspirin, a platelet aggregation inhibitor**
- **orally administered warfarin, a vitamin K antagonist.**

Low molecular weight heparins, unfractionated heparin, fondaparinux, danaparoid, rivaroxaban, dabigatran etexilate, aspirin and warfarin were treated as separate classes of agents for the purposes of the review of evidence for this Guideline.

Various methods for depolymerisation of standard heparin are used by different manufacturers to produce the various low molecular weight heparins. This leads to different pharmacologic profiles and dosages. For the purpose of this Guideline, the Committee have assumed that both types of low molecular weight heparin approved for use in Australia can be used interchangeably, and will produce similar outcomes to alternative forms of low molecular weight heparin used in overseas trials.

Immobility can lead to the development of DVT as normal venous pump function of skeletal muscles is greatly reduced. Patients may be immobilised through confinement to bed, as a consequence of a surgical procedure, because of local immobilisation (e.g. a plaster cast or traction applied to a limb), or a combination of these. Mechanical methods of prophylaxis focus on reducing venous stasis and blood stagnation by promoting venous blood flow through external compression (with graduated compression stockings, intermittent pneumatic compression or venous foot pumps, used alone or in combination).

The mechanical options considered for this Guideline were:

- **knee or thigh length graduated compression stockings (GCS)**
- **knee or thigh length intermittent pneumatic compression (IPC)**
- **venous foot pumps (VFP).**

For further information on indications, contraindications and precautions relating to the agents used in preventing VTE, refer to the TGA approved product information, the Australian Medicines' Handbook,[2] or individual manufacturer's instructions.

Nevertheless, VTE remains a major complication of hospitalisation and the existing guidelines are a response to that risk.

Therapeutic regimens in clinical trials may differ from those in current practice. For example, a preoperative low molecular weight heparin dose is required by many VTE prevention trials in orthopaedic surgery but is almost never administered in current practice in Australia.

Patient risk

Risk factors

The likelihood of developing a VTE is increased by well-recognised risk factors. However, there are few population-based studies on VTE risk in hospitalised patients, and estimates of the magnitude of risk are sometimes contradictory or outdated (for example, by changes in surgical techniques or patient characteristics).

There are no evidence-based algorithms for assigning a patient to 'low' or 'high' risk categories, based on single risk factors or combinations of risk factors. Known risk factors are listed below, and their presence or absence should inform clinical decisions on the use of thromboprophylaxis.

The risk factors are grouped into the following categories: individual patient risk factors; risks related to an acute medical illness; and risks related to an injury or a surgical procedure. Risks related to the individual may be either inherited or acquired. Depending on their magnitude the risk factors related to an injury, a surgical procedure, or an acute medical illness often exert a dominating influence for their duration.

1. **Individual patient risk factors:**
   - **age (the annual incidence of VTE rises with each decade over the age of forty)[25-27]**
   - **pregnancy and the puerperium[28]**
   - **active or occult malignancy[26,27,29-31]**
   - **previous VTE[26,31]**
   - **varicose veins[31]**
   - **marked obesity[31-33]**
   - **prolonged severe immobility (prolonged bed rest, immobilisation in a plaster cast or brace or prolonged travel resulting in limited movement and subsequent venous stasis)[29,34]**
   - **use of oestrogen-containing hormone replacement therapy or oral contraceptives in women[31,32,35]**
   - **inherited or acquired thrombophilia (conditions that carry a high risk of VTE include inherited deficiency of antithrombin, protein C or protein S, homozygosity or double heterozygosity for factor V Leiden or the G20120A prothrombin gene mutation, the phospholipid antibody syndrome).[31,32]**
2. **Risks related to an acute medical illness:**
   - **acute or acute on chronic chest infection[31]**
   - **heart failure[29,31]**
   - **myocardial infarction[31,315]**
   - **stroke with immobility[36]**
   - **some forms of cancer chemotherapy[27,29]**
   - **acute inflammatory bowel disease.[31]**
3. **Risks related to an injury or surgical procedure:**
   - **all surgical procedures but especially abdominal,[37] pelvic,[11] thoracic or orthopaedic surgical procedures.[38-41] Risk is determined by the type of surgery (major joint surgery carries a very high risk,[38-41] as does curative surgery for cancer[42]), the type of anaesthesia,[43] the likely duration of immobility (including duration of surgery),[29,34] and surgical complications**
   - **leg injury that requires surgery or prolonged immobilisation.[44]**

2 Bleeding risk

The risk of bleeding is elevated in the presence of certain risk factors and when certain procedures are undertaken. Pharmacological thromboprophylaxis may add to these risks. As the evidence presented throughout this Guideline is mostly from randomised controlled trials, this may not be an accurate reflection of the incidence of bleeding outside the controlled trial context.

Patient-related risk factors for bleeding include:

- **current active major bleeding (defined as requiring at least two units of blood or blood products to be transfused in 24 hours)**
- **current chronic, clinically significant and measurable bleeding over 48 hours**
- **bleeding disorders (e.g. haemophilia)**
- **recent central nervous system bleeding**

E rA assess ent

It is essential to perform and record a VTE risk assessment in each patient before deciding whether or not to use preventive measures and on the most appropriate measures to use.

VTE risk factors are thought to be additive so the presence of multiple risk factors leads to a higher risk of developing VTE. The presence of multiple risk factors may signal the need for more efficacious VTE prophylactic regimens.

The final decision to provide thromboprophylaxis is a clinical decision based on number and type of risk factors balanced against risk of bleeding

A VTE risk assessment should follow the following steps:

Ev dence and reco i endat ns

urg a pat nts - Ev dence and reco i endat ns for E prop y ax

5.1.1 Total hip replacement

This section summarises the evidence from systematic reviews and individual trials considered for the prevention of VTE in patients undergoing total hip replacement. Full evidence tables on which these summaries are based are provided in Appendix D (tables 1-30, 61, 62 and 65).

The recommendations given below were based on the body of evidence, with consideration of the strength of evidence, consistency across studies, likely clinical impact, and generalisability and applicability of study findings in the Australian context. Details of this process are provided in Appendix B. Explanations are given for those recommendations that are inconsistent with the corresponding evidence summaries. Where necessary, some additional explanation has been provided to help interpret the recommendations in light of the evidence presented.

No recommendations were made where the evidence was of poor quality or not relevant to the current Australian healthcare context. Difficulties in interpreting the evidence are summarised in Section 3.

Good Practice Points (GPP) are consensus-based, and are provided where the available evidence was inadequate or could not be applied in the Australian healthcare context.

VTE PROPHYLACTIC AGENT	EVIDENCE SUMMARY – Thromboprophylaxis for total hip replacement patients	LEVEL	REFERENCES
Rivaroxaban	In two i ut centre ternat na s r aroxaban ora y once per day for days was ore effect e at reduc ng t e occurrence of asy pto at and prox a D t an LM H once per day e er for days or days – ere were no s n cant differences t e rates of PE or adverse events c ud ng deat between t e r aroxaban and LM H an s e pr ary outcome easure of t tr a was reported as a E co pos te co pr sing asy pto at D nonfata PE or deat fro any cause– ere were s n cant y fewer E t e r aroxaban group ora y once per day for days co pared w LM H once per day e er for days or days –	I	
Dabigatran etexilate	In one i ut centre ternat na t ere were s n cant y fewer prox a D w dab atran etex te ig t an LM H– ere were s n cant y ore sy pto at D w dab atran etex te co pared w LM H w en t e dab atran etex te dose was owered to ig ere were no s n cant differences rates of PE w dab atran etex te ig or ig co pared w LM H da y – ere were no s n cant differences t e rates of adverse events between t e groups–	I	

VTE PROPHYLACTIC AGENT	EVIDENCE SUMMARY – Thromboprophylaxis for total hip replacement patients	LEVEL	REFERENCES
Fondaparinux	In two s of pat ents w o rece ved e er LM H g once per day or fondapar ux g once da y for up to n e days t e group rece ng fondapar ux ad s gn cant y ower rates of E or D – However fondapar ux was assoc ated w s gn cant y er rates of a or b eed g t an LM H–	I	7
LMWH	Poo g of seven s co par g LM H w no treat ent s owed s gn cant y fewer asy pto a e D w LM H– ere were no d fferences t e occurrence of adverse events suc as wound ae a to a or a or b eed g between t e groups rece g LM H and no treat ent– ar ous doses of LM H were used across t e s– ar ous doses of LM H were used across t e s–	I	
	In a syste a e rev ew of s s extended dura on of prop y ax s w LM H to days postoperat ve y resu ted n s gn cant y ower rates of bot prox a and sy pto a e D and ower rates of PE co pared w extended p acebo–Extended dura on of prop y ax s was not assoc ated w an ncreased rate of adverse events–	I	
	In one t ere was no advantage n preoperat ve ad n stra on of LM H co pared w postoperat ve ad n stra on–A furt er t ree s nves gated dosage effects of LM H–Fro s ev dence er doses of LM H reduced t e rate of asy pto a e and d sta D but d d not affect t e rate of sy pto a or prox a D –	I	7
UFH	In two s t ere were gn cant y ower rates of D w FH co pared w p acebo w no gn cant d fference n PE between FH and p acebo– ere was no gn cant d fference n b eed g between FH and p acebo n one tr a not recorded n t e ot er tr a –	I	
LMWH or UFH	Across s s rates of asy pto a e D d d not d ffer between pat ents rece ng LM H or FH– However n t ree of t e s s pat ents rece ng LM H d ower rates of prox a D – e occurrence of adverse events nc ud g b eed g d d not d ffer between LM H and FH groups–	I	
GCS	Poo g of seven s s owed s gn cant y ower rates of asy pto a e D w en tota n rep ace ent pat ents wore graduated co press on stoc ngs co pared w no treat ent–Graduated co press on stoc ngs were s own to ave an add t ona bene t w en added to effect ve p an ac o og a prop y ax s owever not w en		

Discussion about the recommendations for total hip replacement

Patients undergoing total hip replacement are in the highest risk category for VTE, on the basis of the procedure itself,[11,29,39,40,102] and in the absence of thromboprophylaxis, risk of VTE is high following total hip replacement.[103,104]

RECOMMENDATION	Grade
Use thromboprophylaxis for patients admitted to hospital for total hip replacement.	GPP

Low molecular weight heparin, fondaparinux, rivaroxaban and dabigatran etexilate are all effective VTE prophylactic agents following total hip replacement. RCTs have shown that rivaroxaban (10mg daily) or fondaparinux (2.5mg daily) significantly reduced VTE compared with low molecular weight heparin[45,46,48,49] while the effectiveness of dabigatran etexilate (220mg or 150mg daily) and low molecular weight heparin was similar.[47] Importantly, the rates of adverse events, including bleeding were similar for rivaroxaban and dabigatran etexilate compared with low molecular weight heparin. Low molecular weight heparin was more effective than unfractionated heparin[64-69] or warfarin.[105-107]

The choice of thromboprophylactic agent to be used after total hip replacement should be based on availability, cost and individual patients' risk characteristics and preferences.

Rivaroxaban and dabigatran etexilate are oral thromboprophylactic agents that were registered by the Therapeutic Goods Administration and became available in Australia in late 2008. Post-marketing surveillance for adverse events has not been completed for rivaroxaban or dabigatran etexilate, so both should be used with caution. The lack of information on post-marketing surveillance for rivaroxaban and dabigatran etexilate, along with the number of available RCTs influenced the grading of the recommendation. When this information becomes available, the recommendation should be reviewed.

In RCTs where low molecular weight heparin was compared with fondaparinux for nine days, fondaparinux significantly reduced DVT but also caused significantly more bleeding.[48,49] Fondaparinux should be used with caution as it may cause bleeding, particularly in those weighing less than 50kg, in the frail, the elderly and those with renal impairment. In addition, because of the longer half-life of fondaparinux than some other thromboprophylactic options, special arrangements should be made between the surgical and anaesthetic teams if it is to be used.

