



CLINICAL PRACTICE GUIDELINE

for the prevention of venous thromboembolism
(deep vein thrombosis and pulmonary embolism)
in patients admitted to Australian hospitals

DRAFT FOR
PUBLIC CONSULTATION
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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 .

Executive summary

Although effective pharmacological and mechanical preventive options have existed for decades, venous thromboembolism (VTE) remains a major cause of morbidity and a significant cause of mortality in hospitalised patients across Australia and internationally. Data from research and clinical audits suggest that the available preventive options are under-utilised and inconsistently applied. Variations in practice and the emergence of new anticoagulants underline the need for an evidence-based VTE prevention guideline suited to the Australian healthcare context.

This Guideline provides recommendations on thromboprophylaxis for adult patients admitted to Australian hospitals. It covers patients undergoing all major types of surgery, patients with acute medical illnesses, trauma patients, patients admitted to intensive care units, cancer patients, and patients hospitalised during pregnancy and the puerperium.

The Guideline was prepared largely through critical appraisal and adaptation of existing high-quality international VTE prevention guidelines, in preference to a re-examination of primary research publications and systematic reviews. From the critical appraisal, the main source of evidence selected was a guideline produced in 2007 by the National Institute for Health and Clinical Excellence (NICE) in the UK. The adaptation of existing guidelines expedited the development of this Guideline, a consultation draft of which was produced within approximately 12 months.

A multidisciplinary VTE Prevention Guideline Adaptation Committee, comprising experts in the prevention of VTE and a consumer representative, was appointed by the NHMRC to provide advice on the following: the questions that directed the search for evidence; the selection of guidelines for adaptation; the adaptation process; the interpretation of primary research findings where existing guidelines did not provide sufficient evidence; and the framing of the clinical practice recommendations.

In assessing the evidence from the existing guidelines and other sources, the Committee took account of potential biases in clinical trials. These biases resulted from the different methods used for the diagnosis of VTE and the different endpoints taken as reflecting the occurrence of VTE. The Committee also examined the applicability of the evidence to current Australian hospital practice.

In framing the Guideline recommendations, the Committee placed great emphasis on balancing the risks of VTE in hospitalised patients against the actual and perceived risks of pharmacological thromboprophylaxis and patients' tolerance of pharmacological (especially injectable) and mechanical prophylaxis. Bleeding is the major complication of pharmacological thromboprophylaxis, and is a potential side-effect of all anticoagulants. The risks of both VTE and bleeding vary with individual patient factors, the presence of acute medical illnesses, types of surgical procedures, and duration and nature of immobilisation. The consequences of bleeding also vary with different surgical procedures and different anatomical sites.

The pharmacological options considered in the Guideline are unfractionated heparin, low molecular weight heparin, fondaparinux, danaparoid (a heparinoid), rivaroxaban, dabigatran etexilate, aspirin and warfarin. The mechanical options are graduated compression stockings, intermittent pneumatic compression devices and foot pumps.

The Guideline contains 64 recommendations. Each recommendation is assigned a grade from 'A' to 'D'. 'A' refers to a recommendation based on a body of evidence that can be trusted to guide practice. 'B' refers to a recommendation based on a body of evidence that can be trusted to guide practice in most situations. Grade 'C' means that the body of evidence provides some support for the recommendation, but care should be taken in its application. Grade 'D' means

that the body of evidence is weak and the recommendation should be applied with caution. Where no good-quality evidence was available but there was consensus among Committee members, consensus-based recommendations are given. Such recommendations are called Good Practice Points. Within the Guideline, recommendations are presented by clinical procedure (e.g. total hip replacement, hip fracture surgery, general surgery, gynaecological surgery) and medical condition (e.g. stroke, myocardial infarction). Specific sections are included for cancer patients surgical and non-surgical) and pregnancy and childbirth. A summary of all the recommendations is provided in [section 5](#). The evidence for each recommendation is presented by clinical procedure and set out in a summary within [section 6](#). Finally, the Guideline sets out a short list of areas for future research.

The recommendations are intended to encapsulate the available evidence on the prevention of VTE. However, they should only be followed subject to the judgement of clinicians caring for individual patients and patients' own preferences.

I Introduction

I.1 Background

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are two aspects of one disease process known as venous thromboembolism (VTE). In DVT, a thrombus (blood clot) forms in the deep veins of the leg or pelvis where it may cause pain, tenderness and swelling of the leg. In PE, some or all of the thrombus becomes detached and moves from the vein through the right side of the heart to lodge in one or more pulmonary arteries. PE may cause shortness of breath, bloody sputum, chest pain, faintness and heart failure. Massive PE leads to death.

Hospitalised patients are over 100 times more likely to develop a DVT or PE compared with the rest of the community.¹ Each year approximately 30,000 people are hospitalised in Australia as a consequence of VTE, and an estimated 2,000 die from VTE.² The majority of VTE cases requiring hospitalisation are related to previous hospital admission for surgery or acute illness. Many of these cases are preventable.² PE is one of the commonest causes of death in hospital, accounting for 10 percent of all hospital deaths.³ Other significant long-term morbidity, costs and consequences are also associated with the occurrence of VTE.³

The options for thromboprophylaxis comprise pharmacological agents (anticoagulants) and mechanical methods, alone or in combination. The most commonly-used pharmacological agents in Australia are the heparins (low molecular weight heparin and unfractionated heparin sodium). Other agents include fondaparinux, danaparoid, warfarin and aspirin. The direct thrombin inhibitor dabigatran etexilate and the selective direct factor Xa inhibitor rivaroxaban were approved by the Therapeutic Goods Administration (TGA) for limited indications in late 2008. Mechanical prophylaxis options include thigh or knee length graduated compression stockings, pneumatic venous pumping devices that intermittently compress the calf muscles and devices that stimulate lower-limb muscle contraction. All the thromboprophylactic options that were considered for inclusion in this Guideline are described in [section 2](#).

I.2 Clinical need for this Guideline

A strong evidence base exists for VTE prevention, and VTE prevention in hospitalised patients has been widely acknowledged in Australia and internationally as a major opportunity to improve patient safety.^{4,5} Although several Australian and international VTE prevention guidelines have been published in recent years,⁶⁻¹² no guidelines for the prevention of VTE have been endorsed by the National Health and Medical Research Council (NHMRC).

Effective VTE prevention measures have been widely reported to be under-utilised and inconsistently applied.^{13,14} For example, a recent UK survey reported that 71 percent of hospitalised patients judged to be at moderate or high risk of DVT did not receive any form of prophylaxis.¹⁵

VTE leads to short and long term morbidity and mortality and is costly to treat. In addition to diagnostic tests, patients with VTE require treatment with anticoagulants and a longer hospital stay. They often require further diagnostic tests and prolonged treatment to manage the complications of VTE post-discharge.¹⁶

An evidence-based prevention guideline that sets out clear nationally-agreed recommendations suitable for the Australian clinical context will help to reduce the incidence of VTE, the occurrence of chronic sequelae, and subsequent costs associated with managing VTE.

1.3 Purpose of this Guideline

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.

1.4 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 health care.

1.5 Scope of this Guideline

This Guideline provides recommendations on thromboprophylaxis for 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 (active or occult, with or without cancer treatment)
- patients admitted during pregnancy and the puerperium.

This Guideline does not provide recommendations on thromboprophylaxis for:

- 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
- travel-related VTE.

1.6 Methods used to develop this Guideline

The National Institute of Clinical Studies (NICS), an institute of the NHMRC, developed this Guideline in accordance with NHMRC guideline development processes.¹⁷⁻¹⁹

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.²⁰ 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)⁸ best met the criteria for a high quality source guideline. This guideline was selected using the Appraisal of Guidelines Research and Evaluation instrument (AGREE),²¹ 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 Committee consulted the American College of Chest Physicians (ACCP) VTE Prevention Guideline to assist in framing the clinical questions as its structure was regarded more clinically useful.⁷

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. Consequently, the evidence in the NICE guideline was re-ordered and re-analysed to match the desired structure of this NHMRC Guideline and the Committee formulated recommendations based on these new analyses.

The Guideline recommendations were developed using procedures outlined in the "NHMRC additional levels of evidence and grades for recommendations for developers of guidelines: Stage 2 consultation 2008-2010".²² 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.²² A standardised evidence statement form used to formulate and grade the recommendations can be found in [Appendix E](#).²² Good practice points were used when the conventional grading of evidence was not possible. These points represent consensus views of the VTE Prevention Guideline Adaptation 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](#).

1.7 Scheduled review of this Guideline

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 this 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 Australian 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.

1.8 Funding

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 pentasaccharide fondaparinux which is a selective inhibitor of activated Factor X (Xa)
- subcutaneously administered heparinoid, danaparoid
- orally administered direct factor Xa inhibitor, rivaroxaban
- orally administered direct thrombin inhibitor, dabigatran etexilate
- orally administered aspirin
- orally administered vitamin K antagonist, warfarin.

Low molecular weight heparin, 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.

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 including foot impulse technology (FIT) and foot impulse devices (FID).

For further information on indications, contraindications and precautions relating to the agents used for preventing VTE, refer to the Australian Medicines Handbook,²³ or individual manufacturer's instructions.

3 Issues to be considered in using this Guideline

3.1 Diagnosis of VTE

A clinical diagnosis of DVT is usually confirmed by compression ultrasonography. Some of the randomised controlled trials that formed the evidence base for this Guideline relied on compression ultrasound as the primary method of detecting or excluding a DVT in both the intervention and control groups as ultrasound is non-invasive. Most trials used ascending venography, considered to be the 'gold standard' diagnostic tool. Venography has a greater sensitivity than compression ultrasound for distal (below-knee) DVT, but is an invasive technique and rarely used in clinical practice.

PE is usually diagnosed or excluded by computed tomographic (CT) pulmonary angiography (helical CT) or ventilation-perfusion isotope scan. Routine screening for PE was not usually performed in the randomised controlled trials reviewed in this Guideline. Instead, trial subjects were assessed only on clinical suspicion of PE, based on symptoms, signs and other investigations. Therefore, the actual incidence of PE may have been underestimated.

When reviewing evidence, the Committee discounted diagnostic methods that are incompletely validated (e.g. Magnetic Resonance Imaging for DVT) or have limited accuracy for sub-clinical DVT (e.g. impedance plethysmography).

3.2 Endpoints for VTE prevention

The Committee accepted evidence on the efficacy of prophylaxis derived using objectively documented outcome measures across the full spectrum of VTE, including asymptomatic, distal or proximal DVT detected by venography or ultrasound imaging, as well as symptomatic and confirmed DVT or PE (non-fatal or fatal).

The Committee acknowledges the continuing debate on the clinical relevance of asymptomatic distal DVT as an indicator of the efficacy of VTE prophylaxis. Some experts have argued that guideline committees should consider evidence only on symptomatic VTE or only symptomatic PE. This Committee's decision to consider outcomes across the broad spectrum was based on the fact that VTE is a spectrum of disease, from asymptomatic distal DVT to PE, and most DVTs (and PE) are initially asymptomatic.

3.3 Applicability of evidence – Issues to consider

The Committee recognised a number of issues concerning the applicability of the evidence to current practice in Australia.

Early comparisons of active VTE prevention (usually using unfractionated or low molecular weight heparin) with a placebo or no intervention were undertaken decades ago, when surgical techniques, anaesthesia and postoperative management were very different. Importantly, the emphasis on early postoperative mobilisation was not as strong as it is today. The results of early studies of VTE prevention may therefore not always apply to contemporary practice. It seems likely that contemporary clinical management may have led to reductions in the risk of VTE, even in the absence of specific prophylactic measures. 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.

The risk of bleeding related to surgery is the main complication of pharmacological prophylaxis. ‘Major bleeding’, as variously defined in clinical trials, bears a limited relation to ‘major bleeding’ as perceived by surgeons or patients. Differing perceptions of risk for ‘major bleeding’ strongly determine surgeons’ attitudes to various forms of prophylaxis – even though recorded likelihood of ‘major bleeding’ has been small in clinical trials.

These perceptions may also influence the choice between pharmacological and mechanical forms of VTE prophylaxis that enhance venous return and/or prevent venous stasis (e.g. with various intermittent pneumatic compression devices).

Finally, there are far fewer studies of mechanical than pharmacological prophylaxis, and fewer studies where one was followed by the other. A lack of available evidence in important areas necessarily limits the scope of evidence-based recommendations.

3.4 Balancing risks

The risk of VTE in hospitalised patients must be balanced against the actual and perceived risks of pharmacological thromboprophylaxis and patients’ tolerance of pharmacological (especially injectable) or mechanical prophylaxis. Evidence presented throughout this Guideline shows that the risk of major bleeding associated with anticoagulant agents is low.

With major orthopaedic surgery, reported 30-day rates of major bleeding in patients receiving heparins were 0.2-1.7 percent; similar to placebo rates in the same trials of 0.2-1.5 percent.^{24,25} However, clinicians’ and patients’ perceive the bleeding risk as significant. In particular, surgeons may be understandably reluctant to expose patients to the risk of excessive intra- or postoperative bleeding and the subsequent complications, especially in procedures such as joint replacement where bleeding can lead to severe infections and a need to explant prostheses.