Duration of thromboprophylaxis: **The duration of pharmacological thromboprophylaxis in trials varied, with ranges as follows: low molecular weight heparin three days[56] to 14 days;[55] fondaparinux five to nine days;[48,108] rivaroxaban 35 days[45,46] and dabigatran etexilate 28 to 35 days.[47] The duration of mechanical prophylaxis also varied, with graduated compression stockings used between seven[73] and 14 days post-operatively.[72] Intermittent pneumatic compression and foot pump were applied for the duration of hospital stay.[82,83]**

The risk of late-occurring DVT following total hip replacement remains high until at least day 35 after surgery.

In two RCTs, the rates of DVT were significantly reduced with unfractionated heparin compared with placebo, with no significant difference in PE or bleeding related complications.[62,63] However, as low molecular weight heparin was more effective than unfractionated heparin,[64-69] the use of unfractionated heparin is only advised where recommended forms of thromboprophylaxis are not available.

In two RCTs, the rates of VTE did not differ between groups of patients given aspirin and no thromboprophylactic treatment following total hip replacement.[88,89] Consequently, aspirin is not recommended as the sole form of thromboprophylaxis. Similarly, the rates of VTE did not differ between groups of patients given warfarin and no treatment.[90,91] Warfarin may be used by some patients for therapeutic reasons other than thromboprophylaxis. In the cases where warfarin use is unavoidable, adjusted therapeutic doses are more likely to be effective in preventing VTE than fixed low-dose warfarin.[95,96]

Given the availability of more efficacious options, warfarin, unfractionated heparin and aspirin are not recommended for thromboprophylaxis following total hip replacement.

RECOMMENDATIONS	Grade
– nfract Anated epar A A not reco i ' ended for t roi boprop y ax A fo ow Ag tota A p rep ace i ent–On y use unfract Anated epar A A reco i ' ended t roi boprop y act A opt Ans are not ava Ab e–	B
– Asp AA A not reco i ' ended as t e so e p an i ac o og Aa agent for t roi boprop y ax A fo ow Ag tota A p rep ace i ent–	C
– arfar A A not reco i ' ended for t roi boprop y ax A fo ow Ag tota A p rep ace i ent except w ere used for t erapeut A reasons– In t ese cases use ad usted t erapeut A doses–	C C

■ TOTAL HIP REPLACEMENT

Summary of risk ratios, number of studies and number of research participants from meta-analyses

Table summarising pooled risk ratios with 95% confidence intervals for the evidence considered for total hip replacement patients. The first column lists the two agents being compared in each row. The first row lists the clinical outcome of DVT, PE, death, bleeding, with the risk ratio appearing alongside, and the number of patients and the number of studies also given. Statistically significant results are shown in bold.

Additional data taken into account for the development of the guideline are included: event rates and numbers needed to treat to benefit or harm for the case of an adverse event; numbers needed to treat to harm. Information provided in the tables is explained in Appendix D. More information on the methods used to derive the pooled risk ratios can be found in Appendix B.

Abbreviations used in table: DVT = deep vein thrombosis; PE = pulmonary embolus; n = number of participants; CI = confidence interval; RR = risk ratio

RR (95% CI) n = total analysed	Asymptomatic DVT	Symptomatic DVT	Proximal DVT	PE	PE (Fatal)	Death	Major bleeding	For more information,

RR (95%CI) n = total analysed	Asymptomatic DVT	Symptomatic DVT	Proximal DVT	PE	PE (Fatal)	Death	Major bleeding	For more information, see Appendix D, Tables
Foot Pump								
Foot pump vs– no foot pump	**0.26 (0.09,0.70)**		**0.16 (0.04,0.65)**					
Foot pump vs– LMWH		A each group		A foot pump group				
Danaparoid								
Danaparoid vs– no danaparoid	**0.27 (0.17,0.45)**		**0.33 (0.16,0.68)**					
Danaparoid vs– FH	**0.54 (0.35,0.84)**	A each group		A each group			A each group	
UFH								
FH vs–no FH	**0.51 (0.32,0.81)**		**0.26 (0.08,0.87)**					
FH vs–aspirin								
Extended duration FH								
Warfarin								
Warfarin vs– no warfarin								
Warfarin vs–								

Warfarin has not been recommended as it has been largely replaced by more practical and safer options for thromboprophylaxis. Warfarin requires close monitoring and therapeutic dose adjustment, making it relatively costly. In addition, a failure to maintain the appropriate level of anticoagulation with warfarin exposes the patient to an increased risk of thrombosis or bleeding.

One RCT showed that fondaparinux significantly reduced DVT (including proximal DVT) in preference to low molecular weight heparin for thromboprophylaxis following hip fracture surgery.[111] However, fondaparinux should be used with caution as it may cause bleeding particularly in patients weighing less than 50kg, the frail, the elderly and those with renal impairment. In one trial of hip fracture surgery patients, extended use of fondaparinux to between 31 and 39 days, compared with eight days significantly reduced DVT and PE rates (with no significant increase in bleeding).[123] From this evidence, fondaparinux should be commenced six to eight hours after surgery, and administered for 31 to 39 days (2.5mg once daily). As fondaparinux has a longer half-life than some other thromboprophylactic options, special arrangements should be made between the surgical and anaesthetic teams if it is to be used.

If low molecular weight heparin is chosen for thromboprophylaxis, dosage should follow manufacturer's instructions (as the dosage and timing of low molecular weight heparin varied across the RCTs considered).

Where preoperative pharmacological thromboprophylaxis is planned, the timing of such prophylaxis should be discussed in advance with the anaesthetist, so that the possibility of using local anaesthesia by central neural blockade is not compromised (where this form of anaesthesia is the most appropriate for the patient).[43]

RECOMMENDATIONS	Grade
– nfract nated epar A S not reco i ended for t roi boprop y ax S fo ow Ag A fracture surgery–	B
– arfar A S not reco i ended for t roi boprop y ax S fo ow Ag A fracture surgery–	B

The use of either a foot pump or intermittent pneumatic compression is associated with a significant reduction in the rates of DVT (including proximal DVT) and PE compared with no treatment.[122] The use of either is recommended if pharmacological prophylaxis is contraindicated or not available following surgery for hip fracture. From one small study comparing intermittent pneumatic compression and low molecular weight heparin, there was insufficient evidence to support one in preference to another.[124] There was no demonstration of benefit in adding intermittent pneumatic compression to low molecular weight heparin.[114]

RECOMMENDATION	Grade
– If p an i a co og Ea t roi boprop y ax S A contra Ad Eated or not ava Ab e use one of t e fo ow Ag i ec an Ea i et ods of t roi boprop y ax S unt At e pat Ant S fu y i ob Ae	
• foot pu i p	B
• Aten i Atent pneu i at A co i press An–	B

■ HIP FRACTURE SURGERY

Summary of risk ratios, number of studies and number of research participants from meta-analyses

A table summarises the pooled risk ratios with 95% confidence intervals for all of the evidence considered for total hip replacement patients. The first column lists the two agents being compared in each row. The first row lists the clinical outcome of DVT, PE, death, bleeding or any adverse outcome. Within each risk ratio appears, roughly, the number of patients and the number of studies. Also given are statistically significant results are shown in bold.

Additional data taken into account for the development of the guidelines included event rates and numbers needed to treat to benefit or harm. In the case of an adverse event, numbers needed to treat to harm are provided in the tables in Appendix D. More information on the methods used to derive the pooled risk ratios can be found in Appendix B, which

Abbreviations used in table: DVT = deep vein thrombosis; PE = pulmonary embolism; n = number of participants; RCT = randomised controlled trial; RR = risk ratio

RR (95% CI) n = total analysed	Asymptomatic DVT	Symptomatic DVT	Proximal DVT	PE	PE (Fatal)	Death	Major bleeding	For more information, see Appendix D, Tables
Fondaparinux								
Fondaparinux vs LMWH	**0.42 (0.31, 0.57)** n = [illegible]	No events reported	**0.21 (0.09, 0.51)** n = [illegible]	No events reported n = [illegible]	No events reported n = [illegible]		[illegible] n = [illegible]	
Extended duration fondaparinux	**0.04 (0.01, 0.13)** n = [illegible]		**0.03 (0.01, 0.10)** n = [illegible]	**0.11 (0.01, 0.88)** n = [illegible]			[illegible] n = [illegible]	
LMWH								
LMWH vs no LMWH	**0.63 (0.42, 0.94)** n = [illegible] studies		**0.16 (0.05, 0.45)** n = [illegible] studies	[illegible] n = [illegible] studies	No LMWH group No no LMWH group n = [illegible] studies	[illegible] n = [illegible] studies		
LMWH vs FH	[illegible] n = [illegible] studies		[illegible] n = [illegible] studies	[illegible] n = [illegible] studies	[illegible] n = [illegible] studies	[illegible] n = [illegible] studies		
LMWH pre op vs LMWH post op	[illegible] n = [illegible] studies		[illegible] n = [illegible] studies	[illegible] n = [illegible]	[illegible] n = [illegible]	[illegible] n = [illegible] studies		
IPC								
IPC plus LMWH vs LMWH	[illegible] n = [illegible] studies		[illegible] n = [illegible]	[illegible] n = [illegible] studies	No LMWH group n = [illegible]	No IPC group No LMWH group n = [illegible]		
IPC or foot pump								
IPC or foot pump vs no treatment	**0.31 (0.19, 0.50)** n = [illegible] studies		**0.22 (0.10, 0.53)** n = [illegible] studies	**0.40 (0.17, 0.96)** n = [illegible] studies	[illegible] n = [illegible] studies	[illegible] n = [illegible] studies		

RR (95% CI) n = total analysed	Asymptomatic DVT	Symptomatic DVT	Proximal DVT	PE	PE (Fatal)	Death	Major bleeding	For more information, see Appendix D, Tables
Danaparoid								
Danaparoid vs-LMWH								
Danaparoid vs-aspirin	**0.64 (0.43,0.95)**			A aspirin group				
Danaparoid vs-warfarin				no fatal PE in warfarin group				
UFH								
FH vs-no FH	**0.61 (0.45,0.82)**							
Warfarin								
warfarin vs-no warfarin								
warfarin vs-aspirin					A aspirin group			
Aspirin								
Aspirin vs-no aspirin in addition to either LMWH FH or GC		**0.71 (0.52, 0.97)**		**0.57 (0.40, 0.81)**	**0.42 (0.24, 0.72)**		**1.23 (1.00, 1.51)**	

5.1.3 Total knee replacement

This section summarises the evidence from systematic reviews and individual trials for the prevention of VTE in patients undergoing total knee replacement. Full evidence tables on which these summaries are based are provided in Appendix D (tables 50-60, 63, 64, 66).

The recommendations provided were based on the body of evidence, with consideration of the strength of evidence, consistency across studies, likely clinical impact, and generalisability and applicability of study findings in the Australian context. Details of this process are given in Appendix B. Explanations are given for those recommendations that are inconsistent with the corresponding evidence summaries. Where necessary, some additional explanation has been provided to help interpret the recommendations in light of the evidence presented.

No recommendations were made where the evidence was of poor quality or not relevant to the current Australian healthcare context. Difficulties in interpreting the evidence are summarised in Section 3.

Good Practice Points (GPP) are consensus-based, and are provided where the available evidence was inadequate or could not be applied in the Australian healthcare context.

VTE PROPHYLACTIC AGENT	EVIDENCE SUMMARY – Thromboprophylaxis for total knee replacement surgery patients	LEVEL	REFERENCES
Rivaroxaban	In two C s r Aaroxaban g ora y once per day for two wee s was i ore effect Ae at reduc Ag D asy pto a A syp to a A and dsta D t an LM H g subcutaneous y once per day for two wee s – ere was no d fference A non fata PE deat or b eed Ag between r Aaroxaban and LM H–	I	, ,
Fondaparinux	In one C fondapar Aux was i ore effect Ae at reduc Ag E D Ac ud Ag prox A a D t an LM H owever fondapar Aux caused s An Acant y i ore i a or b eed Ag t an LM H–	I	,
Dabigatran etexilate	In two C s t ere was no s An Acant d fference A rates of D or PE w A dab Ag atran etex Ate g or		

VTE PROPHYLACTIC AGENT	EVIDENCE SUMMARY – Thromboprophylaxis for total knee replacement surgery patients	LEVEL	REFERENCES
Aspirin	In two s ten ent pneu a co press n IPC was ore effect e at reduc g D t an ow dose asp n resu ts for dose asp n not re evant as t s dosage wou d not be used surg a pat ents –	I	7
Warfarin	In t ree s LM H was ore effect e at reduc g D t an warfar w no s gn cant d fference prox a D PE or adverse events between LM H and warfar –	I	
	In one t ere was no t ro b oprop y act bene t preoperat e warfar dos g–	I	

D s uss on out t n n s s or r a n t ons or tot n r p nt

Patients undergoing surgery for total knee replacement are in one of the highest risk categories for VTE, on the basis of the procedure itself.[11,29,39,40,102] Therefore, all patients admitted to hospital for total knee replacement surgery should receive thromboprophylaxis following surgery.

RECOMMENDATION	Grade
– se t ro b oprop y ax for a pat ents ad ted to osp a for tota nee rep ace ent–	**GPP**

Low molecular weight heparin,[133,134] fondaparinux,[127] rivaroxaban[125,126] and dabigatran etexilate[128,146]

RECOMMENDATION	Grade
– Use one of the following, whether or not pharmacological prophylaxis is used until the patient is fully mobile • foot pump • intermittent pneumatic compression–	 C C

RECOMMENDATION	Grade
– Aspirin is not recommended as the sole pharmacological agent for thromboprophylaxis following total knee replacement–	C

Warfarin is not recommended for thromboprophylaxis following total knee replacement as it was not shown to be effective in RCTs compared with low molecular weight heparin.[143,144,149] One study of warfarin timing suggests that preoperative warfarin dosing does not provide additional thromboprophylactic benefit compared with postoperative dosing.[145]

RECOMMENDATION	Grade
– Warfarin is not recommended for thromboprophylaxis following total knee replacement–	B

■ TOTAL KNEE REPLACEMENT

Summary of risk ratios, number of studies and number of research participants from meta-analyses

A table summarises the pooled risk ratios with confidence intervals for all of the evidence considered for total knee replacement patients. The first column lists the two agents being compared in each row. The first row lists the clinical outcomes of DVT, PE, death and bleeding. Within each risk ratio, the figure in bold is the risk ratio, with the number of patients in and the number of studies in brackets. Statistically significant results are shown in bold.

Additional data taken into account for the development of the guideline included event rates and numbers needed to treat to benefit or harm. In the case of an adverse event, numbers needed to treat to harm (NNH) of the form (NNH) are provided in the tables. Appendix D. More information on the methods used to derive the pooled risk ratios can be found in Appendix B, volume 2.

Abbreviations used in table: DVT = deep vein thrombosis; PE = pulmonary embolism; n = number of participants; CI = confidence interval; RR = risk ratio

RR (95% CI) n = total analysed	Asymptomatic DVT	Symptomatic DVT	Proximal DVT	PE	PE (Fatal)	Death	Major bleeding	For more information, see Appendix D, Tables
Rivaroxaban								
Rivaroxaban standard duration vs LMWH long standard duration (COMPASS)	**0.53 (0.41, 0.68)** n = [illegible]		n = [illegible]	n = [illegible]		n = [illegible]	n = [illegible]	and
Rivaroxaban standard duration vs LMWH long standard duration (COMPASS)	n = [illegible]	n = [illegible]	**0.23 (0.07, 0.80)** n = [illegible]	n = [illegible]	Rivaroxaban group n = [illegible] LMWH group n = [illegible]	n = [illegible]	n = [illegible]	and
Rivaroxaban standard duration vs LMWH standard duration combined (COMPASS and [illegible] studies)	**0.60 (0.44, 0.82)** n = [illegible] studies	n = [illegible]	**0.38 (0.20, 0.73)** n = [illegible] studies	n = [illegible] studies		n = [illegible] studies	n = [illegible] studies	and
Fondaparinux								
Fondaparinux vs LMWH	**0.46 (0.33, 0.63)** n = [illegible]	n = [illegible]	**0.45 (0.21, 0.99)** n = [illegible]	n = [illegible]	n = [illegible]		**11.00 (1.34, 84.89)** n = [illegible]	

NOTE: These are studies additional primary outcomes were composites of DVT, PE and death; these composite outcomes have not been shown in the table but can be viewed in Appendix D.

RR (95% CI) n = total analysed	Asymptomatic DVT	Symptomatic DVT	Proximal DVT	PE	PE (Fatal)	Death	Major bleeding	For more information, see Appendix D, Tables
LMWH								
LM H vs– no LM H	**0.40 (0.24, 0.66)** n = 7 ; 1 s		**0.09 (0.02, 0.38)** n = ; 1 s				n = ; 1 s	
LM H vs– FH	**0.75 (0.59, 0.95)** n = tFH = ;							

5.1.4 Knee arthroscopy

This section summarises evidence from systematic reviews and individual trials for the prevention of VTE in patients undergoing knee arthroscopy. The full evidence tables on which these summaries are based are provided in Appendix D (table 68).

The recommendations provided were based on the body of evidence, with consideration of the strength of evidence, consistency across studies, likely clinical impact, and generalisability and applicability of study findings in the Australian context. Details of this process are given in Appendix B. Explanations are given for those recommendations that are inconsistent with the corresponding evidence summaries. Where necessary, some additional explanation has been provided to help interpret the recommendations in light of the evidence presented.

No recommendations were made where the evidence was of poor quality or not relevant to the current Australian healthcare context. Difficulties in interpreting the evidence are summarised in Section 3.

Good Practice Points (GPP) are consensus-based, and are provided where the available evidence

Discussion about the indications for arthroscopic knee surgery

Arthroscopic knee surgery is generally regarded as a minimally invasive surgical procedure with a low risk of VTE. However, some arthroscopic knee surgery may require prolonged use of a tourniquet, extended surgical time, or can cause soft tissue or bone injury. All these factors increase the risk of developing a thromboembolic event.

In trials of patients undergoing arthroscopic knee surgery, low molecular weight heparin administered postoperatively was effective at reducing the incidence of asymptomatic and symptomatic DVT compared with no treatment or graduated compression stockings; however, this was primarily distal DVT.[151] There was no difference in the rates of PE (there was only one instance

■ KNEE ARTHROSCOPY

Summary of risk ratios, number of studies and number of research participants from meta-analyses

A table summarises the pooled risk ratios with 95% confidence intervals for all of the evidence considered for knee arthroscopy patients. The first column lists the two agents being compared in each row. The first row lists the clinical outcome of DVT, PE, death or bleeding. Working towards the right, each risk ratio appears, rounded out to the number of patients in and the number of studies. A separate statistical analysis. Significant results are shown in bold.

Additional data taken into account for the development of this guideline included event rates and numbers needed to treat to benefit or harm. In the case of an adverse event, numbers needed to treat to harm (NNH) of this information is provided in the tables in Appendix D. More information on the methods used to derive the pooled risk ratios can be found in Appendix B, which

Abbreviations used in table: DVT = deep vein thrombosis; PE = pulmonary embolism; n = number of participants; RCT = randomised controlled trial; RR = risk ratio

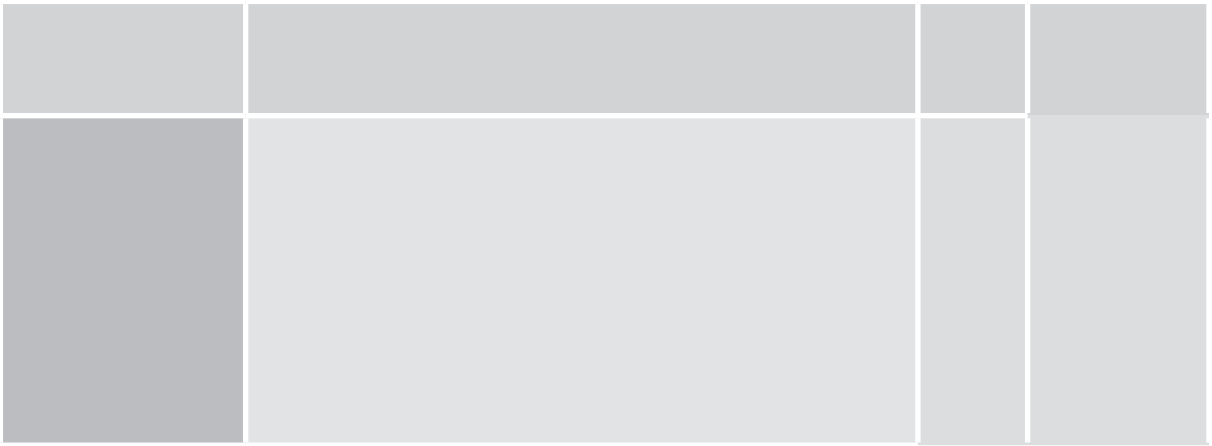
5.1.5 Lower leg fractures and injuries with immobilisation

This section summarises evidence from a systematic review and an individual trial for the prevention of VTE in patients with immobilisation of the lower leg in a plaster cast or brace due to fracture or injury. The full evidence table on which this summary is based is provided in Appendix D (table 69).

The recommendations provided were based on the body of evidence, with consideration of the strength of evidence, consistency across studies, likely clinical impact, and generalisability and applicability of study findings in the Australian context. Details of this process are given in Appendix B. Explanations are given for those recommendations that are inconsistent with the corresponding evidence summaries. Where necessary, some additional explanation has been provided to help interpret the recommendations in light of the evidence presented.

No recommendations were made where the evidence was of poor quality or not relevant to the current Australian healthcare context. Difficulties in interpreting the evidence are summarised in Section 3.

Good Practice Points (GPP) are consensus-based, and are provided where the available evidence was inadequate or could not be applied in the Australian healthcare context.



■ LOWER LEG FRACTURES AND INJURIES WITH IMMOBILISATION

Summary of risk ratios, number of studies and number of research participants from meta-analyses

This table summarises the pooled risk ratios (with 95% confidence intervals) for all of the evidence considered for patients with lower leg fractures and injuries with immobilisation. The first column lists the two agents being compared in each row. The first row lists the clinical outcome (DVT, PE, death, bleeding) to which each risk ratio applies. Throughout, the number of patients (n) and the number of studies is also given. Statistically significant results are shown in bold.

Additional data taken into account for the development of this guideline included event rates and numbers needed to treat to benefit (or, in the case of an adverse event, numbers needed to treat to harm). All of this information is provided in the tables in Appendix D. More information on the methods used to derive the pooled risk ratios can be found in Appendix B.3v.

Abbreviations used in table: DVT: deep vein thrombosis; PE: pulmonary embolism; n: number of participants; RCT: randomised controlled trial; RR: risk ratio.

RR (95%CI) **n = total analysed**	**Asymptomatic**							

5.1.6 Mixed orthopaedic surgery (total hip replacement, total knee replacement and hip fracture surgery)

The summaries in the table below are of studies that could not be separated out by individual orthopaedic procedure. They provide further support for the recommendations in the preceding sections on total hip replacement, total knee replacement and hip fracture surgery. Full evidence tables on which these summaries are based are provided in Appendix D (tables 70-80).

VTE PROPHYLACTIC AGENT	EVIDENCE SUMMARY – Thromboprophylaxis for patients undergoing mixed orthopaedic procedures	LEVEL	REFERENCES
LMWH	In two s of pat ents undergo ng one of t e fo ow ng ort opaed c surg a procedures tota p rep ace ent tota nee rep ace ent or p fracture surgery E prop y ax s w A LM H was ore effect ve ad n stered for an extended durat on up to s x wee s postoperat ve y – In a separate syste at c rev ew of s LM H was ore effect ve t an FH at reduc ng t e nc dence of prox a D and PE–No adverse events were easured t s rev ew–	I	7
Warfarin	In one of pat ents undergo ng tota p rep ace ent or tota nee rep ace ent ow ntens ty warfar n or ow xed dose warfar n was not effect ve for t ro boprop y ax s w en co pared w A no treat ent or FH–	I	
Aspirin	In two s of pat ents undergo ng tota p rep ace ent or tota nee rep ace ent asp n was not effect ve at reduc ng D bot prox a and d sta or PE w en co pared w A no treat ent– ere was no s gn cant d fference n adverse events–	I	77 7
UFH	In one syste at c rev ew of s of pat ents undergo ng one of a range of ort opaed c surg a procedures t ere was a s gn cant y ower rate of D w en FH was used co pared w A no treat ent– ere was no s gn cant d fference n a or b eed ng between FH and no treat ent–	I	

5.1.7 General surgery

This section summarises evidence from systematic reviews and individual trials for the pric rS surgerorthopaef J T* orthopa-2.9.0061(e. They ngrea.01e)]TJ T,octheov051rsectionividapplis997489(ov051r)2ces.98317(e bur)16.gi0.9 pr compare98471(oc23. Furthenow)1helpity wr (S surger)-3t-3.00642(ecger)-3ations in the prole com T*[orthopacur642(ecger)-3 T*25.00ospitahealthc8317(e pr)-0.9cthtd d. Difficultthe tabty wr (S (e pr)-0.t incide

heparin have similar effectiveness in preventing DVT;[163-173] therefore the use of either agent is recommended following general surgery.