This Guideline is intended to assist clinicians in balancing the risks of death and serious morbidity from VTE against the complications and disadvantages of prophylaxis.

4 Patient risk

4.1 VTE risk

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 exogenous. 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)²⁶⁻²⁸
 - pregnancy and the puerperium²⁹
 - active or occult malignancy^{27,28,30-32}
 - previous VTE^{27,32}
 - varicose veins³²
 - marked obesity³²⁻³⁴
 - prolonged severe immobility (prolonged bed rest, immobilisation in a plaster cast or brace or prolonged travel resulting in limited movement and subsequent venous stasis)^{30,35}
 - use of oestrogen-containing hormone replacement therapy or oral contraceptives in women^{32,33,36}
 - 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).³³
2. Risks related to an acute medical illness:
 - acute or acute on chronic chest infection³²
 - heart failure^{30,32}
 - myocardial infarction³²
 - stroke with immobility³⁷
 - some forms of cancer chemotherapy^{28,30}
 - acute inflammatory bowel disease.³²
3. Risks related to an injury or surgical procedure:
 - all surgical procedures but especially abdominal,³⁸ pelvic,⁸ thoracic or orthopaedic surgical procedures³⁹⁻⁴²
 - risk is determined by the type of surgery (major joint surgery carries a very high risk,³⁹⁻⁴² as does curative surgery for cancer⁴³), the type of anaesthesia,⁴⁴ the likely duration of immobility (including duration of surgery),^{30,35} and surgical complications
 - leg injury that requires surgery or prolonged immobilisation.⁴⁵

4.2 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.

Patient-related risk factors for bleeding include abnormal blood coagulation or low platelet count. Pharmacological VTE prophylaxis may also be contraindicated in patients with the following characteristics:

- recent central nervous system bleeding
- intracranial or spinal lesion at high risk for bleeding
- 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
- thrombocytopenia (platelets < 50,000/ μ l)
- severe platelet dysfunction
- recent major surgical procedure at high risk for bleeding
- underlying coagulopathy or coagulation factor abnormalities
- regional axial anaesthesia or recent lumbar puncture for any reason
- high risk of falls.

By nature of its mechanism of action, pharmacological prophylaxis may increase the risk of surgical bleeding. With pharmacological prophylaxis, bleeding risk can be related to dose and treatment schedule (especially the timing of prophylaxis relative to surgery). An assessment of bleeding risk is an essential step in deciding on appropriate prophylaxis for individual patients.

4.3 VTE risk assessment

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.

A VTE risk assessment should follow the following steps:

STEP 1 Assess the patient's baseline risk of VTE, taking into account inherited and acquired risk factors such as those listed in [section 4.1](#).

STEP 2 Assess the patient's additional risk of VTE, taking account of the reasons for hospitalisation (surgical procedures, trauma or specific medical illness).

STEP 3 Assess the patient's risk of bleeding.

STEP 4 Formulate an overall risk assessment (with consideration of VTE risk and bleeding risk).

STEP 5 Select appropriate methods of thromboprophylaxis based on the risk assessment.

5 Summary of recommendations

This summary section provides a list of the evidence-based recommendations detailed in the text of [section 6](#). Each of the recommendations is given an overall grading based on the NHMRC additional levels of evidence and grades of recommendation (2008-2010). 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 evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
NA	Not applicable – unable to grade body of evidence
GPP	Good practice point – consensus-based recommendations

Interpreting guideline recommendations

Where the words “use” or “recommended” are used in this Guideline, the Committee judged that the benefits of the recommended approach clearly exceed the harms, and that the evidence supporting the recommendation was trusted to guide practice.

Where the words “should be considered” are used, either the quality of evidence was underpowered, or the available studies demonstrated little clear advantage of one approach over another or the balance of benefits to harm was unclear.

Where the words “not recommended” are used, there is either a lack of appropriate evidence, or the harms outweigh the benefits.

The full evidence tables supporting the recommendations can be found in Appendix D and for details on contraindications to thromboprophylaxis refer to the 2009 Australian Medicines Handbook.²³

The following tables provide a summary of the recommendations for the prevention of VTE by clinical procedure. For further information on the evidence from which these recommendations are based, as well as dose, duration, timing and precautions, please refer to [section 6](#).

5 Summary of recommendations (cont.)

5.1 Surgical patients

Recommendations by clinical procedure	Grade	Evidence in section
Total hip replacement		
1. Use thromboprophylaxis for all patients admitted to hospital for total hip replacement.	GPP	6.1.1
2. In the absence of contraindications, commence pharmacological thromboprophylaxis postoperatively and continue for up to 35 days following total hip replacement surgery. Use one of the following: <ul style="list-style-type: none"> • low molecular weight heparin • fondaparinux • rivaroxaban • dabigatran etexilate. 	A B B B	6.1.1 6.1.1 6.1.1 6.1.1
3. Preoperative administration of thromboprophylaxis is not recommended for patients undergoing total hip replacement surgery.	C	6.1.1
4. Use graduated compression stockings or intermittent pneumatic compression following total hip replacement until the patient is fully mobile, whether or not pharmacological thromboprophylaxis is used. If possible, use graduated compression stockings with a foot pump where pharmacological thromboprophylaxis is not used.	B B	6.1.1 6.1.1
5. Unfractionated heparin is not recommended for thromboprophylaxis following total hip replacement. Only use unfractionated heparin if recommended thromboprophylactic options are not available.	B	6.1.1
6. Aspirin is not recommended as the sole agent for thromboprophylaxis following total hip replacement.	C	6.1.1
7. Warfarin is not recommended for thromboprophylaxis following total hip replacement except where used for therapeutic reasons. In these cases use adjusted therapeutic doses for four to five weeks.	C C	6.1.1 6.1.1
8. In patients with heparin-induced thrombocytopenia, use heparinoids such as danaparoid as an alternative thromboprophylactic option.	B	6.1.1

Recommendations by clinical procedure	Grade	Evidence in section
Hip fracture surgery		
1. Use thromboprophylaxis for all patients admitted to hospital for hip fracture surgery.	GPP	6.1.2
2. In the absence of contraindications, commence pharmacological thromboprophylaxis and continue for up to 35 days for hip fracture surgery. Use one of the following: <ul style="list-style-type: none"> • fondaparinux • low molecular weight heparin. 	B B	6.1.2 6.1.2
3. If low molecular weight heparin is used, consider the addition of low dose aspirin.	B	6.1.2
4. Aspirin is not recommended as the sole agent for thromboprophylaxis following hip fracture surgery.	B	6.1.2

5 Summary of recommendations (cont.)

Recommendations by clinical procedure	Grade	Evidence in section
Hip fracture surgery (cont)		
5. Unfractionated heparin is not recommended for thromboprophylaxis following hip fracture surgery.	B	6.1.2
6. Warfarin is not recommended for thromboprophylaxis following hip fracture surgery.	B	6.1.2
7. If pharmacological thromboprophylaxis is contraindicated or not available, use one of the following until the patient is fully mobile: <ul style="list-style-type: none"> • foot pump • intermittent pneumatic compression. 	C	6.1.2
8. In patients with heparin-induced thrombocytopenia, use heparinoids such as danaparoid as an alternative thromboprophylactic option.	B	6.1.2

Recommendations by clinical procedure	Grade	Evidence in section
Total knee replacement		
1. Use thromboprophylaxis for all patients admitted to hospital for total knee replacement.	GPP	6.1.3
2. In the absence of contraindications, commence pharmacological thromboprophylaxis postoperatively and continue for up to 14 days following total knee replacement surgery. Use one of the following: <ul style="list-style-type: none"> • low molecular weight heparin • fondaparinux • rivaroxaban • dabigatran etexilate. 	A B B B	6.1.3 6.1.3 6.1.3 6.1.3
3. Use one of the following whether or not pharmacological thromboprophylaxis is used, until the patient is fully mobile: <ul style="list-style-type: none"> • foot pump • intermittent pneumatic compression. 	C	6.1.3
4. Aspirin alone is not recommended for thromboprophylaxis following total knee replacement.	C	6.1.3
5. Warfarin is not recommended for thromboprophylaxis following total knee replacement.	B	6.1.3
Knee arthroscopy		
1. Thromboprophylaxis is not recommended following knee arthroscopy. Consider thromboprophylaxis for patients with additional VTE risk factors, in the absence of contraindications.	B GPP	6.1.4 6.1.4
Lower leg fractures and injuries		
1. Use low molecular weight heparin for all patients admitted to hospital with a lower leg fracture or injury with immobilisation in a brace or a plaster cast. Thromboprophylaxis should be continued for the entire period of immobilisation.	A	6.1.5

5 Summary of recommendations (cont.)

Recommendations by clinical procedure	Grade	Evidence in section
General surgery		
1. Use thromboprophylaxis for all patients admitted to hospital for general surgery.	GPP	6.1.6
2. In the absence of contraindications, commence pharmacological thromboprophylaxis postoperatively and continue for up to one week or until the patient is fully mobile following major general surgery. Use one of the following: <ul style="list-style-type: none"> • low molecular weight heparin • unfractionated heparin. 	B A	6.1.6 6.1.6
3. Use graduated compression stockings for all general surgical patients, whether or not pharmacological thromboprophylaxis is used, until the patient is fully mobile.	B	6.1.6
4. If recommended thromboprophylaxis is contraindicated or not available, use a foot pump following general surgery, until the patient is fully mobile.	C	6.1.6
Urological surgery		
1. Consider thromboprophylaxis for patients admitted to hospital for urological surgery based on an assessment of the patient's risk of VTE and bleeding.	GPP	6.1.7

Recommendations by clinical procedure	Grade	Evidence in section
Gynaecological surgery		
1. Use thromboprophylaxis for all patients admitted to hospital for major gynaecological surgery.	GPP	6.1.8
2. In the absence of contraindications, commence pharmacological thromboprophylaxis postoperatively and continue for up to one week or until the patient is fully mobile following major gynaecological surgery. Use one of the following: <ul style="list-style-type: none"> • low molecular weight heparin • unfractionated heparin. 	B	6.1.8
3. Consider the additional use of graduated compression stockings or other mechanical thromboprophylaxis following major gynaecological surgery, especially if pharmacological thromboprophylaxis is contraindicated.	GPP	6.1.8
4. Warfarin is not recommended for thromboprophylaxis following major gynaecological surgery.	C	6.1.8
Abdominal surgery		
1. Use thromboprophylaxis for all patients admitted to hospital for major abdominal surgery.	GPP	6.1.9
2. In the absence of contraindications, commence pharmacological thromboprophylaxis postoperatively with low molecular weight heparin and continue for at least five to nine days.	B	6.1.9
3. Fondaparinux is not recommended for thromboprophylaxis following major abdominal surgery.	C	6.1.9
4. Use graduated compression stockings for all patients following abdominal surgery, whether or not pharmacological thromboprophylaxis is used, until the patient is fully mobile.	B	6.1.9

5 Summary of recommendations (cont.)

Recommendations by clinical procedure	Grade	Evidence in section
Cardiac, thoracic and vascular surgery		
1. Use thromboprophylaxis for all patients admitted to hospital following cardiac, thoracic or vascular surgery.	GPP	6.1.0
2. In the absence of contraindications, commence pharmacological thromboprophylaxis postoperatively and continue for up to one week or until the patient is fully mobile following cardiac, thoracic, or vascular surgery. Use one of the following: <ul style="list-style-type: none"> • low molecular weight heparin • unfractionated heparin. 	B	6.1.0
3. Use one of the following for all patients following cardiac, thoracic, or vascular surgery, whether or not pharmacological thromboprophylaxis is used, until the patient is fully mobile: <ul style="list-style-type: none"> • graduated compression stockings • intermittent pneumatic compression. 	C	6.1.0

Recommendations by clinical procedure	Grade	Evidence in section
Neurosurgery		
1. Use intermittent pneumatic compression following neurosurgery, until the patient is fully mobile.	A	6.1.11
2. Use pharmacological thromboprophylaxis with extreme caution in patients following neurosurgery, due to the high risk of bleeding.	GPP	6.1.11
3. Where pharmacological thromboprophylaxis is appropriate and not contraindicated, use low molecular weight heparin or unfractionated heparin.	B	6.1.11
4. Consider the use of graduated compression stockings following neurosurgery (alone or in combination with pharmacological thromboprophylaxis).	C	6.1.11
Trauma surgery or spinal surgery		
1. Use thromboprophylaxis for all patients admitted to hospital for trauma surgery or spinal surgery.	GPP	6.1.12
2. In the absence of contraindications, use a foot pump from hospital admission with the addition of low molecular weight heparin five days after admission for trauma patients undergoing surgery.	C	6.1.12

5.2 Anaesthesia

Recommendation	Grade	Evidence in section
1. Consider central neural blockade as an alternative to general anaesthesia if feasible. If central neural blockade is used there is a risk of developing an epidural haematoma. To minimise this risk, timing of pharmacological thromboprophylaxis should be carefully planned and discussed in advance with the anaesthetist.	A GPP	6.2 6.2