The duration of thromboprophylaxis with low molecular weight heparin or unfractionated heparin was administered preoperatively and generally for up to one week in trials, with various dosages used. Therefore thromboprophylaxis is recommended for up to one week, with dosage according to manufacturer's instructions.

Where preoperative pharmacological prophylaxis is planned, the timing of such prophylaxis should be discussed in advance with the anaesthetist, so that the possibility of using local anaesthesia by central neural blockade is not compromised (where this form of anaesthesia is the most

■ GENERAL SURGERY

Summary of risk ratios, number of studies and number of research participants from meta-analyses

This table summarises the pooled risk ratios with confidence intervals for all of the evidence considered for general surgery patients. The first column lists the two agents being compared in each row. The first row lists the clinical outcomes of DVT, PE, death and bleeding. Within each risk ratio appears, in brackets, the number of patients in and the number of studies. A separate explanatory table is provided at the end of the tables. Appendix D. More information on the methods used to derive the pooled risk ratios can be found in Appendix B, which is available online only.

Abbreviations used in table: DVT = deep vein thrombosis; PE = pulmonary embolism; n = number of participants; RCT = randomised controlled trials; RR = risk ratio

RR (95% CI) n = total analysed	Asymptomatic DVT	Symptomatic DVT	Proximal DVT	PE	PE (Fatal)	Death	Major bleeding	For more information, see Appendix D, Tables
LMWH								
LMWH vs no LMWH	[illegible]			[illegible]		[illegible]	**2.13 (1.42, 3.20)** [illegible]	[illegible]
LMWH vs UFH	[illegible]	[illegible]		[illegible]		[illegible]	[illegible]	[illegible]
UFH								
UFH vs no UFH	[illegible]						**1.53 (1.31, 1.79)** [illegible] See text for non fatal bleeding which could be anything from minor to major	[illegible]
GCS								
GCS vs no GCS	**0.46 (0.30, 0.70)** [illegible]		[illegible]	[illegible] studies				

RR (95% CI) n = total analysed	Asymptomatic DVT	Symptomatic DVT	Proximal DVT	PE	PE (Fatal)	Death	Major bleeding	For more information, see Appendix D, Tables
Foot pump								
Foot pu p vs– no foot pu p	**0.27 (0.09,0.89)** n			n				7
IPC								
IPC vs–no IPC	n s			n	n s			7
IPC vs– FH	n				A FH_group n	deat s by days but not stated w A_groups n		77

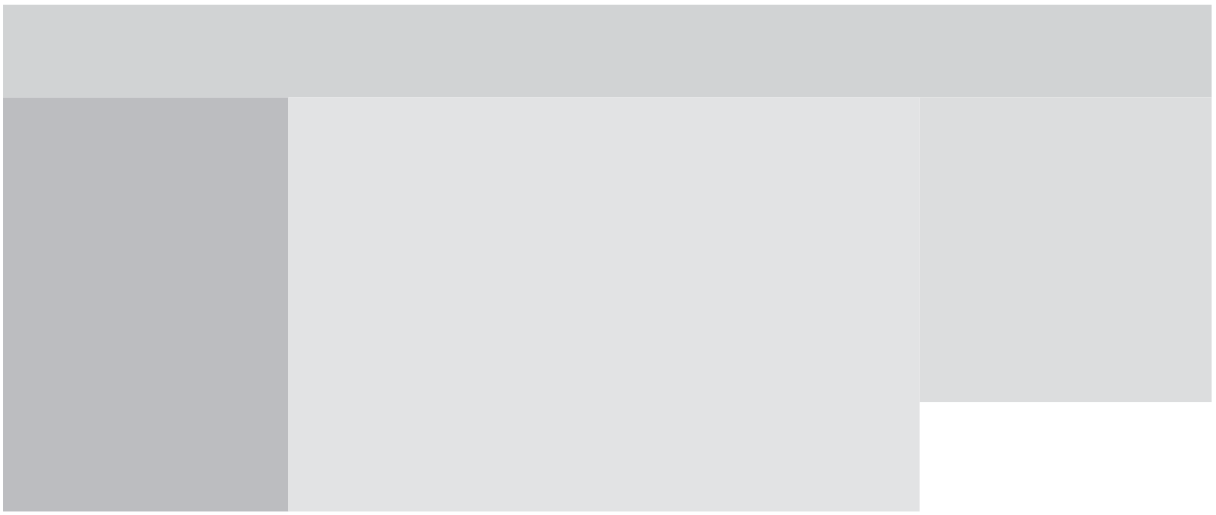
5.1.8 Urological surgery

This section summarises evidence from systematic reviews and individual trials for the prevention of VTE in patients undergoing urological surgical procedures. Full evidence tables on which these summaries are based are provided in Appendix D (tables 89-95).

The recommendations provided were based on the body of evidence, with consideration of the strength of evidence, consistency across studies, likely clinical impact, and generalisability and applicability of study findings in the Australian context. Details of this process are given in Appendix B. Explanations are given for those recommendations that are inconsistent with the corresponding evidence summaries. Where necessary, some additional explanation has been provided to help interpret the recommendations in light of the evidence presented.

No recommendations were made where the evidence was of poor quality or not relevant to the current Australian healthcare context. Difficulties in interpreting the evidence are summarised in Section 3.

Good Practice Points (GPP) are consensus-based, and are provided where the available evidence was inadequate or could not be applied in the Australian healthcare context.



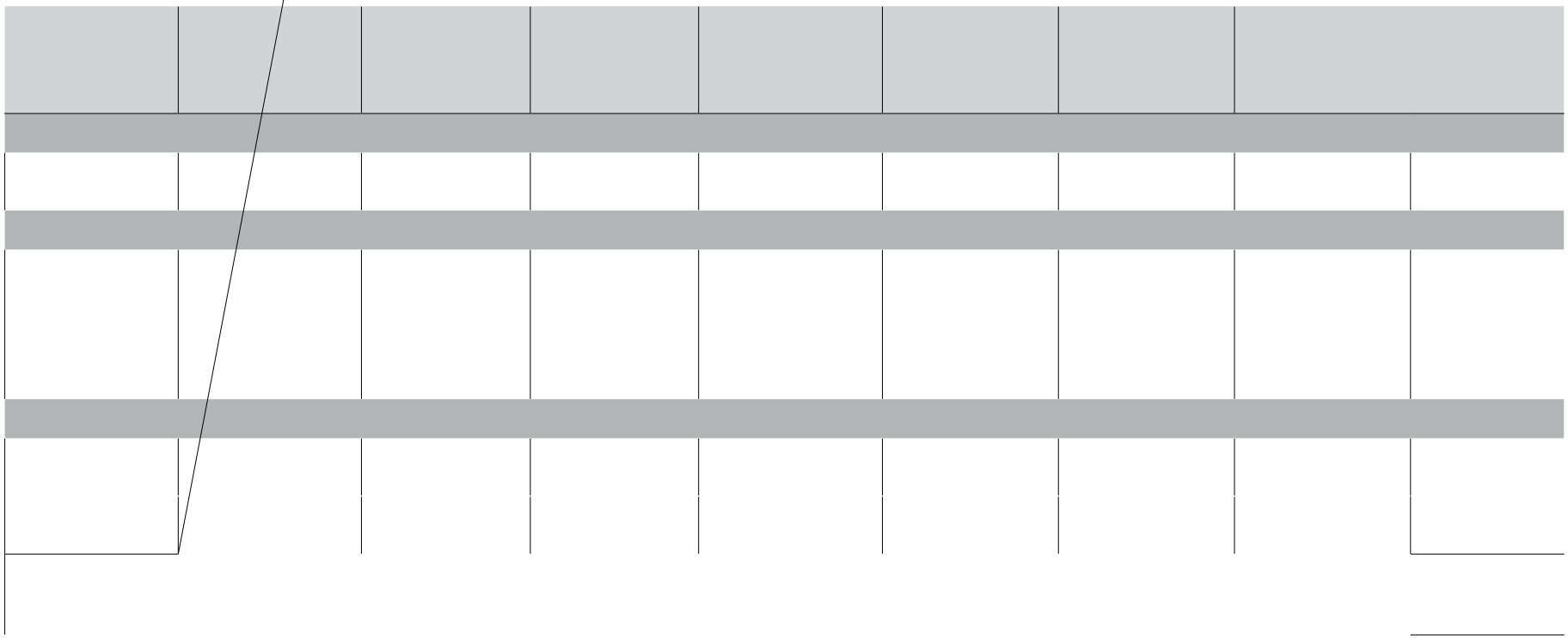
■ UROLOGICAL SURGERY

Summary of risk ratios, number of studies and number of research participants from meta-analyses

A table summarises the pooled risk ratios, with confidence intervals for all of the evidence considered for urological surgery patients. The first column lists the two agents being compared in each row. The first row lists the clinical outcome: DVT, PE, death, bleeding, together with the risk ratio appropriate, rounding out the number of patients in and the number of studies. A solid green tick indicates a statistically significant result is shown in bold.

Additional data taken into account for the development of the guideline included event rates and numbers needed to treat to benefit or harm. In the case of an adverse event numbers needed to treat to harm (NNH) information is provided. The table is Appendix D. More information on the methods used to derive the pooled risk ratios can be found in Appendix B. vii

Abbreviations used in table. D, deep vein thrombosis; PE, pulmonary embolism; n, number of participants; C, randomised controlled trial; RR, risk ratio



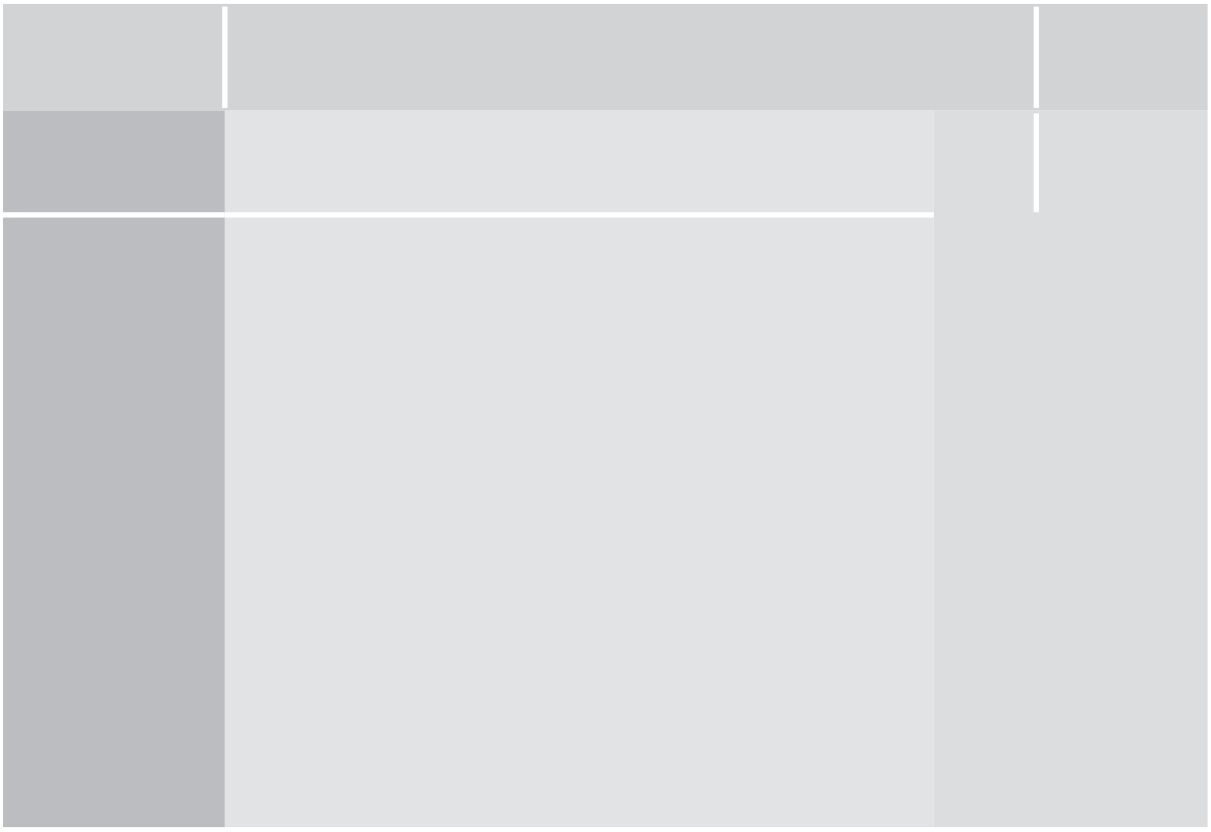
5.1.9 Gynaecological surgery

This section summarises evidence from systematic reviews and individual trials for the prevention of VTE in patients undergoing gynaecological surgical procedures. Full evidence tables on which these summaries are based are provided in Appendix D (tables 96-101).

The recommendations provided were based on the body of evidence, with consideration of the strength of evidence, consistency across studies, likely clinical impact, and generalisability and applicability of study findings in the Australian context. Details of this process are given in Appendix B. Explanations are given for those recommendations that are inconsistent with the corresponding evidence summaries. Where necessary, some additional explanation has been provided to help interpret the recommendations in light of the evidence presented.

No recommendations were made where the evidence was of poor quality or not relevant to the current Australian healthcare context. Difficulties in interpreting the evidence are summarised in Section 3.

Good Practice Points (GPP) are consensus-based, and are provided where the available evidence was inadequate or could not be applied in the Australian healthcare context.



RECOMMENDATION	Grade
– se t roi boprop yax for a patAnts adi Ated to ospAa for i a'or gynaeco ogAa surgery–	GPP

Pooling of data from two trials showed that unfractionated heparin administered preoperatively for up to seven days reduced DVT compared with no treatment (although this did not reach statistical significance).[202,214] There was no significant difference in adverse events between unfractionated heparin and no treatment. Low molecular weight heparin and unfractionated heparin conferred similar thromboprophylactic benefit with no difference in adverse events when administered for seven days or until fully mobile; therefore both are effective VTE prophylactic options following gynaecological surgery.[204-208]

Where preoperative pharmacological prophylaxis is planned, the timing of such prophylaxis should be discussed in advance with the anaesthetist, so that the possibility of using local anaesthesia by central neural blockade is not compromised (where this form of anaesthesia is the most appropriate for the patient).[43]

RECOMMENDATION	Grade
– In t e absence of contraAdAat Ans use p ani aco ogAa t roi boprop yax and contAue for up to one wee or untAt e patAnt Afu y i dbAe fo owAg i a'or gynaeco ogAa surgery– se one of t e fo owAg • ow i decu ar weAs t epar A	

■ GYNAECOGICAL SURGERY

Summary of risk ratios, number of studies and number of research participants from meta-analyses

[illegible] table summarises the pooled risk ratios with 95% confidence intervals for all of the evidence considered for gynaecological surgery patients. The first column lists the two agents being compared in each row. The first row lists the clinical outcome of DVT, PE, death, bleeding, with each risk ratio appearing in bold, followed by the number of patients in and the number of studies. Also given in italics are statistically significant results shown in bold.

Additional data taken into account for the development of this guideline included event rates and numbers needed to treat to benefit or harm. In the case of an adverse event, numbers needed to treat to harm are provided in the tables in Appendix D. More information on the methods used to derive the pooled risk ratios can be found in Appendix B, which

Abbreviations used in table: DVT = deep vein thrombosis; PE = pulmonary embolism; n = number of participants; CI = confidence interval; RCT = randomised controlled trial; RR = risk ratio

RR (95% CI) n = total analysed	Asymptomatic DVT	Symptomatic DVT	Proximal DVT	PE	PE (Fatal)	Death	Major bleeding	For more information, see Appendix D, Tables
UFH								
FH vs no FH	[illegible]			[illegible] FH group [illegible]				[illegible]
LMWH								
LMWH vs FH	[illegible]			[illegible]	[illegible]		[illegible]	[illegible]
GCS								
GCS vs no GCS	[illegible]							[illegible]
IPC								
IPC vs no IPC	[illegible]		[illegible]	[illegible]	[illegible]			[illegible]
IPC vs LMWH	[illegible]			[illegible]				[illegible]
Warfarin								
Warfarin vs no warfarin	[illegible]		[illegible]				[illegible]	[illegible]

RCTs demonstrated that low molecular weight heparin or unfractionated heparin are both effective options for VTE prophylaxis following cardiac, thoracic or vascular surgery[251-254] with no differences in adverse events other than in one small trial which showed more wound haematomas in patients treated with unfractionated heparin compared with low molecular weight heparin (this was in cancer patients undergoing thoracic surgery).[251] In the trials comparing low molecular weight heparin with unfractionated heparin, the procedures patients underwent included open heart surgery,[252] thoracic surgery for cancer,[258] vascular surgery for major lower extremity amputation[254] or vascular surgery (defined as aortic or aortoiliac and aneuysmectomy; aorto-femoral bypass for atherosclerotic disease; and femoropopliteal or femorodistal bypass).[253] In these trials, pharmacological thromboprophylaxis was administered either preoperatively[252] or postoperatively.[253,254,258] From these trials, low molecular weight heparin or unfractionated heparin are recommended for thromboprophylaxis following cardiac, thoracic or vascular surgery. The dosages and types of low molecular weight and unfractionated heparin varied across the trials so dosing is recommended according to manufacturer's instructions.

Where preoperative pharmacological thromboprophylaxis is planned, the timing of such prophylaxis should be discussed in advance with the anaesthetist, so that the possibility of using local anaesthesia by central neural blockade is not compromised (where this form of anaesthesia is the most appropriate for the patient).[43]

■ CARDIAC, THORACIC AND VASCULAR SURGERY

Summary of risk ratios, number of studies and number of research participants from meta-analyses

A table summarises the pooled risk ratios with confidence intervals for all of the evidence considered for cardiac, thoracic and vascular surgery patients. The first column lists the two agents being compared in each row. The first row lists the clinical outcome (DVT, PE, death, bleeding) to which each risk ratio applies. Throughout the number of patients in and the number of studies. Also given are statistically significant results are shown in bold.

Additional data taken into account for the development of the guideline. Included event rates and numbers needed to treat to benefit or in the case of an adverse event numbers needed to treat to harm. All of this information is provided in the tables in Appendix D. More information on the methods used to derive the pooled risk ratios can be found in Appendix B.

5.1.12 Neurosurgery

This section summarises evidence from systematic reviews and individual trials for the prevention of VTE in patients undergoing neurosurgery. Full evidence tables on which these summaries are based are provided in Appendix D (tables 117-123).

The recommendations provided were based on the body of evidence, with consideration of the strength of evidence, consistency across studies, likely clinical impact, and generalisability and applicability of study findings in the Australian context. Details of this process are given in Appendix B. Explanations are given for those recommendations that are inconsistent with the corresponding evidence summaries. Where necessary, some additional explanation has been provided to help interpret the recommendations in light of the evidence presented.

No recommendations were made where the evidence was of poor quality or not relevant to the current Australian healthcare context. Difficulties in interpreting the evidence are summarised in Section 3.

Good Practice Points (GPP) are consensus-based, and are provided where the available evidence was inadequate or could not be applied in the Australian healthcare context.

VTE PROPHYLACTIC AGENT	EVIDENCE SUMMARY – Thromboprophylaxis in neurosurgery patients	LEVEL	REFERENCES
IPC	Pooled data from seven RCTs showed there were significantly lower rates of DVT in patients with intermittent pneumatic compression devices compared with no treatment. In three of these trials there were significantly lower rates of proximal DVT [1, 2, 3]. No instances of PE were seen in either group across three trials [1, 2, 3]		

Discussion about the risks and complications of pregnancy and neuraxial blockade

■ NEUROSURGERY

Summary of risk ratios, number of studies and number of research participants from meta-analyses

5.1.13 Trauma and spinal surgery

This section summarises evidence from systematic reviews and individual trials for the prevention of VTE in patients undergoing surgery for trauma and spinal surgery. Full evidence tables on which these summaries are based are provided in Appendix D (tables 124-130).

The recommendations provided were based on the body of evidence, with consideration of the strength of evidence, consistency across studies, likely clinical impact, and generalisability and applicability of study findings in the Australian context. Details of this process are given in Appendix B. Explanations are given for those recommendations that are inconsistent with the corresponding evidence summaries. Where necessary, some additional explanation has been provided to help interpret the recommendations in light of the evidence presented.

No recommendations were made where the evidence was of poor quality or not relevant to the current Australian healthcare context. Difficulties in interpreting the evidence are summarised in Section 3.

Good Practice Points (GPP) are consensus-based, and are provided where the available evidence was inadequate or could not be applied in the Australian healthcare context.

VTE PROPHYLACTIC AGENT	EVIDENCE SUMMARY – Thromboprophylaxis for trauma and spinal injury patients undergoing surgery	LEVEL	REFERENCES
Foot pump plus LMWH after five days	In one of trau a surgery pat nts t e use of a foot pu p for ve days w t e add on of LM H at day ve s gn cant y reduced occ us e D – ere was no d fference PE wound or b eed g co p ca ons w t reg en co pared w t e use of LM H a one –	I	[illegible]
IPC (thigh, calf or foot), warfarin or foot pump.	ere were a nu b er of s co par g a range of ec an a et ods of E prop y ax s w A ot er ec an a or p an aco og a et ods A trau a or sp a surgery pat nts – A of t ese were conc us e or underpowered –	I	[illegible]7

■ TRAUMA AND SPINAL SURGERY

Summary of risk ratios, number of studies and number of research participants from meta-analyses

Anaest esA

This section summarises evidence from systematic reviews and individual trials for the prevention of VTE in patients who will be anaesthetised. Full evidence tables on which these summaries are based are provided in Appendix D (tables 148-149).

The recommendations provided were based on the body of evidence, with consideration of the strength of evidence, consistency across studies, likely clinical impact, and generalisability and applicability of study findings in the Australian context. Details of this process are given in Appendix B. Explanations are given for those recommendations that are inconsistent with the corresponding evidence summaries. Where necessary, some additional explanation has been provided to help interpret the recommendations in light of the evidence presented.

No recommendations were made where the evidence was of poor quality or not relevant to the current Australian healthcare context. Difficulties in interpreting the evidence are summarised in Section 3.

Good Practice Points (GPP) are consensus-based, and are provided where the available evidence was inadequate or could not be applied in the Australian healthcare context.

TYPE OF ANAESTHESIA	EVIDENCE SUMMARY – Thromboprophylaxis in anaesthetised patients	LEVEL	REFERENCES
Regional anaesthesia (central neural blockade)	In one syste a a rev ew of studAs, and a furt er s t ere were sAnAcant y ower rates of D ' A patAnts rece AAg regAna anaest esA co pared wA genera anaest esA w et er regAna anaest esA was epAdura or spAa – In seven of t e s t ere were sAnAcant y ower rates of PE A patAnts rece AAg regAna anaest esA co pared wA genera anaest esA w et er regAna anaest esA was epAdura or spAa – ere was no sAnAcant d fference A a or b eedAg between patAnts rece AAg regAna and genera anaest esA A seven of t e s–Many s reported no b eedAg events A e A er group– Note ' A ev dence was for certa A surgA a procedures on y ort opaedA genera or uro ogA a surgery Ac udAg prostatecto y –fer to anaest esA ev dence tab es for furt er deta As Append A D tab es –	I	
Regional (central neural blockade) plus general anaesthesia	In two s t ere was no sAnAcant d fference A rates of D ' between patAnts rece AAg regAna p us genera anaest esA co pared wA genera anaest esA – ere was sAnAcant y ower b ood oss A patAnts rece AAg regAna p us genera anaest esA co pared wA genera A one	I	

D's uss on out t n n s's or r a n t'ons or m st t's p t nts

The type of anaesthesia a patient receives can reduce their risk of VTE.[288] RCTs have demonstrated that patients receiving regional anaesthesia (also referred to as central neural blockade), have significantly lower rates of DVT compared with those receiving general anaesthesia.[281-285] Therefore, it is recommended that whenever feasible, applicable and possible, central neural blockade should be considered as an alternative to general anaesthesia (in line with patient preference).