5 Summary of recommendations (cont.)

5.3 Medical patients

Recommendations by medical condition	Grade	Evidence in section
Stroke		
1. Consider the use of thromboprophylaxis for all patients admitted to hospital with ischaemic stroke based on an assessment of the patient's degree of immobility and risk of bleeding.	B	6.3.1
2. Pharmacological thromboprophylaxis is not recommended for haemorrhagic stroke patients due to the risk of intracranial bleeding.	GPP	6.3.1
3. Where thromboprophylaxis is appropriate and not contraindicated, use low molecular weight heparin for patients with ischaemic stroke.	B	6.3.1
If low molecular weight heparin is contraindicated or not available, use unfractionated heparin.	B	6.3.1
Myocardial infarction		
1. Use thromboprophylaxis for patients admitted to hospital for myocardial infarction, where full anticoagulation is not in use.	C	6.3.2
2. In the absence of contraindications, use unfractionated heparin for thromboprophylaxis following myocardial infarction.	C	6.3.2
General medical		
1. Consider the use of thromboprophylaxis for patients admitted to hospital for medical conditions based on an assessment of the patient's risk of VTE and bleeding.	GPP	6.3.3
2. In the absence of contraindications, use one of the following: <ul style="list-style-type: none"> • low molecular weight heparin • unfractionated heparin. 	B	6.3.3

5.4 Cancer patients

Recommendations for surgical and non-surgical cancer patients	Grade	Evidence in section
1. Use thromboprophylaxis for all cancer patients undergoing general surgical procedures including abdominal or pelvic surgery or neurosurgery, provided there are no contraindications. Commence pharmacological thromboprophylaxis postoperatively and continue for at least seven to 10 days following major general surgery for cancer. Use one of the following: <ul style="list-style-type: none"> • low molecular weight heparin • unfractionated heparin 	GPP	6.4
2. Consider using extended thromboprophylaxis with low molecular weight heparin for up to 28 days after major abdominal or pelvic surgery for cancer, especially in patients who are obese, slow to mobilise or have a past history of VTE.	GPP	6.4
3. In the absence of other significant risk factors, thromboprophylaxis is not recommended for cancer patients undergoing head and neck surgery.	GPP	6.4
4. In non-surgical cancer patients in the absence of contraindications, commence thromboprophylaxis on admission and continue until discharge. Use one of the following: <ul style="list-style-type: none"> • low molecular weight heparin • unfractionated heparin. 	GPP	6.4
5. For both non-surgical and surgical cancer patients, use graduated compression stockings if pharmacological thromboprophylaxis is contraindicated.	GPP	6.4

5 Summary of recommendations (cont.)

5.5 Pregnancy and childbirth

Recommendations	Grade	Evidence in section
1. Minimise immobilisation of women during pregnancy, labour and the puerperium and ensure adequate hydration at all times.	GPP	6.5
2. All women who deliver by caesarean section are at increased risk of VTE and should be mobilised promptly after surgery.	GPP	6.5
3. Where pharmacological thromboprophylaxis is appropriate and not contraindicated, use low molecular weight heparin after caesarean delivery for five to seven days, or until the patient is fully mobile.	GPP	6.5
4. Extend pharmacological thromboprophylaxis with low molecular weight heparin or adjusted dose warfarin to six weeks for high-risk women, after caesarean or vaginal delivery.	GPP	6.5
5. Consider the use of graduated compression stockings if pharmacological thromboprophylaxis is contraindicated or not used.	GPP	6.5
6. Consider the use of intermittent pneumatic compression during caesarean and in the postoperative period for up to 24 hours.	GPP	6.5

Summary of availability of evidence for use of thromboprophylactic agents by clinical category

	UFH	LMWH	HEPARINOID	RIVAROXABAN	DABIGATRAN	FONDAPARINUX	WARFARIN	ASPIRIN	GCS	IPC	FOOT PUMP
Total hip replacement	x	✓	✓	✓	✓	✓	x	x	✓±	✓	✓ use with GCS
Hip fracture surgery	x	✓	✓	–	–	✓	x	✓+	–	✓	✓
Total knee replacement	–	✓	–	✓	✓	✓	x	x	–	✓	✓
Knee arthroscopy	–	x	–	–	–	–	–	–	–	–	–
Lower leg fractures and injuries	–	✓	–	–	–	–	–	–	–	–	–
General surgery	✓	✓	–	–	–	–	–	–	✓±	–	✓
Urological surgery	x	–	–	–	–	–	–	–	–	–	–
Gynaecological surgery	✓	✓	–	–	–	–	x	–	✓±	✓±	✓±
Abdominal surgery	–	✓	–	–	–	x	–	–	✓	–	–
Cardiac, thoracic and vascular surgery	✓	✓	–	–	–	–	–	–	✓	✓	–
Neurosurgery	✓	✓	–	–	–	–	–	–	✓±	✓	–
Trauma surgery and spinal surgery	–	✓ at day 5	–	–	–	–	–	–	–	–	✓+ use with LMWH
Ischaemic stroke	✓	✓	–	–	–	–	–	–	–	–	–
Myocardial infarction	✓	–	–	–	–	–	–	–	–	–	–
Mixed medical	✓	✓	–	–	–	–	–	–	–	–	–
Cancer	–	–	–	–	–	–	–	–	–	–	–
Pregnancy and childbirth	–	–	–	–	–	–	–	–	–	–	–

✓	Evidence supports use of this agent for thromboprophylaxis for this clinical category
✓±	Evidence supports use of this agent for thromboprophylaxis with or without other thromboprophylactic agents for this clinical category
✓+	Evidence supports use of this agent for thromboprophylaxis only in addition with another thromboprophylactic agent for this clinical category
x	Evidence does not support use of this agent for thromboprophylaxis for this clinical category
x	This agent is not recommended for this clinical category
–	There is no evidence about this form of thromboprophylaxis for this clinical category

6 Evidence and recommendation

6.1 Surgical patients – Evidence and recommendations for VTE prophylaxis

6.1.1 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 multi-centre international RCTs, rivaroxaban (10mg orally once per day for 35 days) was more effective at reducing the occurrence of DVT than LMWH (40mg once per day, either for 35 days or 14 days). There were no significant differences in the rates of PE or adverse events, including death, between the rivaroxaban and LMWH arms.	I	46,47
Dabigatran etexilate	In one multi-centre international RCT, there were no significant differences in rates of DVT or PE with dabigatran etexilate (220mg or 150mg) compared with LMWH (40mg daily). There were no significant differences in the rates of adverse events between the two groups.	I	48
Fondaparinux	In two RCTs of patients who received either LMWH (40mg once per day) or fondaparinux (2.5mg once daily) for up to nine days, the group receiving fondaparinux had significantly lower rates of VTE or DVT. However, fondaparinux was associated with significantly higher rates of major bleeding than LMWH.	I	49,50

VTE prophylactic agent	Evidence summary - thromboprophylaxis for total hip replacement patients	Level	References
LMWH	Pooling of seven RCTs comparing LMWH with no treatment showed significantly fewer asymptomatic DVTs with LMWH. There were no differences in the occurrence of adverse events, such as wound haematoma or major bleeding, between the groups receiving LMWH and no treatment. Various doses of LMWH were used across the RCTs.	I	51-57
	In a systematic review of six RCTs, extended duration of prophylaxis with LMWH (to 28–35 days postoperatively) resulted in significantly lower rates of both proximal and symptomatic DVT and lower rates of PE compared with extended placebo. Extended duration of prophylaxis was not associated with an increased rate of adverse events.	I	58
	In one RCT, there was no advantage in preoperative administration of LMWH compared with postoperative administration. A further three RCTs investigated dosage effects of LMWH. From this evidence, higher doses of LMWH reduced the rate of asymptomatic and distal DVT, but did not affect the rate of symptomatic or proximal DVT.	I	59-62
LMWH or UFH	Across six RCTs, rates of asymptomatic DVT did not differ between patients receiving LMWH or UFH. However, in three of the six RCTs, patients receiving LMWH had lower rates of proximal DVT. The occurrence of adverse events, including bleeding, did not differ between LMWH and UFH groups.	I	63-68
GCS	Pooling of eight RCTs showed significantly lower rates of asymptomatic DVT when total hip replacement patients wore graduated compression stockings compared with no treatment. Graduated compression stockings were shown to have an additional benefit when added to effective pharmacological prophylaxis (however, not when added to fondaparinux). ⁶⁹	I	51,70-76
IPC	In one RCT of patients not on effective pharmacological prophylaxis, significantly fewer asymptomatic DVT were detected in the intermittent pneumatic compression (IPC) group compared with the group receiving no treatment. ⁷⁷ In one small RCT of patients receiving IPC or LMWH, rates of proximal DVT did not differ between the groups. ⁷⁸ In two RCTs, continuous enhanced circulation therapy was the form of IPC evaluated. ^{79,80} These trials were excluded from analysis as the method of thromboprophylaxis is not available in Australia.	I	77-80
GCS or IPC	Two small RCTs comparing graduated compression stockings with IPC were inconclusive. One RCT suggested a benefit of adding IPC to LMWH compared with adding GCS to LMWH for asymptomatic DVT but not other outcomes. ⁸¹	I	81,82
Foot pump	In one RCT of patients not receiving pharmacological prophylaxis, the addition of a foot pump to graduated compression stockings was more effective in preventing VTE than the stockings alone. Two small unblinded studies comparing LMWH with a foot pump were inconclusive.	I	83-85
Danaparoid	In two RCTs, danaparoid was more effective in preventing DVT (including proximal DVT) than UFH, or no treatment.	I	86,87
Aspirin	In two RCTs there were no significant differences in the rates of proximal DVT, distal DVT, PE and the rates of adverse events between groups given aspirin or no treatment.	I	88,89

VTE prophylactic agent	Evidence summary - thromboprophylaxis for total hip replacement patients	Level	References
Warfarin	In two RCTs, there were no differences in the rate of DVT and the rates of adverse events between groups given warfarin and no treatment.	I	90,91
	In three RCTs, there was a small but non-significant difference in the rate of DVT between groups given warfarin or aspirin; this favoured warfarin.	I	92-94
	In two RCTs, adjusted therapeutic doses of warfarin were more effective than fixed, low-dose warfarin in preventing VTE.	I	95,96
	In one RCT of patients receiving standard therapeutic doses of warfarin, extended duration (28-35 days) was more effective than shorter-term administration of warfarin for preventing VTE.	I	97
	RCTs comparing IPC with warfarin were not applicable to the Australian healthcare context.	I	98-101

Discussion about the evidence and basis for 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,^{30,102} and in the absence of thromboprophylaxis, risk of VTE is high following total hip replacement.^{103,104}

Recommendation	Grade
I. Use thromboprophylaxis for all 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^{46,47,49,50} while the effectiveness of dabigatran etexilate (220mg or 150mg daily) and low molecular weight heparin was similar.⁴⁸ 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 heparin⁶³⁻⁶⁸ 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, so both should be used with caution. The lack of information on post-marketing surveillance for rivaroxaban and dabigatran, 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.^{49,50} 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.

Duration of thromboprophylaxis: The risk of late-occurring DVT following total hip replacement remains high until at least day 35 after surgery.¹⁰⁸ In trials of extended duration low molecular weight heparin, thromboprophylaxis was more effective when administered for up to 35 days after surgery than for shorter durations, with no significant increase in bleeding.⁵⁸ Therefore, pharmacological prophylaxis has been recommended for up to 35 days following total hip replacement surgery.

Timing of thromboprophylaxis: Preoperative administration of pharmacological prophylaxis was shown to provide no additional benefit compared with postoperative administration.⁵⁹ Based on this and the practical difficulties of preoperative administration in the context of the increasing frequency of same-day admissions, all pharmacological thromboprophylaxis should only be administered postoperatively following total hip replacement.

Dosage of thromboprophylaxis: In RCTs comparing low molecular weight heparin with no treatment, there were various doses of low molecular weight heparin used across the trials. If low molecular weight heparin is chosen for thromboprophylaxis, it should commence postoperatively and dosage should follow manufacturer's instructions.

Recommendation	Grade
2. In the absence of contraindications, commence pharmacological thromboprophylaxis postoperatively and continue for up to 35 days following total hip replacement surgery. Use one of the following: <ul style="list-style-type: none"> • low molecular weight heparin • fondaparinux# • rivaroxaban* • dabigatran etexilate.* 3. Preoperative administration of thromboprophylaxis is not recommended for patients undergoing total hip replacement surgery.	A B B B C
* Rivaroxaban and dabigatran etexilate are newly approved agents and post-marketing surveillance on adverse events is not yet available. #Use fondaparinux with caution as it may cause bleeding in those weighing less than 50kg, in the frail, the elderly and those with renal impairment.	

Mechanical methods reduce the risk of VTE following total hip replacement^{70-75,83} and are recommended whether or not pharmacological prophylaxis is used. In one RCT of patients wearing graduated compression stockings and not on effective pharmacological prophylaxis, the addition of a foot pump was associated with a significant decrease in the rate of DVT (including proximal DVT).⁸³ Graduated compression stockings or intermittent pneumatic compression do not increase the risk of bleeding. The effectiveness of graduated compression stockings can be increased if used in conjunction with a foot pump. RCTs comparing graduated compression stockings with intermittent pneumatic compression were inconclusive.^{81,82}

Intermittent pneumatic compression significantly reduced the occurrence of asymptomatic DVT compared with no treatment⁷⁷ and there was some suggestion from a small study from 1996 that intermittent pneumatic compression could be used as an alternative to low molecular weight heparin.⁷⁸ Studies comparing foot pump with low molecular weight heparin were inconclusive^{84,85} but there was some suggestion that intermittent pneumatic compression added to low molecular weight heparin reduces asymptomatic DVT.⁸¹ Intermittent pneumatic compression is also an option if pharmacological prophylaxis is contraindicated.

Recommendation	
	Grade
4. Use graduated compression stockings or intermittent pneumatic compression following total hip replacement until the patient is fully mobile, whether or not pharmacological thromboprophylaxis is used.	B
If possible, use graduated compression stockings with a foot pump where pharmacological thromboprophylaxis is not used.	B

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 should not be used for thromboprophylaxis following total hip replacement.

Recommendation	
	Grade
5. Unfractionated heparin is not recommended for thromboprophylaxis following total hip replacement. Only use unfractionated heparin if recommended thromboprophylactic options are not available.	B
6. Aspirin is not recommended as the sole agent for thromboprophylaxis following total hip replacement.	C
7. Warfarin is not recommended for thromboprophylaxis following total hip replacement except where used for therapeutic reasons. In these cases, use adjusted therapeutic doses for four to five weeks.	C

Heparin-induced thrombocytopenia (HIT) is the development of thrombocytopenia (low platelet counts) due to the administration of the anticoagulant heparin, either in its unfractionated or low molecular weight form. Upon diagnosis of HIT, treatment of HIT requires both protection from thrombosis and choice of a thromboprophylactic agent that will not reduce the platelet count further. The heparinoid danaparoid does not reduce the platelet count. In two RCTs of patients undergoing total hip replacement, the heparinoid danaparoid was more effective for thromboprophylaxis than unfractionated heparin or no treatment.^{86,87} Therefore, in patients with heparin-induced thrombocytopenia, heparinoids such as danaparoid are an alternative thromboprophylactic option following total hip replacement surgery.

Recommendation	
	Grade
8. In patients with heparin-induced thrombocytopenia, use heparinoids such as danaparoid as an alternative thromboprophylactic option.	B

6.1.2 Hip fracture surgery

This section summarises the evidence from systematic reviews and individual trials for the prevention of VTE in patients undergoing surgery for hip fracture. Full evidence tables on which these summaries are based are provided in Appendix D (tables 31-49).

The recommendations 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 hip fracture surgery patients	Level	References
Fondaparinux	In one RCT comparing fondaparinux with LMWH, there were significantly lower rates of total VTE and DVT (including proximal DVT) in patients receiving fondaparinux (and no differences in bleeding). There was no difference in the rates of PE between the two groups.	I	109
	In one RCT, there were significantly lower rates of VTE (including proximal DVT and PE) in patients receiving fondaparinux for between 31 to 39 days compared with up to eight days postoperatively. There was no difference in the occurrence of bleeding.	I	110
LMWH	A systematic review of five RCTs showed that rates of DVT (including proximal DVT) were lower in patients receiving LMWH than in those receiving no treatment. There was no significant difference in the rates of adverse events such as wound haematoma, wound infections or death. The trials on preoperative versus postoperative administration of LMWH were inconclusive.	I	111
Foot pump or IPC	In an RCT of patients undergoing hip fracture surgery and not on effective pharmacological prophylaxis, patients with foot pumps or IPC devices applied had lower rates of DVT and PE than those receiving no treatment. There were no direct comparisons between IPC and foot pump. In a separate RCT, rates of VTE did not differ between patients on IPC in addition to LMWH compared with those on LMWH alone. ¹¹²	I	111,112
Danaparoid	Rates of DVT were lower in patients receiving danaparoid than those receiving aspirin ¹¹³ or warfarin. ¹¹⁴ There was no difference in adverse events.	I	113,114
Warfarin	In four RCTs, patients receiving warfarin had lower rates of DVT than those receiving aspirin or no treatment. In two of the four RCTs that reported on major bleeding, there was no significant difference in the occurrence of major bleeding between warfarin and no treatment. ^{115,116}	I	115-118
Aspirin	In the pulmonary embolism prevention trial (PEP), patients receiving aspirin (160mg/day) along with other thromboprophylactic agents LMWH or UFH or GCS, had lower rates of VTE than those who did not receive the added aspirin.	I	89

VTE prophylactic agent	Evidence summary – thromboprophylaxis for hip fracture surgery patients	Level	References
UFH	In a systematic review that included 10 RCTs, there were significantly lower rates of DVT. No significant differences for any PE however for causes of death other than PE, this just reached statistical significance in favour of no treatment. From the RCTs that compared UFH with LMWH, there was insufficient evidence to recommend one in preference to the other.	I	111
GCS	One RCT compared GCS plus fondaparinux with fondaparinux alone. This evidence was discounted as it was a sub-group analysis with very few patients.	I	69

Discussion about the evidence and basis for recommendations for hip fracture surgery

Patients undergoing hip fracture surgery are in the highest risk category for VTE, on the basis of the procedure itself^{30,102,119} and in the absence of thromboprophylaxis, reported rates of VTE are high following surgery for hip fracture.^{102,104} Thromboprophylaxis has been shown to reduce the risk of PE and mortality.¹²⁰ Therefore, all patients admitted to hospital for surgery for hip fracture should receive thromboprophylaxis following surgery.

Recommendation	Grade
I. Use thromboprophylaxis for all patients admitted to hospital for hip fracture surgery.	GPP

Whilst low molecular weight heparin,¹¹¹ unfractionated heparin,¹¹¹ warfarin¹¹⁵⁻¹¹⁸ and fondaparinux¹⁰⁹ were all effective in preventing VTE, only low molecular weight heparin and fondaparinux are recommended for thromboprophylaxis following hip fracture surgery. Warfarin has largely been 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.¹⁰⁹ 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).¹²¹ From this evidence, fondaparinux should be commenced six to eight hours after surgery, and administered for 31 to 39 days (2.5mg once daily).

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

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.

Recommendation	
	Grade
2. In the absence of contraindications, commence pharmacological thromboprophylaxis and continue for up to 35 days for hip fracture surgery. Use one of the following: <ul style="list-style-type: none"> • fondaparinux# • low molecular weight heparin. 	B B
#Use fondaparinux with caution as it may cause bleeding in those weighing less than 50kg, in the frail, the elderly and those with renal impairment.	

In the pulmonary embolism prevention trial (PEP),⁸⁹ low dose aspirin (160mg/day) added to other more efficacious options such as low molecular weight heparin or unfractionated heparin or graduated compression stockings following hip fracture surgery provided additional thromboprophylactic benefit. Importantly, in this trial aspirin alone was not effective. Therefore, low dose aspirin may be considered in combination with other more effective thromboprophylactic agents following surgery for hip fracture.

Recommendation	
	Grade
3. If low molecular weight heparin is used, consider the addition of low dose aspirin.	B
4. Aspirin is not recommended as the sole agent for thromboprophylaxis following hip fracture surgery.	B

Recommendation	
	Grade
5. Unfractionated heparin is not recommended for thromboprophylaxis following hip fracture surgery.	B
6. Warfarin is not recommended for thromboprophylaxis following hip 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.¹¹¹ 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.¹²² There was no demonstration of benefit in adding intermittent pneumatic compression to low molecular weight heparin.¹¹²

Recommendation	
	Grade
7. If pharmacological thromboprophylaxis is contraindicated or not available, use one of the following until the patient is fully mobile: <ul style="list-style-type: none"> • foot pump • intermittent pneumatic compression. 	B

Heparin-induced thrombocytopenia (HIT) is the development of thrombocytopenia (low platelet counts) due to the administration of the anticoagulant heparin, either in its unfractionated or low molecular weight form. Upon diagnosis of HIT, treatment of HIT requires both protection from thrombosis and choice of a thromboprophylactic agent that will not reduce the platelet count further. The heparinoid danaparoid does not reduce the platelet count. In two RCTs of patients undergoing hip fracture surgery, the heparinoid danaparoid was more effective than warfarin¹¹⁴ or aspirin.⁸⁹ Therefore, in patients with heparin-induced thrombocytopenia, heparinoids such as danaparoid are an alternative thromboprophylactic option following hip fracture.

Recommendation		Grade
8. In patients with heparin-induced thrombocytopenia, use heparinoids such as danaparoid as an alternative thromboprophylactic option.		B

6.1.3 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).

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 RCTs rivaroxaban (10mg orally once per day for two weeks) was more effective at reducing DVT (asymptomatic, symptomatic and distal DVT) than LMWH (40mg subcutaneously once per day for two weeks). There was no difference in non-fatal PE, death or bleeding between rivaroxaban and LMWH.	I	123,124
Fondaparinux	In one RCT fondaparinux was more effective at reducing VTE and DVT (including proximal DVT) than LMWH; however fondaparinux caused significantly more major bleeding than LMWH.	I	125
Dabigatran Etexilate	In two RCTs there was no significant difference in rates of DVT or PE with dabigatran etexilate (220mg or 150mg) compared with LMWH (40mg daily). There was no significant difference in any adverse events between dabigatran etexilate and LMWH.	I	126,127

VTE prophylactic agent	Evidence summary – thromboprophylaxis for total knee replacement surgery patients	Level	References
LMWH, UFH or IPC	In two RCTs there were significantly fewer DVT events (including proximal DVT) in those receiving LMWH compared with no treatment or UFH ^{125,128} or IPC. ¹²⁹ There was no difference in adverse events for either UFH or IPC compared with LMWH.	I	128-132
Foot pump or IPC	In RCTs where patients were not on effective pharmacological prophylaxis, the use of foot pump ¹³³ or intermittent pneumatic compression devices ¹³⁴ conferred thromboprophylactic benefits compared with no treatment or aspirin; ^{135,136} however there were no head-to-head comparisons of foot pumps versus IPC so one cannot be recommended in preference to the other. There were a number of studies that compared foot pump or IPC with pharmacological prophylaxis all of which were inconclusive. ¹³⁷⁻¹³⁹	I	133-139
Aspirin	In two RCTs intermittent pneumatic compression was more effective at reducing DVT than low-dose aspirin (results for high dose aspirin not relevant as this dosage would not be used in surgical patients). One RCT compared IPC plus aspirin with IPC plus warfarin. ¹³⁹ This trial was excluded from analysis as it had a small sample size and was underpowered.	I	135,136,139
Warfarin	In three RCTs, LMWH was more effective at reducing DVT than warfarin with no significant difference in proximal DVT, PE or adverse events between LMWH and warfarin.	I	140-142
	In one RCT, there was no thromboprophylactic benefit in preoperative warfarin dosing.	I	143

Discussion about the evidence and basis for recommendations for total knee replacement

Patients undergoing surgery for total knee replacement are in one of the highest risk categories for VTE, on the basis of the procedure itself.^{30,102,119} Therefore, all patients admitted to hospital for total knee replacement surgery should receive thromboprophylaxis following surgery.

Recommendation	Grade
I. Use thromboprophylaxis for all patients admitted to hospital for total knee replacement.	GPP

Low molecular weight heparin,^{130,131} fondaparinux,¹²⁵ rivaroxaban^{123,124} and dabigatran etexilate^{126,127} are all effective VTE prophylactic agents following total knee replacement. RCTs have shown that rivaroxaban^{123,124} or fondaparinux¹²⁵ reduce VTE in preference to low molecular weight heparin, while the effectiveness of dabigatran etexilate^{126,144} and low molecular weight heparin was similar. Importantly, there was no difference in adverse events including bleeding for both rivaroxaban and dabigatran etexilate compared with low molecular weight heparin. Low molecular weight heparin reduced DVT significantly compared with unfractionated heparin^{128,132} effective at reducing DVT (with no difference in proximal DVT or PE between the two agents).

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

rivaroxaban and dabigatran, along with the number of available RCTs influenced the grading of the recommendation. When this information becomes available, the recommendation should be reviewed.

While fondaparinux was more effective than low molecular weight heparin at reducing VTE (including total and proximal DVT), it also resulted in significantly more bleeding.¹²⁵ Fondaparinux should be used with caution as it may cause bleeding particularly in those weighing less than 50kg, in the frail, the elderly or those with renal impairment.

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

Duration of thromboprophylaxis: In the total knee replacement RCTs, low molecular weight heparin was provided for a period of up to 14 days^{25,130} as was rivaroxaban.¹²³ Therefore pharmacological prophylaxis is recommended for a period of up to 14 days following total knee replacement. It's important to note that in the trial of fondaparinux compared with low molecular weight heparin, prophylaxis was given for a period of between five to nine days¹⁴⁵ and in the trials of dabigatran etexilate, thromboprophylaxis was provided for between six to 10 days in one trial¹²⁶ and 14 days in a second trial.¹⁴⁴

Dosage of thromboprophylaxis: Some of the trials comparing low molecular weight heparin with placebo used a 60mg daily dosage of low molecular weight heparin; this dose is not available in Australia. Given the variability in dosages of the thromboprophylactic agents across the trials, dosing of thromboprophylaxis is recommended according to manufacturer's instructions following surgery for total knee replacement.