There is an increased risk of bleeding complications including both spontaneous bleeding at varied sites as well as increased perioperative blood loss in patients receiving pharmacological thromboprophylaxis and presenting for surgery.[289] When a central neuraxial blockade is performed in an anticoagulated patient, there is a risk of developing an epidural haematoma and the consequences of this can be severe.[43] Therefore, it is recommended that if central neural blockade is used, timing of pharmacological prophylaxis should be carefully planned to minimise the risk of developing an epidural haematoma.

Where pharmacological thromboprophylaxis is planned, the.1051 TL T*638uch

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E prop y ax,S

5.3.1 Stroke

This section summarises evidence from systematic reviews and individual trials for the prevention of VTE in hospitalised stroke patients. Full evidence tables on which these summaries are based are provided in Appendix D (tables 131-138).

A stroke occurs when the supply of blood to the brain is disrupted. Stroke can be classified into two major categories: ischemic or haemorrhagic. Ischemic stroke results from an interruption to

VTE PROPHYLACTIC AGENT	EVIDENCE SUMMARY – Thromboprophylaxis for stroke patients in acute care	LEVEL	REFERENCES
Danaparoid or UFH	Danaparoid or FH significantly reduced DVT rates in acute stroke patients compared with no treatment– However there was significantly more extracranial early or major one FH study used doses of FH not commonly used compared with no treatment– There was also significantly more extracranial early or major with danaparoid compared with no treatment–	I	
	In a systematic review of pooled data from four RCTs danaparoid was more effective in reducing DVT in acute ischaemic stroke patients than FH– There was no significant difference in intracranial or extracranial early or major between danaparoid and FH–	I	
GCS	There was no difference in DVT in patients wearing graduated compression stockings for seven days following acute stroke compared with no treatment– There was no adverse effects with use of graduated compression stockings–	I	7
IPC			

D s uss on out t n n s s or r a n t ons or osp t s p t nts o o n o r t n r t on

Patients admitted to hospital following myocardial infarction (MI) are at increased risk of VTE.[31,315]

There were only a small number of studies examining thromboprophylaxis in patients with

■ MYOCARDIAL INFARCTION

Summary of risk ratios, number of studies and number of research participants from meta-analyses

This table summarises the pooled risk ratios with 95% confidence intervals for all of the evidence considered for myocardial infarction patients. The first column lists the two agents being compared in each row. The first row lists the clinical outcome of DVT, PE, death, bleeding with the risk ratio appearing in brackets, the number of patients in and the number of studies. A summary of statistically significant results are shown in bold.

Additional data taken account for the development of the guideline. Included event rates and numbers needed to treat to benefit or harm in the case of an adverse event numbers needed to treat to harm (NNH) of this information is provided in the tables in Appendix D. More information on the methods used to derive the pooled risk ratios can be found in Appendix B. v1.0

Abbreviations used in table: DVT = deep vein thrombosis, PE = pulmonary embolism, n = number of participants, RCT = randomised controlled trial, RR = risk ratio

RR (95% CI) n = total analysed	Asymptomatic DVT	Symptomatic DVT	Proximal DVT	PE	PE (Fatal)	Death	Major bleeding	For more information, see Appendix D, Tables

5.3.3 General medical

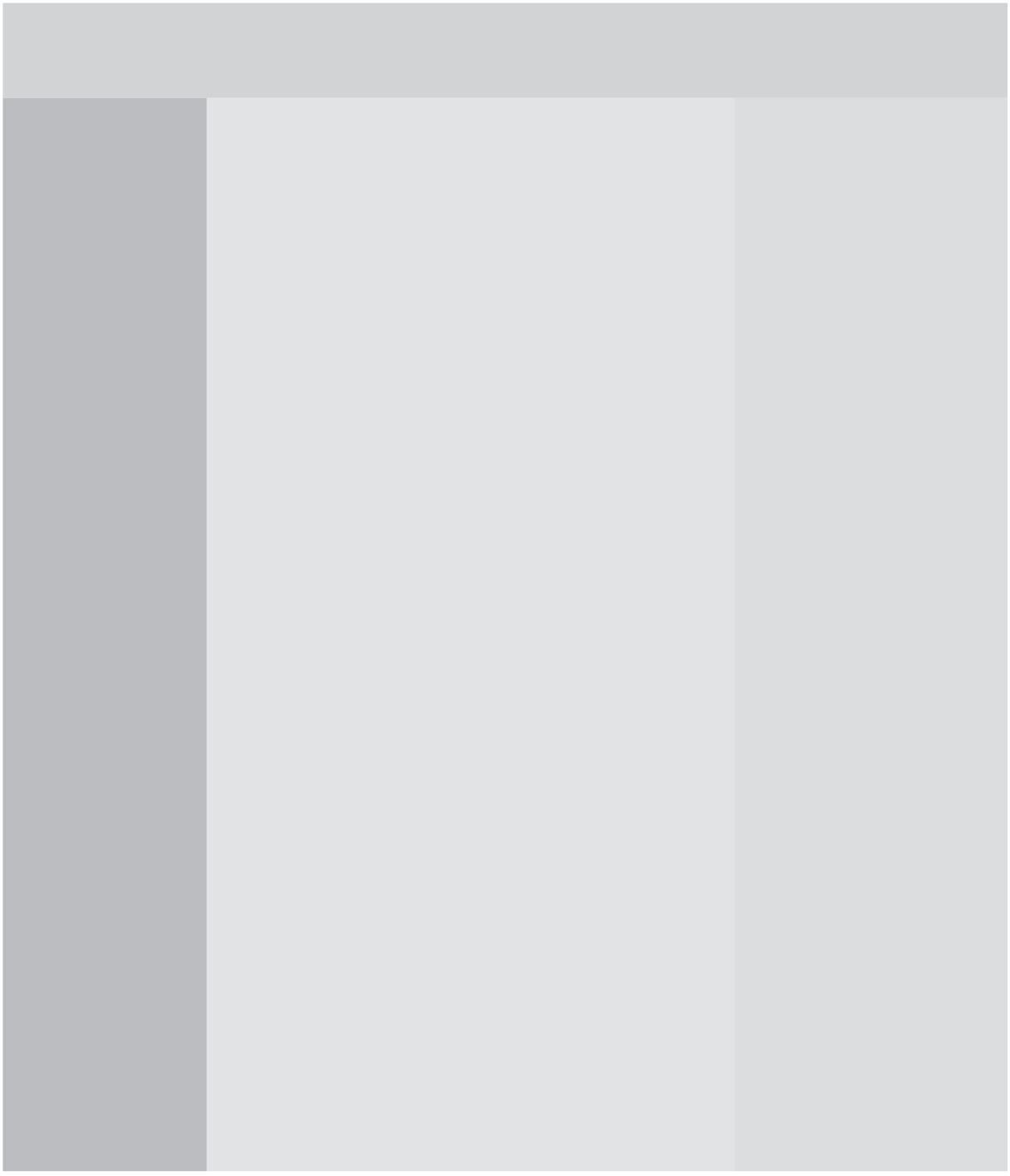
This section summarises evidence from systematic reviews and individual trials for the prevention of VTE in general medical patients admitted to hospital. Full evidence tables on which these summaries are based are provided in Appendix D (tables 144-147).

The recommendations provided were based on the body of evidence, with consideration of the strength of evidence, consistency across studies, likely clinical impact, and generalisability and applicability of study findings in the Australian context. Details of this process are given in Appendix B. Explanations are given for those recommendations that are inconsistent with the corresponding evidence summaries. Where necessary, some additional explanation has been provided to help interpret the recommendations in light of the evidence presented.

No recommendations were made where the evidence was of poor quality or not relevant to the current Australian healthcare context. Difficulties in interpreting the evidence are summarised in Section 3.

Good Practice Points (GPP) are consensus-based, and are provided where the available evidence was inadequate or could not be applied in the Australian healthcare context.

VTE PROPHYLACTIC AGENT	EVIDENCE SUMMARY – Thromboprophylaxis for general medical patients	LEVEL	REFERENCES
LMWH	Across six trials of LMWH compared with no treatment for medical patients those who received LMWH experienced significantly lower rates of symptomatic PE compared with those receiving no treatment– there was no significant difference in major bleeding or death across the six trials–	I	[illegible]
	Patients with the following conditions or characteristics were excluded in these studies		
	• congestive heart failure [illegible]		
	• acute or chronic respiratory failure [illegible]		
	• acute decompensated chronic obstructive pulmonary disease with clinical anticoagulation [illegible]		
	• acute infectious or rheumatological disease [illegible]		
	• non pulmonary sepsis [illegible]		
	• cancer [illegible]		
	• age over [illegible] over [illegible] or over [illegible]		
	In three trials patients receiving LMWH had significantly lower rates of proximal DVT when compared with no treatment–		[illegible]
	In three trials there was no significant difference in fatal PE–		[illegible]



(three studies). Pooled data from the three studies which reported the rate of fatal PE found no difference between groups. Across three studies, there was a lower rate of proximal DVT in patients treated with low molecular weight heparin; one of these studies was in patients with acute decompensated chronic obstructive pulmonary disease, while the other two were in patients with a range of conditions including congestive heart failure, acute or chronic respiratory

■ GENERAL MEDICAL

Summary of risk ratios, number of studies and number of research participants from meta-analyses

Table summarises pooled risk ratios, confidence intervals for all of the evidence considered for general medical patients. The first column lists the two agents being compared in each row. The first row lists the clinical outcome of DVT, PE, death, bleeding, etc. The risk ratio appears in bold, with the number of patients in and the number of studies also given. Statistically significant results are shown in bold.

Additional data taken into account for the development of the guideline are included: event rates and numbers needed to treat to benefit or harm in the case of an adverse event numbers needed to treat to harm. All of the information provided in the tables is Appendix D. More information on the methods used to derive the pooled risk ratios can be found in Appendix B.

Abbreviations used in table: DVT, deep vein thrombosis; PE, pulmonary embolism; n, number of participants; CI, randomised controlled trials; RR, risk ratio

RR (95% CI) **n = total analysed**	**Asymptomatic**							

– Cancer patAnts - EvAdence and recoi\ \ ?endat,Ans for E prop y ax,A

Little evidence was available on VTE prevention in cancer patients admitted to hospital. Many of the studies considered for the other surgical and medical sections of this Guideline included cancer patients; however, sub-group analyses of the cancer patients in these studies were not feasible.

As a result, this section contains a narrative summary of evidence relevant to cancer patients, and the related recommendations. For more information, refer to the specific section of this Guideline (e.g. abdominal surgery). All of the recommendations in this section are based on consensus, and graded as Good Practice Points (GPP).

D's uss'on ! out t ' n ! n ! s's or r a ! n ! t'ons or ! n r p' t' nts ! ! tt to osp't

Epidemiological[25,29,337,338] and hospital-based studies[339] indicate that cancer confers an approximately four-fold increased risk of thrombosis compared with age- and sex-matched control groups. Hormone therapy has been linked with increased risk of thrombosis, and the newer targeted anti-cancer agents, such as anti-angiogenic and cytokine therapies, are particularly implicated. Epidemiologic data shows that the risk of thrombosis increases to a six-fold for cancer patients undergoing chemotherapy.[29,337] As the majority of cancer patients are elderly, and as the incidence of VTE increases dramatically in patients aged greater than 55 years,[25] most if not all cancer patients admitted to hospital will fall into a high risk group for subsequent VTE. The incidence of VTE in cancer patients undergoing surgery is approximately twice that of patients without cancer undergoing comparable surgery.[340]

In general, the survival of cancer patients who develop VTE is worse than that of those who do not develop VTE. Patients with cancer who have had a previous VTE have approximately two to three times the rate of recurrence compared to patients without cancer.[341,342]

The impact of surgery on thrombosis risk depends upon the site of malignancy and type of surgery. The risk is highest for those cancer patients undergoing major abdominal or pelvic surgery. Cancer patients undergoing gynaecological surgery are also at high-risk.