Recommendation	Grade
2. In the absence of contraindications, commence pharmacological thromboprophylaxis postoperatively and continue for up to 14 days following total knee replacement surgery. Use one of the following: <ul style="list-style-type: none"> • low molecular weight heparin • fondaparinux# • rivaroxaban* • dabigatran etexilate.* 	A B B B
* Rivaroxaban and dabigatran etexilate are newly approved agents and post-marketing surveillance on adverse events is not yet available.	
# Use fondaparinux with caution as it may cause bleeding in those weighing less than 50kg, in the frail, the elderly and those with renal impairment.	

Low molecular heparin was more effective at reducing DVT than intermittent pneumatic compression¹²⁹ while studies comparing foot pump with low molecular weight heparin were inconclusive.^{137,138} Application of a foot pump¹³³ or intermittent pneumatic compression¹³⁴ was shown to be beneficial in reducing DVT (including proximal DVT) compared with no treatment. Intermittent pneumatic compression was also shown to significantly reduce DVT compared with aspirin.^{135,136} Therefore, the use of aspirin has not been recommended. A further study evaluated intermittent pneumatic compression plus low molecular weight heparin against intermittent pneumatic compression plus aspirin;¹³⁹ however, no conclusions could be drawn about the benefits of combination pharmacological prophylaxis with intermittent pneumatic compression as this study was small in sample size and was underpowered.

Recommendation	
	Grade
3. Use one of the following whether or not pharmacological thromboprophylaxis is used, until the patient is fully mobile: <ul style="list-style-type: none"> • foot pump • intermittent pneumatic compression. 	B

Recommendation	
	Grade
4. Aspirin alone is not recommended 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.^{141,142,146} One study of warfarin timing suggests that preoperative warfarin dosing does not provide additional thromboprophylactic benefit compared with postoperative dosing.¹⁴³

Recommendation	
	Grade
5. Warfarin is not recommended for thromboprophylaxis following total knee replacement.	B

6.1.4 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 was inadequate or could not be applied in the Australian healthcare context.

VTE prophylactic agent	Evidence summary - thromboprophylaxis for knee arthroscopy patients	Level	References
LMWH	In one systematic review of four RCTs ¹⁴⁷ that compared LMWH with no treatment or in a further RCT comparing LMWH with GCS, ¹⁴⁸ there were significantly lower rates of asymptomatic and symptomatic DVT with LMWH. There was no significant difference in the rates of PE between LMWH and no treatment/GCS groups. There was significantly more bleeding with LMWH in all five RCTs.	I	147,148
	One RCT comparing extended duration LMWH with extended duration placebo was not relevant as magnetic resonance venography was the diagnostic technique employed and this is not a validated diagnostic technique for detection of DVT.	I	149

Discussion about the evidence and basis for recommendations for knee arthroscopy

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 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.¹⁵⁰ There was no difference in the rates of PE (there was only one instance of PE in a treatment group from one of the included studies).¹⁵¹ Importantly, instances of bleeding were significantly more common in patients receiving low molecular weight heparin. These trials included arthroscopic procedures involving tourniquet time of up to one hour,¹⁴⁸ with no evidence available for prolonged arthroscopic knee surgery.

Based on the studies considered, although thromboprophylaxis may provide some benefit, this was primarily for distal DVT and crucially, low molecular weight heparin caused significantly more bleeding. Therefore, risk of prophylaxis outweighed benefits and in this case, thromboprophylaxis is not recommended.

No studies on mechanical methods alone were available for arthroscopic knee surgery. In addition, there was no evidence for thromboprophylaxis in patients undergoing arthroscopic knee surgery who have additional VTE risk factors. A Good Practice Point (GPP) has been suggested for these patients.

Recommendation	Grade
I. Thromboprophylaxis is not recommended following knee arthroscopy. Consider thromboprophylaxis for patients with additional VTE risk factors, in the absence of contraindications.	B GPP

6.1.5 Lower leg fractures and injuries with immobilisation

This section summarises evidence from a systematic review for the prevention of VTE in patients with immobilisation of the lower leg in a plaster cast or brace due to fracture or injury. Full evidence tables on which these summaries are based are 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.

VTE prophylactic agent	Evidence summary – thromboprophylaxis for patients with lower leg fractures and injuries with immobilisation	Level	References
LMWH	In a systematic review of six RCTs which included patients of varying ages with either <ul style="list-style-type: none"> • lower leg injuries with immobilisation or • a lower limb in a plaster cast or brace (with or without surgery), there were significantly fewer instances of symptomatic VTE, DVT and proximal DVT in patients that received LMWH compared with no treatment. Major adverse events were rare in either the LMWH or no treatment groups.	I	45

Discussion about the evidence and basis for recommendations for patients with immobilisation of the lower leg in a plaster cast or brace due to fracture or injury

Immobilisation of the lower leg is a significant risk factor for the development of VTE.^{152,153} In a systematic review of six RCTs, thromboprophylaxis with low molecular weight heparin for patients with a leg immobilised in a cast or brace following lower leg fracture or injury significantly lowered rates of both symptomatic and proximal DVT.⁴⁵ Major adverse events such as haematoma, acute bleeding, allergy and thrombocytopenia were rare.

Patients who had a leg injury that had been immobilised in a plaster cast or brace, (regardless of whether they were operated on, or whether the injury was a fracture or soft tissue damage) had significantly reduced occurrence of DVT (proximal and distal) when treated with low molecular weight heparin. There was no difference in PE with low molecular weight heparin. Importantly, low molecular weight heparin was administered daily during the entire period of immobilisation.⁴⁵ This suggests all patients who have had a lower leg fracture or injury (which involves immobilisation in a brace or a plaster cast for a prolonged period) should receive low molecular weight heparin for the entire period of immobilisation to prevent DVT.

Recommendation	Grade
1. Use low molecular weight heparin for all patients admitted to hospital with a lower leg fracture or injury with immobilisation in a brace or a plaster cast. Thromboprophylaxis should be continued for the entire period of immobilisation.	A

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 (table 70-80).

VTE prophylactic agent	Evidence summary – thromboprophylaxis for patients undergoing mixed orthopaedic procedures	Level	References
LMWH	In two RCTs of patients undergoing one of the following orthopaedic surgical procedures (total hip replacement, total knee replacement or hip fracture surgery), VTE prophylaxis with LMWH was more effective if administered for an extended duration (up to six weeks postoperatively). In a separate systematic review of 11 RCTs, LMWH was more effective than UFH at reducing the incidence of proximal DVT and PE. No adverse events were measured in this review.	I	154,155 156
Warfarin	In one RCT of patients undergoing total hip replacement or total knee replacement, low intensity warfarin or low fixed dose warfarin was not effective for thromboprophylaxis when compared with no treatment or UFH.	I	157,158
Aspirin	In two RCTs of patients undergoing total hip replacement or total knee replacement, aspirin was not effective at reducing DVT (both proximal and distal), or PE when compared with no treatment. No significant difference in adverse events.	I	88,89
UFH	In one systematic review of 21 RCTs of patients undergoing one of a range of orthopaedic surgical procedures, there was a significantly lower rate of DVT when UFH was used compared with no treatment. There was no significant difference in major bleeds between UFH and no treatment.	I	159

6.1.6 General surgery

This section summarises evidence from systematic reviews and individual trials for the prevention of VTE in patients undergoing general surgical procedures. Full evidence tables on which these summaries are based are provided in Appendix D (table 81-88).

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 surgery patients	Level	References
UFH	In a systematic review of 46 RCTs, there were significantly lower rates of DVT in patients treated with unfractionated heparin (UFH) until discharge (up to one week postoperatively) compared with those not receiving any treatment. There was no significant difference in major bleeding between UFH and no treatment.	I	159
LMWH or UFH	Across 10 RCTs comparing LMWH and UFH, both agents had similar effects in preventing DVT and PE with no difference in adverse events other than lower incidence of wound haematoma with LMWH (in seven of the trials which reported this outcome).	I	160-170
GCS	Across 11 RCTs comparing graduated compression stockings (both thigh and knee length) with no treatment, graduated compression stockings were more effective at reducing DVT than no treatment (when used alone or in combination with heparin or intermittent pneumatic compression).	I	171-181
	In one RCT there was inconclusive evidence of benefit of graduated compression stockings (GCS) compared with UFH. It was not possible to conclude that whether UFH is better than GCS or vice versa.	I	182
Foot pump	In one RCT there were significantly lower rates of DVT in those patients treated with a foot pump compared with those receiving no treatment. No PE events were recorded in either group.	I	183
IPC	There were a number of RCTs that compared IPC with no treatment or UFH, all of which were inconclusive.	I	184-190

Discussion about the evidence and basis for recommendations for general surgery

Patients undergoing major general surgery may be anaesthetised for a prolonged periods or have limited postoperative mobility. These factors along with surgical procedure itself increase the risk of VTE; therefore, thromboprophylaxis is recommended for all patients undergoing major general surgery.

Recommendation	Grade
I. Use thromboprophylaxis for all patients admitted to hospital for general surgery.	GPP

RCTs showed that low molecular weight heparin¹⁹¹⁻¹⁹³ or unfractionated heparin¹⁵⁹ both effectively reduced the occurrence of DVT compared with no treatment. Compared with no treatment, unfractionated heparin did not increase bleeding, however low molecular weight heparin caused significantly more bleeding following general surgery. Low molecular weight heparin and unfractionated heparin have similar effectiveness in preventing DVT;¹⁶⁰⁻¹⁷⁰ therefore the use of either agent is recommended following general surgery. The duration of thromboprophylaxis with low molecular weight heparin or unfractionated heparin was 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.

Recommendation	Grade
2. In the absence of contraindications, commence pharmacological thromboprophylaxis postoperatively and continue for up to one week or until the patient is fully mobile following major general surgery. Use one of the following: <ul style="list-style-type: none"> • low molecular weight heparin • unfractionated heparin. 	B A

A number of RCTs evaluated the effectiveness of graduated compression stockings at reducing venous thromboembolism following general surgery.¹⁷¹⁻¹⁸¹ These demonstrated that graduated compression stockings can significantly reduce the occurrence of DVT. Graduated compression stockings were shown to be beneficial as the sole prophylactic agent or in addition to heparin. Most of these trials evaluated thigh-length graduated compression stockings; however two trials used knee-length stockings.^{174,181} There were no direct comparisons available on the effectiveness of knee versus thigh length graduated compression stockings. The application of graduated compression stockings is recommended following general surgery, whether or not pharmacological prophylaxis is used. Graduated compression stockings should be worn for as long as possible until the patient is fully mobile. The choice of thigh or knee length graduated compression stockings will be influenced by availability, compliance and patient preference.

Recommendation	Grade
3. Use graduated compression stockings for all general surgical patients, whether or not pharmacological thromboprophylaxis is used, until the patient is fully mobile	B

The effectiveness of foot pump at preventing VTE following general surgery was evaluated in one relatively small RCT from the early 1980's.¹⁸³ A foot pump applied bilaterally significantly reduced DVT compared with providing no thromboprophylaxis following general surgery. A further study evaluated the effectiveness of intermittent pneumatic compression compared with unfractionated heparin. No conclusions could be drawn about the benefits of mechanical thromboprophylaxis against pharmacological prophylaxis as this study was of poor quality.¹⁹⁰

Recommendation	Grade
4. If recommended thromboprophylaxis is contraindicated or not available, use a foot pump following general surgery, until the patient is fully mobile.	C

6.1.7 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 (table 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.

VTE prophylactic agent	Evidence summary – thromboprophylaxis for urological surgery patients	Level	References
UFH	In patients undergoing urological surgery, unfractionated heparin significantly reduced the incidence of DVT compared with no treatment. However, unfractionated heparin also resulted in significantly more major bleeding compared with no treatment.	I	159
LMWH, IPC, GCS, low dose warfarin	There were a number of RCTs which compared a range of mechanical methods of prophylaxis with other mechanical methods or pharmacological methods. All of these RCTs were inconclusive.	I	194-197
LMWH	In one RCT of prostatectomy patients, there was inconclusive evidence of benefit of LMWH compared with no treatment (due to lack of power of the study).	I	198

Discussion about the evidence and basis for recommendations for urological surgery

Many of the urological surgery RCTs used a broad categorisation of patients undergoing urological surgery. It was not possible to separate the evidence from this heterogeneous group of patients. Surgical procedures may have included prostatectomy, renal surgery or transurethral resection of the prostate (TURP). This limited the ability to apply the evidence as these procedures present different VTE and bleeding risk. For example, TURP may cause significant bleeding as the surgery involves sharp dissection and electrocautery. This type of urological surgery procedure may cause significantly more bleeding than renal surgery. In the absence of information about benefits and harms for specific procedures, it was not possible to make a recommendation regarding VTE prophylaxis following urological surgery. VTE prophylaxis should be an individual clinician decision in patients undergoing urological surgery based on other VTE risk factors, with consideration of the patient's bleeding risk.

Recommendation	Grade
1. Consider thromboprophylaxis for patients admitted to hospital for urological surgery based on an assessment of the patient's risk of VTE and bleeding.	GPP

6.1.8 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 (table 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.