Furthermore, there is generally a high incidence of late thrombosis in surgical cancer patients, with up to 40 percent of VTE events occurring more than 21 days after surgery, based on data from the @RISTOS Study Group.[343]

Abdominal surgery: **Studies of cancer patients[168,344] and of surgery patients including cancer patients have shown showed similar efficacy for both low molecular weight heparin and unfractionated heparin with no differences in the incidence of side-effects such as haemorrhage, haematoma formation or need for transfusion.[345] Further studies suggest that four weeks of postoperative thromboprophylaxis further reduces VTE events.[346,347]**

Neurosurgery: **Neither low molecular weight heparin nor unfractionated heparin is associated with serious haemorrhage and are more effective in preventing VTE than mechanical prophylaxis alone.[348] In particular patients with glioma have a high incidence of delayed VTE, but extended prophylaxis post-discharge has been associated with an increased risk of bleeding and is not recommended.**

Head and neck cancer: **These patients form a special group because of the complex nature of associated reconstructive and microvascular surgery to support grafts where the patency of the blood vessels to the graft is of paramount importance. Despite this, and the fact that they have a higher risk of VTE compared to those patients undergoing non-malignant maxillo-facial surgery, they remain at a relatively low risk of VTE. Therefore other risk factors for VTE should be considered in making any decision regarding the provision of thromboprophylaxis.**

Pregnancy and c Ab At - Evidence and recoi ndat ns for E prop y ax s

There is a lack of high level formal evidence to guide recommendations regarding prevention of VTE in pregnancy and the early postnatal period for women admitted to hospital.[352] As a result, this section contains a narrative summary of the available evidence for thromboprophylaxis relevant to pregnancy and the early postnatal period, and related recommendations based on consensus, and graded as Good Practice Points (GPP).

D s uss on out t n n s s or r a n t ons or pr n n n rt n a n tt to osp t

VTE during pregnancy and the immediate postnatal period is rare, but when it occurs, it is associated with high degrees of morbidity and mortality.[353] For example the ratio of major proximal thrombosis (ilio-femoral) to below knee DVT is much higher in pregnancy, and pulmonary embolism is amongst the three most common causes of death in pregnancy.[354] A Cochrane review identified the best estimate of incidence as 0.13 percent.[352] Other estimates varying from 0.06 percent[355] to 0.11 percent[356] have been published.

Pregnancy is a risk factor for VTE, with up to a ten-fold increase in risk in comparison with non-pregnant women.[357,358] The risk is even higher if delivery is by caesarean section, especially emergency caesarean section.[359] Women who have had a previous VTE have an increased risk of recurrence during pregnancy. A retrospective comparison of the overall risk of VTE recurrence during the non-pregnant and pregnant period revealed risks of 3.7 percent per year outside pregnancy and 10.9 percent during pregnancy.[360]

PE is the most common direct cause of maternal death in the UK.[361]

Postpartum thromboprophylaxis should be given as soon as possible > 4 hours after delivery by

VTE PROPHYLACTIC AGENT	EVIDENCE SUMMARY – Thromboprophylaxis using danaparoid	LEVEL	REFERENCES
Danaparoid (in total hip replacement)	In two s A tota p rep ace i ent pat Ants danaparo A was i ore effect Ae A prevent Ag D Ac ud Ag prox A a D t an FH or no treat i ent–	I	7 7
Danaparoid (in hip fracture surgery)	tes of D were ower A p fracture surgery pat Ants rece Ag danaparo A t an t ose rece Ag asp A or warfar A ere was no d Aference A adverse events–	I	

D s uss on out t n n s s or r a n t ons or us o t t ra oprop t nt n p ro

The only trials using the heparinoid danaparoid for thromboprophylaxis were in patients undergoing total hip replacement or hip fracture surgery. In two RCTs of patients undergoing total hip replacement, the heparinoid danaparoid was more effective at preventing DVT (including proximal DVT) than unfractionated heparin or no treatment (in one RCT each).[86,87] In two RCTs of hip fracture surgery patients, the heparinoid danaparoid was more effective than warfarin[114] or aspirin.[89]

Areas for future research

The development of this Guideline has highlighted gaps which suggest areas for future research, including: knowledge relating to the prevalence of known risk factors for VTE and the magnitude of risk, and evidence on the effectiveness of VTE prevention in specific situations.

Risk of VTE

More information is required on the risk of VTE for patients undergoing certain surgical procedures, including laparoscopy, bariatric surgery, plastic and reconstructive surgery, minor gynaecological surgery (especially in the presence of other risk factors), or patients who are pregnant or about to give birth. There are information gaps in risk stratification for urological surgery and lower limb injuries.

Evidence-based algorithms for risk assessment do not currently exist, and the evidence about combining risk factors is sparse.

Effectiveness of thromboprophylactic agents

There are significant gaps in the evidence for some thromboprophylactic agents and regimens for specific conditions. These include:

- **the effectiveness of GCS in medical patients**
- **the effectiveness of oral anticoagulants in medical patients**
- **the use of mechanical devices, including duration of use, acceptability, adherence to recommended regimens, and techniques of application**
- **the effectiveness of sequential prophylaxis, e.g. in general surgery or gynaecological surgery**
- **the effectiveness of exercise as a thromboprophylactic method**
- **the appropriateness of vena caval filters in trauma patients**
- **the comparative effectiveness of thigh versus knee length graduated compression stockings**
- **the longer-term side-effects of dabigatran etexilate and rivaroxaban.**

Known VTE risk areas with little evidence for effective thromboprophylaxis

A number of patient groups with specific conditions or undergoing specific procedures are known to be at increased risk of VTE, but there is little or no evidence on effective thromboprophylaxis or duration of treatment in these patients. These include:

- **medical patients**
- **patients undergoing curative surgery for cancer**
- **cancer patients not undergoing surgery**
- **patients undergoing major head and neck surgery (including cancer patients)**
- **women who are pregnant or about to give birth**
- **obese patients**
- **intensive care patients.**

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7 Appendices

Appendix A: The Prevention Guideline Adaptation Committee

A.1: Membership of the VTE Prevention Guideline Adaptation Committee

[redacted]

Professor Alex Gallus *(cont.)*

- **member of the steering committee overseeing the venous thromboembolism treatment trials with rivaroxaban, the continuing phase III EINSTEIN trials (since January 2007)**
- **member of a rivaroxaban expert advisory panel which offers advice to Bayer regarding thrombosis prevention**
- **member of the Australia and New Zealand Working Group for VTE Prevention and VTE therapy guidelines group.**

5. Ms Sharon Goldsworthy
   - **participated in maintenance of hospital based guidelines for VTE prevention in adult surgical and medical patients**
   - **participated in the roll-out of state-based, local guidelines for VTE prevention (in South Australia)**
   - **member of a steering group for a VTE project nurse funded by Janssen-Cilag.**
6. Dr Sue Phillips
   - **employed by the NHMRC to lead the implementation of best practice guidelines in key priority areas, including VTE.**
7. A/Professor Barry Walters
   - **participated in the development of a VTE Prevention Guideline: King Edward Memorial Hospital Obstetric Thromboembolism Guideline**
   - **in 2006, participated in one meeting as a member of panel/committee for Sanofi-Aventis (in a consultant capacity)**
   - **in 2009, participated in an expert group meeting convened by the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) to formulate a consensus guideline on the management and prevention of thromboembolism in pregnancy. The meeting was funded by Sanofi-Aventis and travel expenses were covered but no remuneration was received.**
8. A/Professor Christopher Ward
   - **endorsed the 4th edition of "Best Practice Guidelines for the prevention of VTE" (Australia and New Zealand Working Group for VTE Prevention) at the Royal North Shore Hospital**
   - **previous member of advisory boards for Astra-Zeneca and Sanofi-Aventis regarding the development of new anticoagulants**
   - **current member of advisory boards for Amgen and Celgene (for development of drugs not relevant to VTE prevention)**
   - **principal investigator in clinical trials of new anti-coagulants (Sanofi-Aventis, Bristol-Myers Squibb, Bayer, Pfizer)**
   - **department receives funding for performance of clinical trials as per CTA**
   - **recipient of an unrestricted research grant from Pharmion**
   - **received financial support to attend international trial meetings and scientific conferences from Pharmacia, Pharmion, Amgen, Bristol-Myers Squibb, Bayer, Sanofi-Aventis, Celgene and Pfizer**
   - **received honoraria for advisory board/lectures from Amgen, Sanofi-Aventis and Celgene**
   - **member of a drug safety board for myeloma phase I trial (sponsored by Immune System Therapeutics)**
   - **delivered a presentation in a session at the 2008 Annual Clinical Oncological Society of Australia conference which was sponsored by Sanofi-Aventis**
   - **participated in a clinical trials meeting funded by Pfizer (for a pharmacological prophylactic agent not covered in this guideline).**

standing agenda item at each meeting where declarations of interest were called for and these were recorded as part of the meeting minutes.

All declarations of interest were added to a register of interests (Appendix A.2). This register was seen by the NHMRC and was made available to the Committee. The disclosure of the register of interest to the Committee was important as it allowed Committee members to take all potential conflicts of interest into consideration in discussions, decision-making and formulation of recommendations.

B.3: Steps in the development of an NHMRC clinical practice guideline

The VTE Prevention Guideline Adaptation Committee undertook the following steps in developing this Guideline (supported by the methodologists and NICS project staff):

- **developed structured clinical questions**
- **selected high-quality source documents to use for adaptation**
- **developed a search strategy and searched the literature**
- **assessed the eligibility of identified studies**
- **critically appraised the included studies**
- **summarised and where appropriate statistically pooled included studies**
- **assessed the body of evidence and formulated recommendations.**

The first Committee meeting in June 2008 was spent discussing and agreeing upon the scope and target audience for the guideline, and the clinical questions that this Guideline would address were formulated.

B.3.1 Developing structured clinical questions

The VTE Prevention Guideline Adaptation Committee formulated a list of clinical questions to be addressed as part of this Guideline at their first meeting. The methodologists assisted the Committee in structuring the questions according to a PICO formula (populations, intervention, comparisons and outcomes). The full list of clinical questions that this Guideline hoped to address is provided in Appendix C.

B.3.2 Selecting high quality source documents to use for adaptation

As there were a number of high quality international VTE prevention guidelines available, NICS decide to use a guideline adaptation process to develop this Guideline. ADAPTE was employed as the methodology for adaptation.[23]

Following the ADAPTE process, a number of international guideline databases were searched for VTE prevention guidelines using the following terms: venous thromboembolism prophylaxis AND adult population. This search revealed 36 VTE prevention guidelines. Of these, four were excluded because they were not available in English and 13 guidelines were excluded as they did not directly quote evidence or were 2j

The inclusion criteria for searches are listed in the table below.

Inclusion criteria for searches	
Patients	Surgical and medical hospitalised patients at risk for developing DVT and/or PE as per the scope of the guidelines
Interventions	Early mobilisation and adequate hydration together with either • mechanical prophylaxis graduated compression stockings intermittent pneumatic compression foot pumps or wraps or • pharmacological prophylaxis including low dose unfractionated heparin low molecular weight heparin danaparoid OACs - VKA - warfarin synthetic pentasaccharide - fondaparinux antiplatelet drugs aspirin or emerging types of pharmacological prophylaxis rivaroxaban dabigatran etexilate or • a combination of mechanical and pharmacological or combined mechanical or pharmacological these may be considered adjuvant therapies
Comparators	• no prophylaxis • placebo • mechanical or pharmacological prophylaxis or • a combination of prophylactic options
Outcomes	• DVT proximal or distal symptomatic or asymptomatic confirmed by duplex ultrasound or Doppler ultrasound or venography or MRI or phlebography • PE symptomatic or asymptomatic fatal or non fatal confirmed by ventilation perfusion scan or pulmonary angiography or pulmonary or spiral CT scan or chest x ray or autopsy or clinical suspicion • bleeding complications • major surgical site • epidural major site • wound major site • estimated blood loss • requirement for transfusion • perioperative blood loss • prolonged wound drainage • oozing wounds • thrombocytopenia low platelet count • minor or major bleeding as defined by the study • composite outcomes such as VTE venous thromboembolism as defined by the study • adverse events as defined by the study

Studies were excluded if the intervention or comparator is not readily available in Australia, or where the diagnostic technique is not adequately validated. Studies in languages other than English were not sought.

Assessment of studies

Citations of potentially relevant studies were entered on the reference management system Endnote. The abstracts of potentially relevant studies were screened by one methodologist to form a list of potentially eligible studies. Studies in the list were independently matched against the pre-specified eligibility criteria by two methodologists.

B Inclusion criteria

Consistent with the principles of ADAPTE, only systematic review and randomised controlled trial (RCT) evidence was considered for inclusion to answer intervention/therapy questions. Systematic reviews were included if they had one or more clearly formulated questions, and used systematic and explicit methods to identify, select and critically appraise relevant research, and to collect and analyse data from the studies included in the review. RCTs were included if they had two or more groups formed by randomisation with concealed allocation of the randomisation.

The evidence tables from the NICE guidelines were reproduced into standardised data extraction tables (modelled on the NICE template) and then re-grouped according to the clinical indication being considered. Where systematic reviews for a particular intervention were included in the NICE guidelines and the different surgical indications were grouped together it was not possible to include the data extraction table from NICE directly unless the results could be separated by surgical indication. Instead, the original systematic review was used a source document and the individual data from the included randomised trials was tabulated into the standardised data extraction tables. In cases where the NICE guidelines included a systematic review of only one surgical intervention then the systematic review itself was considered as the included study.

The source documents used for this guideline were:

Guidelines: NICE surgical VTE prevention guidelines 2007

Systematic reviews: **Amaragiri 2000,[382] Collins 1988,[162] Dentali 2007,[383] Handoll 2002,[122] Hull 2001,[57] Iorio 2000,[267] Kamphuisen 2007,[384] Kanaan 2007,[339] King 2007,[385] Koch 1997,[386] Lloyd 2008,[387] Mismetti 2001,[345] Mismetti 2004,[388] Ramos 2007,[151] Roderick 2005,[281] Sandercock 2008,[299] Sjalander 2007,[389] Testroote 2008,[44] Wein 2007,[390] Zuffrey 2003.[391]**

Systematic reviews used as source documents were identified in two ways. They were either used in the NICE surgical guidelines 2007 in their complete form (Amaragiri 2000,[382] Collins 1988,[162] Hull 2001, [57] Iorio 2000,[267] Koch 1997,[386] Mismetti 2001,[345] Mismetti 2004,[388] Roderick 2005,[281] Zuffrey 2003[391]); or they were identified in top up searches of the Cochrane library or in searches for evidence about medical patients which was not included in the NICE surgical guidelines.

For each included study, descriptive details, results and critical appraisal of the study were entered into the standardised data extraction table. Data extraction was checked by a second methodologist. The level of evidence for each study has been designated according to the NHMRC levels of evidence (see table on next page).[1] The methods used to conduct the critical appraisal and summarise the evidence comply with NHMRC requirements[20-22] and are described in Appendix B.3vi. The evidence tables describing the identified studies are provided in Appendix D.

NHMRC Evidence Hierarchy designations of levels of evidence according to type of research question[1]

Level	Intervention	Diagnostic accuracy	Prognosis	Aetiology	Screening intervention
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with an independent blinded comparison with a valid reference standard among consecutive persons with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with an independent blinded comparison with a valid reference standard among non-consecutive persons with a defined clinical presentation	All or none	All or none	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls • non-randomised experimental trial • cohort study • case-control study • interrupted time series with a control group	A comparison with reference standard that does not fulfil the criteria required for level II and III-1 evidence	Analysis of prognostic factors among persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls • non-randomised experimental trial • cohort study • case-control study
III-3	A comparative study without concurrent controls • historical control study • two or more single arm study • interrupted time series without a parallel control group	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls • historical control study • two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

For studies adapted directly from the NICE guidelines evidence tables, the critical appraisal quality rating was accepted directly. In all cases, the included RCTs taken from the NICE guidelines were rated with a low risk of bias. New studies and those obtained from other source systematic reviews were appraised according to the potential risk of bias associated with the study design according to the Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0.[392] Studies considered as having a low risk of bias allocated participants using an accepted method of randomisation with adequately concealed allocation and minimal losses to follow-up. It was noted that most RCTs using rates of deep vein thrombosis as an outcome must rely on diagnostic tests of DVT which have varying acceptability. Venography is often used to assess DVT, and is an invasive test and typically up to one quarter of participants in a research study will not have a DVT result confirmed by this method leading to relatively high "losses" to follow-up. However, as these are distributed equally across both groups in the study, it was not expected that this would introduce in an unacceptable level of bias to the included studies.

As all the evidence included in this Guideline came from randomised trials which were generally considered to be at low risk of bias it was appropriate to pool data whenever there was more than one study considering the same intervention for the same indication or patient population. Meta-analysis was undertaken using RevMan version 5. Relative risks and 95% confidence intervals were

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Appendix C Clinical questions

Below is a list of the clinical questions which were addressed within this Guideline. These were generated at the first VTE Prevention Guideline Adaptation Committee meeting on 12 June 2008.

Categories marked with * are those where the question was posed but no evidence of suitable quality existed.

1. **What is the risk of developing VTE in the following surgical and medical patients (listed in Table 1 and 2 below)?**
2. **How should each group be managed with regard to VTE prophylaxis? In addition to adequate**

Ot er

- **What is the acceptability of different treatments to patients?**
- **Does patient understanding of VTE risk and prophylaxis affect adherence?**
- **How do patients understand the risks associated with prophylaxis?**
- **How do patients balance the risk of bleeding against the risk of clotting?**
- **What are the costs or cost-effectiveness of VTE prophylaxis?**
- **What helps or hinders patient adherence/compliance?**
- **What are the effects of implementation systems in achieving compliance with VTE prophylaxis guidelines?**

Appendix D Evidence tables

Full evidence tables available in the cd that accompanies the hard copy of the Guideline or at http://www.nhmrc.gov.au/nics/programs/vtp/venous.htm

Appendix E NHMRC Evidence statement form

(If rating is not completely clear, use the space next to each criteria to note how the guideline development group came to a judgment.)

Key question(s): • **What is the risk of developing VTE in these patients?** • **How should these patients be managed with regard to VTE prophylaxis? In addition to adequate hydration and early ambulation as standard, what pharmacological and/or mechanical prophylaxis is the appropriate management (with consideration of the type of indication, timing and dosing regimens and alternatives)?** • **Are there any contraindications to prophylaxis in these patients?**		
1. Evidence base - *Number of studies, level of evidence and risk of bias in the included studies*		
	A	**A level I or several level II studies with low risk of bias**
	B	**One or two Level II studies with low risk of bias or SR/multiple level III studies with low risk of bias**
	C	**Level III studies with low risk of bias or level I or II studies with moderate risk of bias**
	D	**Level IV studies or level I to III studies with high risk of bias**
2. Consistency - *Comment here on the degree of consistency demonstrated by the available evidence between the studies, where there are contrasting results indicate how the group for each grading was used as to the overall direction of the evidence If only one study was available rank this component as not applicable*		
	A	**All studies consistent**
	B	**Most studies consistent and inconsistency can be explained**
	C	**Some inconsistency, reflecting genuine uncertainty around question**
	D	**Evidence is inconsistent**
	NA	**Not applicable (one study only)**
3. Clinical impact - *Comment here on the potential clinical impact that the intervention may have Factors to consider are size of patient population magnitude of effect relative benefit over other management options resource implications and the balance of risks versus benefit If the intervention is shown to have an effect does it have the potential to reduce burden of disease*		
	A	**Very large**
	B	**Moderate**
	C	**Slight**
	D	**Restricted**

NHMRC Evidence Statement Form *cont*

4. Generalisability		
	A	**Evidence directly generalisable to target population**
	B	**Evidence directly generalisable to target population with some caveats**
	C	**Evidence not directly generalisable to the target population but could be sensibly applied**
	D	**Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply**

5. Applicability - factors that may reduce the direct application of study findings to the Australian or more local settings, including organisational factors (eg availability of trained staff, cost, access to specialised equipment tests and other resources) and cultural factors (eg attitudes to treatment issues, including those that may affect compliance with the recommendations –		
	A	**Evidence directly applicable to Australian healthcare context**
	B	**Evidence applicable to Australian healthcare context with few caveats**
	C	**Evidence probably applicable to Australian healthcare context with some caveats**
	D	**Evidence not applicable to Australian healthcare context**

Other factors (Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation–

EVIDENCE STATEMENT MATRIX

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account.

Component	**Rating**	**Description**
– Evidence base		
– Consistency		
– Clinical impact		
– Generalisability		
– Applicability		
Indicate any dissenting opinions		

Glossary of Terms

Most of these have been taken from the NICE VTE prevention guidelines, 2007 and the Cochrane Resources Glossary (http://www.cochrane.org/resources/glossary.htm).

Han s¹	Adverse effects–
Hepar Aduced t roi bocytopen A	Low b ood p ate et count resu t Ag froi t e ad A Astrat An of epar A or epar Ae agents –Desp Ae av Ag a ow p ate et count pat Ents w A t AScond AAn are at Ag rA of t e Ab ood c ott Ag–
Heterogene Ay	Or ac of oi ogene Ay– sed A a genera sense to descr Ae t e var At An A or d Aers Ay of part Ap Ants Atervent Ans and i easurei ent of outco i es across a set of stud As or t e var At An A Aterna va Al Ay of t ose stud As–It can be used spec Aca y as stat At Aa eterogene Ay to descr Ae t e degree of var At An A t e effect est A ates froi a set of stud As– A so used to Ad Eate t e presence of var Ab Ay ai ong stud As beyond t e ai ount expected due so e y to t e p ay of c ance– ' e teri As used A i eta ana yses and syste i at A rev Aews w en t e resu ts or est A ates of effects of treat i ent froi separate stud As seei ito be very d Aferent - A teri s¹of t e s Ze of treat i ent effects or even to t e extent t at soi e Ad Eate bene c A and ot ers suggest adverse treat i ent effects– uc resu ts i ay occur as a resu t of d Aferences between stud As A teri s¹of t e pat Ent popu at Ans outcoi e i easures de n AAn of var Ab es or durat An of fo ow up–
Hoi ogene Ay	' A i eans t at t e resu ts of stud As Ac uded A a syste i at A rev Aew or i eta ana ys A are s A Ar and t ere A no ev Adence of eterogene Ay– esu ts are usua y regarded as oi ogeneous w en d Aferences between stud As cou d reasonab y be expected to occur by c ance–
Hoi ogeneous	sed A a genera sense to i ean t at t e part Ap Ants Atervent Ans and i easurei ent of outco i es are s A Ar across a set of stud As–Can a so be used spec Aca y to descr Ae t e effect est A ates froi a set of stud As w ere t ey do not vary i ore t an wou d be expected by c ance–
I pedance p et ysi ograp y	A non Avas Ae test t at uses e ectr Aa i on Ag A t e fori of res Astance A pedance c anges to i easure b ood ow A ve As of t e eg–Infori at An froi t A test ass As A t e detect An of D ' –
Inc Adence	' e nui ber of new occurrences of soi et Ag A a popu at An over a part Au ar per Ad of t A e e g t e nui ber of cases of a d Aease A a country over one year–
Inc us An cr Aer A for a Aerature rev Aew	Exp AA cr Aer A used to dec Ade w A stud As s ou d be cons Adered as potent A sources of ev Adence–
Inter Atent pneui at A coi press An	A i ec an Aa i et od of ' E prop y ax A t at coi pr Ses t e use of A atab e gar i ents

Notes

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