VTE prophylactic agent	Evidence summary – thromboprophylaxis for gynaecological surgery patients	Level	References
UFH	In two RCTs, UFH was more effective at reducing DVT compared with no treatment following major gynaecological surgery.	I	199,200
LMWH or UFH	Across five RCTs of major gynaecological surgery patients, LMWH and UFH conferred similar benefits for the prevention of DVT. PE rates were only reported in one trial, with no statistically significant difference between LMWH and UFH. In one RCT there were significantly more transfusions in the LMWH group compared with the UFH group. ²⁰¹ In three RCTs ²⁰²⁻²⁰⁴ there was no significant difference between LMWH and UFH for major haemorrhage or wound haematoma.	I	201-205
GCS	In one RCT there was no significant difference in rates of DVT between GCS and no treatment.	I	206
IPC	In two RCTs there was no significant difference in DVT, proximal DVT or PE between IPC and no treatment.	I	207,208
	In one RCT of patients undergoing major gynaecological surgery for malignancy, there was insufficient evidence to recommend IPC in preference to LMWH, or vice versa. There were no significant differences in adverse events (blood loss or thrombocytopenia).	I	209
Warfarin	From one RCT there was no significant difference in DVT, proximal DVT or major bleeding between warfarin and no treatment.	I	210

Discussion about the evidence and basis for recommendations for gynaecological surgery

Gynaecological surgery encompasses a range of surgical procedures from simple procedures to complex curative surgery for cancer. Major gynaecological surgery increases the risk of VTE and therefore thromboprophylaxis is recommended for all patients in this group. Thromboprophylaxis may also be appropriate following other gynaecological procedures that increase the patient's risk of VTE.

Recommendation	Grade
I. Use thromboprophylaxis for all patients admitted to hospital for major gynaecological surgery.	GPP

Pooling of data from two trials showed that unfractionated heparin reduced DVT compared with no treatment (although this did not reach statistical significance).^{199,200} 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; therefore both are effective VTE prophylactic options following gynaecological surgery.²⁰¹⁻²⁰⁵

Recommendation	Grade
2. In the absence of contraindications, commence pharmacological thromboprophylaxis postoperatively and continue for up to one week or until the patient is fully mobile following major gynaecological surgery. Use one of the following: <ul style="list-style-type: none"> • low molecular weight heparin • unfractionated heparin. 	B

There was no conclusive evidence regarding the effectiveness of graduated compression stockings or intermittent pneumatic compression compared with no treatment following gynaecological surgery.²⁰⁶⁻²⁰⁸ Mechanical methods of thromboprophylaxis may be considered for patients following gynaecological surgery.

Recommendation	Grade
3. Consider the additional use of graduated compression stockings or other mechanical thromboprophylaxis following major gynaecological surgery, especially if pharmacological thromboprophylaxis is contraindicated.	GPP

An RCT of fixed low dose warfarin demonstrated that warfarin provided no thromboprophylactic benefit following gynaecological surgery.²¹⁰ Therefore, the use of warfarin is not recommended following major gynaecological surgery.

Recommendation	Grade
4. Warfarin is not recommended for thromboprophylaxis following major gynaecological surgery.	C

6.1.9 Abdominal surgery

This section summarises evidence from systematic reviews and individual trials for the prevention of VTE in patients undergoing abdominal surgical procedures. Full evidence tables on which these summaries are based are provided in Appendix D (table 102-113).

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 abdominal surgery patients	Level	References
LMWH	In three RCTs, LMWH was effective at reducing the rate of DVT compared with no treatment (when prophylaxis is begun 1-2 hours preoperatively and continued for between five to nine days postoperatively). There was no difference in total haemorrhage or wound haematoma in patients treated with LMWH compared with placebo.	I	211-213
LMWH or UFH	There were 23 RCTs comparing LMWH and UFH; LMWH was more effective at reducing DVT (including symptomatic DVT) than UFH. There were no significant differences in PE or adverse events including haemorrhage, wound haematoma, transfusions or death between LMWH and UFH.	I	214-236
LMWH dose	In one RCT comparing doses of LMWH, standard doses of LMWH (5000IU) were more effective than lower doses (2500IU); however, standard doses caused significantly more major bleeding than lower doses.	I	237
LMWH extended duration	In one RCT of high risk cancer patients undergoing curative abdominal surgery, extended duration LMWH (40mg LMWH for between 25 to 31 days post surgery) was more effective at reducing rates of DVT than 40mg of LMWH administered for up to 10 days. There was no difference in adverse events such as major bleeding or death between the 10 day duration and extended duration LMWH groups.	I	238
Fondaparinux	In one RCT fondaparinux was more effective at reducing asymptomatic DVT than no treatment or IPC alone. However, fondaparinux significantly increased major bleeding complications compared with no treatment (with no difference in death rates). In a separate trial comparing fondaparinux with LMWH, both agents were shown to have similar effects on DVT and PE with no difference in bleeding or death between the two groups.	I	239 240
GCS	In three RCTs there was a lower incidence of DVT among patients wearing thigh-length graduated compression stockings compared with no treatment (stockings worn alone or in combination with other more effective forms of prophylaxis such as pharmacological prophylaxis). No adverse events were recorded in these RCTs. There was inconclusive evidence from one RCT comparing GCS with UFH. ¹⁸¹	I	181, 241-243
Aspirin	There was one RCT comparing aspirin with UFH. The aspirin and UFH doses used in this trial were not applicable to the Australian healthcare setting.	I	244
IPC	There was inconclusive evidence from one RCT comparing IPC with UFH (alone or in combination).	I	245

Discussion about the evidence and basis for recommendations for abdominal surgery

Major abdominal surgery increases the risk of VTE and therefore thromboprophylaxis is recommended for all patients following major abdominal surgery.

Recommendation	Grade
1. Use thromboprophylaxis for all patients admitted to hospital for major abdominal surgery.	GPP

Fondaparinux²³⁹ or low molecular weight heparin²¹¹⁻²¹³ were both effective VTE prophylactic options compared with no treatment following abdominal surgery. However, fondaparinux significantly increased major bleeding compared with no treatment, and therefore is not recommended.²³⁹

Across 23 RCTs comparing low molecular weight heparin with unfractionated heparin, low molecular weight heparin significantly reduced DVT (including symptomatic DVT) compared with unfractionated heparin, with no difference in adverse events including major haemorrhage.²¹⁴⁻²³⁶ Therefore, low molecular weight heparin is recommended for thromboprophylaxis following abdominal surgery.

Dosage and duration of thromboprophylaxis: In 1995, one trial examined optimal thromboprophylactic dosage of low molecular weight heparin.²³⁷ This showed that whilst higher doses were more effective for thromboprophylaxis than lower doses, higher doses also caused significantly more bleeding. The dosage of low molecular weight heparin varied across the other trials so dosing is recommended according to manufacturer's instructions.

In one trial, the duration of low molecular weight heparin was investigated and it demonstrated that thromboprophylaxis with low molecular weight heparin was more effective if extended to between 25 and 31 days compared with 10 days. However, this study was carried out in a sub-set of abdominal surgery patients that were considered high risk as they were undergoing curative surgery for cancer.²³⁸ Therefore, thromboprophylaxis with low molecular weight heparin has been recommended for between five to nine days for abdominal surgery patients.

Recommendation	Grade
2. In the absence of contraindications, commence pharmacological thromboprophylaxis postoperatively with low molecular weight heparin and continue for at least five to nine days.	B

Recommendation	Grade
3. Fondaparinux is not recommended for thromboprophylaxis following major abdominal surgery.	C

Graduated compression stockings significantly reduced DVT compared with no treatment²⁴¹⁻²⁴³ and therefore have been recommended following abdominal surgery, whether or not pharmacological prophylaxis is used. A further trial examined intermittent pneumatic compression compared with unfractionated heparin;²⁴⁵ however no conclusions could be drawn from this study as the results were inconclusive.

Recommendation	Grade
4. Use graduated compression stockings for all patients following abdominal surgery, whether or not pharmacological thromboprophylaxis is used, until the patient is fully mobile.	B

6.1.10 Cardiac, thoracic and vascular surgery

This section summarises evidence from systematic reviews and individual trials for the prevention of VTE in patients undergoing cardiac, thoracic or vascular surgical procedures. Full evidence tables on which these summaries are based are provided in Appendix D (table 114-116).

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 cardiac, thoracic or vascular surgery patients	Level	References
LMWH or UFH	In four RCTs no difference was detected in the rate of DVT between LMWH and UFH. There were no differences in adverse events other than in one trial which showed more wound haematomas in patients treated with UFH compared with LMWH. ²⁴⁶	I	246-249
IPC	In one RCT of cardiac surgery patients, thigh-length intermittent pneumatic compression significantly reduced symptomatic PE when it was added to thromboprophylaxis with heparin.	I	250
	In one trial, thigh-length intermittent pneumatic compression (IPC) did not have any additional benefit when applied to coronary artery bypass surgery patients who were already receiving 325mg/day aspirin and wearing graduated compression stockings.	I	251
UFH dose	In patients undergoing cardiothoracic surgery, there was no evidence of benefit of using higher doses of UFH (7500BD) compared with lower doses of UFH (5000 BD).	I	252

Discussion about the evidence and basis for recommendations for patients undergoing cardiac, thoracic or vascular surgery

Cardiac, thoracic or vascular surgery increases the risk of VTE and therefore thromboprophylaxis is recommended for all patients following cardiac, thoracic or vascular surgery.

Recommendation	
	Grade
1. Use thromboprophylaxis for all patients admitted to hospital following cardiac, thoracic or vascular surgery.	GPP

RCTs demonstrated that low molecular weight heparin or unfractionated heparin are both effective options for VTE prophylaxis following cardiac, thoracic or vascular surgery²⁴⁶⁻²⁴⁹ 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 a cancer patients undergoing thoracic surgery).²⁴⁶ Either 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 heparin varied across the trials so dosing is recommended according to manufacturer's instructions.

Recommendation	
	Grade
2. In the absence of contraindications, commence pharmacological thromboprophylaxis postoperatively and continue for up to one week or until the patient is fully mobile following cardiac, thoracic, or vascular surgery. Use one of the following: <ul style="list-style-type: none"> • low molecular weight heparin • unfractionated heparin. 	B

Thigh-length intermittent pneumatic compression significantly reduced symptomatic PE when applied to patients receiving heparin.²⁵⁰ The application of intermittent pneumatic compression did not provide any further thromboprophylactic benefit when applied to coronary artery bypass patients that were wearing graduated compression stockings and receiving 325mg/day of aspirin. The application of graduated compression stockings or intermittent pneumatic compression is recommended following cardiothoracic surgery, whether or not pharmacological prophylaxis is used (until the patient is fully mobile).

Recommendation	
	Grade
3. Use one of the following for all patients following cardiac, thoracic, or vascular surgery, whether or not pharmacological thromboprophylaxis is used, until the patient is fully mobile: <ul style="list-style-type: none"> • graduated compression stockings • intermittent pneumatic compression. 	C

6.1.11 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 (table 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 (mostly knee-length) compared with no treatment. In three of these trials, there were significantly lower rates of proximal DVT. ²⁵³⁻²⁵⁵ No instances of PE were seen in either group across three trials. ^{253,255,256} In a separate RCT of LMWH versus IPC, this evidence was not considered as the trial was terminated early. ²⁵⁷	I	253-260
LMWH	In a systematic review of three trials, ²⁶¹ LMWH significantly reduced DVT (including proximal DVT) compared with no treatment. There was no significant difference in PE or adverse events such as bleeding or death.	I	261
UFH	In one RCT there were significantly lower rates of DVT in patients receiving UFH compared with no treatment. ²⁶² There was no significant difference in bleeding (including major bleeding) or death. No instances of clinically overt PE were seen in either the UFH or no treatment groups. Two RCTs examined the effectiveness of LMWH or UFH; ^{263,264} there was insufficient evidence from these RCTs to draw definitive conclusions.	I	262-264
GCS	In one RCT comparing the effects of using GCS compared with no treatment, there was some suggestion of benefit on DVT of using GCS but this was not statistically significant. There were no instances of fatal PE in either the GCS or no treatment groups. One study which compared IPC with GCS in craniotomy patients was excluded as it used an unreliable diagnostic technique. ²⁶⁵	I	265,266

Discussion about the evidence and basis for recommendations for patients undergoing neurosurgery

Neurosurgery presents a high risk of VTE but the consequences of bleeding can be severe following neurosurgery. Pharmacological prophylaxis should be used with caution in neurosurgery patients depending on the risk of VTE and bleeding. Mechanical methods may be an appropriate alternative. Intermittent pneumatic compression significantly reduced DVT (including proximal DVT) compared with no treatment^{253-256,258-260} and therefore is recommended until the patient is fully mobile.

Recommendation	
	Grade
1. Use intermittent pneumatic compression following neurosurgery, until the patient is fully mobile.	A

Recommendation	
	Grade
2. Use pharmacological thromboprophylaxis with extreme caution in patients following neurosurgery, due to the high risk of bleeding.	GPP

Both low molecular weight heparin²⁶¹ and unfractionated heparin²⁶² significantly reduced DVT following neurosurgery, with no difference in adverse events. Either low molecular weight heparin or unfractionated heparin are recommended for thromboprophylaxis following neurosurgery.

Dosage and duration of thromboprophylaxis: As the balance between risk and benefit is particularly important in this group of patients given the consequences of intracranial bleeding, the duration of thromboprophylaxis should be an individual clinician decision based on the patient risk assessment. The appropriateness of pharmacological thromboprophylaxis should be closely monitored. Dosage is recommended according to manufacturer's instructions.

Recommendation	
	Grade
3. Where pharmacological thromboprophylaxis is appropriate and not contraindicated, use low molecular weight heparin or unfractionated heparin.	B

There was some suggestion of benefit of wearing graduated compression stockings for patients following neurosurgery (however this was not statistically significant).²⁶⁶ Therefore, the use of graduated compression stockings may be considered following neurosurgery. There was insufficient evidence from one small trial to recommend graduated compression stockings in preference to intermittent pneumatic compression (or vice versa).²⁶⁵

Recommendation	
	Grade
4. Consider the use of graduated compression stockings following neurosurgery (alone or in combination with pharmacological thromboprophylaxis).	C

6.1.12 Trauma surgery or spinal surgery

This section summarises evidence from systematic reviews and individual trials for the prevention of VTE in patients undergoing surgery for trauma or spinal surgery. Full evidence tables on which these summaries are based are provided in Appendix D (table 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 or spinal injury patients undergoing surgery	Level	References
Foot pump plus LMWH after five days	In one RCT of trauma surgery patients, the use of a foot pump for five days with the addition of LMWH at day five, significantly reduced DVT and occlusive DVT. There was no difference in PE, wound or bleeding complications with this regimen (compared with the use LMWH alone).	I	267
IPC (thigh, calf or foot), warfarin or foot pump.	There were a number of RCTs comparing a range of mechanical methods of VTE prophylaxis with other mechanical or pharmacological methods in trauma or spinal surgery patients. All of these were inconclusive or underpowered.	I	268-272

Discussion about the evidence and basis for recommendations for patients undergoing surgery for trauma or spinal cord injury

Patients with major trauma are at high risk of VTE and those with spinal cord injury are at even higher risk of VTE following trauma. Therefore thromboprophylaxis is recommended for all trauma or spinal injury patients undergoing surgery.

Recommendation	Grade
1. Use thromboprophylaxis for all patients admitted to hospital for trauma surgery or spinal surgery.	GPP

RCTs comparing a range of mechanical methods of VTE prophylaxis with other mechanical or pharmacological methods in trauma or spinal surgery patients were all inconclusive or underpowered so no recommendations could be formulated from these.²⁶⁸⁻²⁷² There was only one RCT that provided conclusive evidence of thromboprophylactic benefit in trauma surgery patients.²⁶⁷ This trial demonstrated that foot pump initiated at time of admission with the addition of low molecular weight heparin five days after admission significantly reduced DVT and occlusive DVT in trauma patients undergoing surgery.

Recommendation	Grade
2. In the absence of contraindications, use a foot pump from hospital admission with the addition of low molecular weight heparin five days after admission for trauma patients undergoing surgery.	C

6.2 Anaesthesia

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 (table 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.

	Evidence summary – thromboprophylaxis in anaesthetised patients	Level	References
Regional anaesthesia (central neural blockade)	<p>In one systematic review of 11 studies²⁷³ and a further four RCTs, there were significantly lower rates of DVT in patients receiving regional anaesthesia compared with general anaesthesia (whether regional anaesthesia was epidural or spinal).</p> <p>In seven of the RCTs, there were significantly lower rates of PE in patients receiving regional anaesthesia compared with general anaesthesia (whether regional anaesthesia was epidural or spinal).</p> <p>There was no significant difference in major bleeding between patients receiving regional and general anaesthesia in seven of the RCTs. Many RCTs reported no bleeding events in either group.</p> <p>Note: This evidence was for certain surgical procedures only (orthopaedic, general or urological surgery including prostatectomy). Refer to anaesthesia evidence tables for further details. (Appendix D 148-149)</p>	I	273-277
Regional (central neural blockade) plus general anaesthesia	<p>In two RCTs there was no significant difference in rates of DVT between patients receiving regional plus general anaesthesia compared with general anaesthesia. There was significantly lower blood loss in patients receiving regional plus general anaesthesia compared with general in one RCT.²⁷⁸</p>	I	278,279

Discussion about the evidence and basis for recommendations for anaesthetised patients

RCTs 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.²⁷³⁻²⁷⁷ 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.²⁸⁰ 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.⁴⁴ 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 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).⁴⁴

Recommendation	Grade
I. Consider central neural blockade as an alternative to general anaesthesia if feasible. If central neural blockade is used, there is a risk of developing an epidural haematoma. To minimise this risk, timing of pharmacological thromboprophylaxis should be carefully planned and discussed in advance with the anaesthetist.	A GPP

6.3 Medical patients – Evidence and recommendations for VTE prophylaxis

6.3.1 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 (table 131-138).

A stroke occurs when the supply of blood to the brain is disrupted. Stroke can be classified into two major categories: ischaemic or haemorrhagic. Ischaemic stroke results from an interruption to blood supply whilst haemorrhagic stroke is due to rupture of a blood vessel or an abnormal vascular structure. Ischaemic stroke can result from an artery becoming blocked by a thrombosis or an embolism.

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 relating to stroke patients in acute care	Level	References
LMWH	<p>Across eight of nine RCTs, stroke patients* receiving LMWH had significantly lower rates of PE when compared with those not receiving any prophylaxis.</p> <p>In seven of the RCTs, there was no significant difference in intracranial haemorrhage in patients receiving LMWH compared with no treatment.</p> <p>In six of the RCTs, there was no significant difference in extracranial haemorrhage in patients receiving LMWH compared with no treatment.</p> <p>*The defined stroke patient populations across the trials included:</p> <ul style="list-style-type: none"> stroke²⁸¹⁻²⁸³ acute ischaemic stroke²⁸⁴⁻²⁸⁶ acute stroke²⁸⁷ non-embolic ischaemic stroke²⁸⁸ ischaemic stroke.²⁸⁹ 	I	281-286,288,289 283-289 281,283-287
	<p>In a systematic review of five RCTs, there was significantly lower incidence of DVT with LMWH compared with UFH following acute ischaemic stroke with no significant difference in intracranial haemorrhage between the two groups. In three of the five RCTs, there was no significant difference in extracranial haemorrhage between LMWH and UFH.</p>	I	290

VTE prophylactic agent	Evidence summary relating to stroke patients in acute care	Level	References
Danaparoid or UFH	Danaparoid or UFH significantly reduced DVT rates in acute stroke patients compared with no treatment. However, there was significantly more extracranial haemorrhage in one UFH RCT which used high doses of UFH (12500IU) compared with no treatment. There was also significantly more extracranial haemorrhage with danaparoid compared with no treatment.	I	291-297 298 296,297
	In a systematic review of pooled data from four RCTs, danaparoid was more effective in reducing DVT in acute ischaemic stroke patients than UFH. There was no significant difference in intracranial or extracranial haemorrhage between danaparoid and UFH.	I	290
GCS	There was no difference in DVT in patients wearing graduated compression stockings for seven days following acute stroke compared with no treatment. There were no adverse effects with use of graduated compression stockings.	I	299
IPC	One RCT comparing IPC with no treatment in acute stroke patients was inconclusive.	I	300

Most acute ischaemic strokes take place when a blood clot blocks a blood vessel leading to the brain. Anticoagulation may improve outcomes in ischaemic stroke patients where bleeding risk is low.³⁷ Thromboprophylaxis should be considered in acute ischemic stroke patients, taking into account the patient's degree of immobility and their risk of bleeding. Thromboprophylaxis is not recommended in haemorrhagic stroke patients due to the risk and consequences of intracranial bleeding.

Recommendation	Grade
1. Consider the use of thromboprophylaxis for all patients admitted to hospital with ischaemic stroke based on an assessment of the patient's degree of immobility and risk of bleeding.	B

Recommendation	Grade
2. Pharmacological thromboprophylaxis is not recommended for haemorrhagic stroke patients due to the risk of intracranial bleeding.	GPP

Low molecular weight heparin, unfractionated heparin and danaparoid are all effective VTE prophylactic agents following acute ischaemic stroke. Unfractionated heparin²⁹¹⁻²⁹⁵ or danaparoid^{296,297} significantly reduced DVT following acute ischaemic stroke. Whilst low molecular weight heparin did not significantly reduce the rate of DVT across six RCTs, but did significantly reduce the rate of PE compared with no treatment.^{281-286,288,289} Therefore, low molecular weight heparin has been recommended in preference to unfractionated heparin for thromboprophylaxis following acute ischaemic stroke.

Recommendation	Grade
3. Where thromboprophylaxis is appropriate and not contraindicated, use low molecular weight heparin for patients with ischaemic stroke. If low molecular weight heparin is contraindicated or not available, use unfractionated heparin.	B B

6.3.2 Myocardial infarction (MI)

This section summarises evidence from systematic reviews and individual trials for the prevention of VTE in medical patients hospitalised for myocardial infarction. Full evidence tables on which these summaries are based are provided in Appendix D (table 139 and 140).

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](#).

VTE prophylactic agent	Evidence summary – thromboprophylaxis for myocardial infarction patients	Level	References
UFH	Across six RCTs of MI patients where full anticoagulation was not employed post MI, UFH significantly reduced rates of DVT and PE compared with no treatment. There was no difference in adverse events such as bleeding or death.	I	301-306
LMWH	There was one RCT which compared LMWH and UFH in acute MI patients, however this evidence was not relevant as treatment doses were used and the trial did not report the outcomes of interest (other than mortality).	I	307

Discussion about the evidence and basis for recommendations for hospitalised patients following myocardial infarction

Patients admitted to hospital following myocardial infarction (MI) are at increased risk of VTE.³² There were only a small number of studies examining thromboprophylaxis in patients with myocardial infarction, most of which were more than 30 years old. Pooling of data from these studies demonstrated that unfractionated heparin significantly reduced the rates of DVT and PE following MI and did not increase the rate of bleeding (although there was no effect on proximal DVT or death). One small RCT of 39 patients compared the effect on mortality of low molecular weight heparin or unfractionated heparin; this study was excluded as it did not report any outcomes other than mortality and treatment rather than prophylactic doses were used.³⁰⁷

In current practice, many patients are fully anticoagulated following myocardial infarction, and therefore will not require further thromboprophylaxis. Where full anticoagulation is not employed post myocardial infarction, thromboprophylaxis with unfractionated heparin is recommended.

Recommendation	Grade
1. Use thromboprophylaxis for patients admitted to hospital for myocardial infarction, where full anticoagulation is not in use.	C
2. In the absence of contraindications, use unfractionated heparin for thromboprophylaxis following myocardial infarction.	C

6.3.3 General medical

This section summarises evidence from systematic reviews and individual trials for the prevention of VTE in medical patients admitted to hospital. Full evidence tables on which these summaries are based are provided in Appendix D (table 144 and 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 relating to general medical patients	Level	References
LMWH	<p>Across six RCTs 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.</p> <p>Patients with the following conditions or characteristics were included in these studies:</p> <ul style="list-style-type: none"> • congestive heart failure³⁰⁸⁻³¹¹ • acute or chronic respiratory failure³⁰⁸⁻³¹¹ • acute decompensated chronic obstructive pulmonary disease with mechanical ventilation³¹² • acute infectious or rheumatologic disease^{308,310} • non-pulmonary sepsis³⁰⁹ • cancer³⁰⁹ • age over 40,^{309,310,312} over 60,^{312,313} or over 65.³¹² <p>In three trials, patients receiving LMWH had significantly lower rates of proximal DVT when compared with no treatment.</p> <p>In three trials, there was no significant difference in fatal PE.</p>	I	<p>308-313</p> <p>308,310,312</p> <p>309-311</p>

VTE prophylactic agent	Evidence summary relating to general medical patients	Level	References
UFH	<p>Across four RCTs of medical patients there was no difference in the rate of DVT for patients receiving UFH compared with no treatment. However, when one study which used autopsy to diagnose DVT in patients with infection was excluded,³¹⁴ there were significantly lower rates of DVT in medical patients who received UFH compared with no treatment.</p> <p>Patients with the following conditions or characteristics were included in these studies:</p> <ul style="list-style-type: none"> • heart failure^{315,316} • chest infection³¹⁵ • complete bed rest³¹⁶ • obesity³¹⁶ • previous vte³¹⁶ • cancer³¹⁶ • recent surgery³¹⁶ • infection³¹⁴ • critical care³¹⁷ • age over 40^{316,318} or 55.³¹⁴ <p>Pooled data from two RCTs showed that UFH significantly reduced rates of PE.^{314,315}</p> <p>In the one study which reported the rates of serious fatal bleeding or death, there was no difference for patients receiving UFH compared with no treatment.³¹⁴</p>	I	314,315, 319,320
LMWH or UFH	<p>Pooled data from five RCTs of medical patients showed that LMWH and UFH conferred similar thromboprophylactic benefits and there was no significant difference in adverse events.</p> <p>Patients with the following conditions or characteristics were included in these studies:</p> <ul style="list-style-type: none"> • severe respiratory disease³²¹ • heart failure³²¹ • age over 18,^{321,322} 40,³²³ 50³²⁴ or 65.³²⁵ 	I	321-325
Fondaparinux	<p>From one RCT of medical patients greater than 60 years of age, fondaparinux appeared to reduce asymptomatic distal DVT, but did not reduce symptomatic DVT or PE. There was no difference in deaths or major bleeding between fondaparinux and no treatment.</p>	I	326

Discussion about the evidence and basis for recommendations for general medical patients

Many medical patients admitted to hospital will be at increased risk of VTE due to individual patient risk factors, or risks related to an acute medical illness. These are detailed in [section 4, Patient Risk](#). Therefore, individual assessment of the VTE risk is recommended for each patient.

Pooled data from six randomised controlled trials of low molecular weight heparin in a group of mixed medical patients found that the rate of symptomatic PE was significantly lower for patients receiving low molecular weight heparin compared with no treatment. These studies included a range of medical conditions and patient groups, including congestive heart failure (three studies), acute or chronic respiratory disease (three studies), and acute infectious or rheumatologic disease (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 disease and acute infectious or rheumatologic disease. Therefore, low molecular weight heparin is recommended for thromboprophylaxis in medical patients at risk of VTE.

Four studies compared medical patients who received unfractionated heparin with no treatment.

These studies included patients with a range of VTE risk factors (including immobility, increasing age and obesity) and conditions which carry increased VTE risk (including heart failure). When data from all of these studies were pooled, there was no difference between groups in the rate of DVT. One study of patients with infection used autopsy to assess DVT, and found significantly different results from the other three studies.³¹⁴ When this study was excluded from the analyses, the rate of DVT in patients receiving unfractionated heparin was significantly lower than the no treatment group. There were no differences for death and bleeding (either bleeding complications or serious fatal bleeding) between groups. Therefore, unfractionated heparin is recommended for use in medical patients at risk of VTE.

Five studies compared medical patients receiving low molecular weight heparin with those receiving unfractionated heparin.³²¹⁻³²⁵ These studies included patients with congestive heart failure and respiratory disease (other conditions were not listed). When data from these studies were pooled, there was no difference between the rates of DVT, proximal DVT, PE, bleeding (major or minor) or death. Therefore, either low molecular weight heparin or unfractionated heparin may be used, depending on availability, cost and individual patients' risk characteristics and preferences.

One study compared fondaparinux with no treatment for the prevention of VTE in medical patients aged over 60.³²⁶ Compared with the no treatment group, patients receiving fondaparinux were less like to develop an asymptomatic distal DVT; however there was no difference for asymptomatic proximal DVTs, fatal PE, death, or major bleeding. No symptomatic DVTs were reported in either group. The evidence from this trial was not sufficient to make a recommendation about the use of fondaparinux in medical patients.

All of the evidence identified for prevention of VTE in general medical patients admitted to hospital for this Guideline concerned pharmacological thromboprophylaxis. No randomised controlled trials for mechanical methods of thromboprophylaxis were identified; therefore no recommendations have been made for the use of mechanical thromboprophylaxis for this group of patients.

Recommendation	Grade
1. Consider the use of thromboprophylaxis for patients admitted to hospital for medical conditions based on an assessment of the patient's risk of VTE and bleeding.	GPP
2. In the absence of contraindications, use one of the following: <ul style="list-style-type: none"> • low molecular weight heparin • unfractionated heparin. 	B

6.4 Cancer patients – Evidence and recommendations for VTE prophylaxis

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 the Guideline (e.g. Abdominal surgery). All of the recommendations in this section are based on consensus, and graded as Good Practice Points (GPP).

Discussion about the evidence and basis for recommendations for cancer patients admitted to hospital

Epidemiological^{26,30,327,328} and hospital-based studies³²⁹ 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 six-fold for cancer patients undergoing chemotherapy.^{30,327} As the majority of cancer patients are elderly, and as the incidence of VTE increases dramatically in patients aged greater than 55 years²⁶, 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.³³⁰

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.^{331,332}

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 VTE events occurring more than 21 days after surgery, based on data from the @RISTOS Study Group.³³³

Abdominal surgery: Studies of cancer patients^{165,334} and of surgery including cancer patients have shown 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.³³⁵ Further studies suggest that four weeks of postoperative prophylaxis further reduces VTE events.^{336,337}

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.³³⁸ 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. However, other risk factors for VTE should be considered in making any decision regarding the provision of thromboprophylaxis.

Non-surgical cancer patients: Although there are no large RCTs specifically addressing thromboprophylaxis in non-surgical cancer patients, both RCTs and observational studies have shown a 50 to 70 percent reduction in VTE in medical in-patients receiving prophylaxis with low molecular weight heparin.^{308,339} Sub-group analysis of a cohort of cancer patients (118 out of a total of 1102) within the MEDENOX study of acutely ill medical patients showed a halving in VTE occurrence (from 19.5 percent to 9.7 percent) although this did not reach statistical significance because of the relatively small numbers.³⁴⁰

Recommendation	Grade
1. Use thromboprophylaxis for all cancer patients undergoing general surgical procedures including abdominal or pelvic surgery or neurosurgery, provided there are no contraindications*. Commence pharmacological thromboprophylaxis postoperatively and continue for at least seven to 10 days following major general surgery for cancer. Use one of the following: <ul style="list-style-type: none"> • low molecular weight heparin • unfractionated heparin. 	GPP
2. Consider using extended thromboprophylaxis with low molecular weight heparin for up to 28 days after major abdominal or pelvic surgery for cancer, especially in patients who are obese, slow to mobilise or have a past history of VTE.	GPP
3. In the absence of other significant risk factors, thromboprophylaxis is not recommended for cancer patients undergoing head and neck surgery.	GPP
4. In non-surgical cancer patients in the absence of contraindications, commence thromboprophylaxis on admission and continue until discharge. Use one of the following: <ul style="list-style-type: none"> • low molecular weight heparin • unfractionated heparin. 	GPP
5. For both non-surgical and surgical cancer patients, use graduated compression stockings if pharmacological thromboprophylaxis is contraindicated.	GPP

*In patients with the following characteristics, pharmacological prophylaxis is contraindicated:³⁴¹

- recent central nervous system bleeding
- intracranial or spinal lesion at high risk for bleeding
- 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
- thrombocytopenia (platelets < 50,000/ μ l)
- severe platelet dysfunction (due, for example to uraemia, medications, or myelodysplasia)
- recent major surgical procedure at high risk for bleeding
- underlying coagulopathy or coagulation factor abnormalities
- regional axial anaesthesia or recent lumbar puncture for any reason
- high risk of falls.

6.5 Pregnancy and childbirth – Evidence and recommendations for VTE prophylaxis

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.³⁴² 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).

Evidence and recommendations for pregnancy and childbirth in women admitted to hospital

VTE during pregnancy and the immediate postnatal period is rare, but when it occurs, it is associated with high degrees of morbidity and mortality.³⁴³ 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.³⁴⁴ A Cochrane review identified the best estimate of incidence as 0.13 percent.³⁴² Other estimates varying from 0.06 percent³⁴⁵ to 0.11 percent³⁴⁶ 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.^{347,348} The risk is even higher if delivery is by caesarean section, especially emergency caesarean section.³⁴⁹ 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 in women with a previous VTE revealed risks of 3.7 percent per year outside pregnancy and 10.9 percent during pregnancy and the post-partum period.³⁵⁰

PE is the most common direct cause of maternal death in the UK.³⁵¹ Although most VTE occurs antenatally, the risk per day is greatest in the six weeks immediately after delivery.³⁵²

Recommendation	Grade
1. Minimise immobilisation of women during pregnancy, labour and the puerperium and ensure adequate hydration at all times.	GPP
2. All women who deliver by caesarean section are at increased risk of VTE and should be mobilised promptly after surgery.	GPP

Thromboprophylaxis with low molecular weight heparin has been proven effective in many postoperative settings and has been adopted for use in the period after caesarean. Both low molecular weight heparin and warfarin are safe for women who are breast feeding.²³ Low molecular weight heparin has been shown to be associated with abnormal bleeding less often than unfractionated heparin³⁴² although both are associated with bleeding in some cases. Low molecular weight heparin in prophylactic dose is recommended for at least five to seven days after caesarean (and longer if return to full mobility is delayed) for women who have additional risk factors.³⁵³ The first dose should be administered no less than four hours after surgery, with due attention to guidelines relating to the removal of epidural or spinal cannulae.

Note: When used after caesarean section, low molecular weight heparin may increase the frequency of bleeding and wound haematoma. Anticoagulation is contraindicated in women with primary postpartum haemorrhage >1000mls. Pharmacological prophylaxis is not recommended in these women but may be used in high risk cases when haemostasis is considered secure by the obstetrician.

Timing

Postpartum thromboprophylaxis should be given as soon as possible after delivery by caesarean section, provided that there is no postpartum haemorrhage.

Those with **postpartum haemorrhage** should be fitted with graduated compression stockings.

If the woman has been given **regional analgesia**, low molecular weight heparin should be withheld until four hours after insertion or removal of the epidural catheter (or six hours if either insertion or removal were traumatic). The first postpartum dose can be given after insertion but before removal of the epidural catheter.

Given the absence of evidence about mechanical methods, it was not possible to make a graded recommendation about their use. However, these have been shown to be beneficial in many other clinical categories, and therefore should be considered for women admitted to hospital during pregnancy and continuing into the early postnatal period.

Recommendation	Grade
3. Where pharmacological thromboprophylaxis is appropriate and not contraindicated, use low molecular weight heparin after caesarean delivery for five to seven days, or until the patient is fully mobile.	GPP
4. Extend pharmacological thromboprophylaxis with low molecular weight heparin or adjusted dose warfarin to six weeks for high risk women, after caesarean or vaginal delivery.	GPP
5. Consider the use of graduated compression stockings if pharmacological thromboprophylaxis is contraindicated or not used.	GPP
6. Consider the use of intermittent pneumatic compression during caesarean and in the postoperative period for up to 24 hours.	GPP

7 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.

7.1 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, and minor gynaecological surgery (especially in the presence of other risk factors). 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.

7.2 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 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.

7.3 Areas with little evidence for 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 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)
- pregnant women
- obese patients.

7.4 Other issues

The following issues also warrant consideration for research:

- the detection of VTE
- the relationship between asymptomatic and symptomatic DVT
- an agreed definition of 'major bleeding'
- the incidence of epidural haematoma (with or without neuraxial regional anaesthesia) when thromboprophylaxis is used.

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9 Appendices

Appendix A: VTE Prevention Guideline Adaptation Committee

A.1 Membership of the VTE Prevention Guideline Adaptation Committee

Members	Expertise	Details
Chair	Clinical Epidemiologist	Adjunct Professor, School of Public Health, The University of Sydney Director – Sydney Health Projects Group
Prof Michael Frommer		
Prof A.B. Baker (Barry)	Anaesthetist	Emeritus Professor, The University of Sydney Director Professional Affairs, Australian and New Zealand College of Anaesthetists Nominee of the Australian and New Zealand College of Anaesthetists
Ms Kay Currie	Guidelines Research	Director, Guidelines Research Program National Institute of Clinical Studies (NICS)
Prof John Fletcher	Vascular Surgeon	Professor of Surgery, The University of Sydney Westmead Hospital, Sydney Rep of the Australia and New Zealand Working Party on the Management and Prevention of Venous Thromboembolism (Chairman)
Prof Alex Gallus	Physician/ Pathologist	Professor of Haematology, Flinders University and Director of Pathology Services at Flinders Medical Centre, SA Rep of the Australia and New Zealand Working Party on the Management and Prevention of Venous Thromboembolism (Member)
Ms Sharon Goldsworthy	Pharmacist	Clinical Pharmacy Team Leader The Queen Elizabeth Hospital & Health Service, Woodville South, SA Nominee of the Society for Hospital Pharmacists Australia
Ms Christine Griffiths	Patient Representative	Nominee of Health Issues Centre
Ms Jeannette Kamar	Nurse	Injury Prevention The Northern Hospital, Epping Nominee of the Royal College of Nursing, Australia
Ms Philippa Middleton	Methodologist	Research Leader with the Australian Research Centre for Health of Women and Babies (ARCH) in the Discipline of Obstetrics and Gynaecology The University of Adelaide, SA Contracted Methodologist
Dr Sue Phillips	Research Implementation	Director, Research Implementation Program National Institute of Clinical Studies (NICS) * Dr Sue Phillips has been represented by Ms Sonja Hood since August 2008
Dr Rebecca Tooher	Methodologist	Research Fellow with the Australian Research Centre for Health of Women and Babies (ARCH) in the Discipline of Obstetrics and Gynaecology The University of Adelaide, SA Contracted Methodologist
A/Prof Barry Walters	Obstetrics Physician	Clinical Assoc Professor, Obstetrics and Internal Medicine Royal Perth Hospital and King Edward Memorial Hospital for Women, Perth Nominee of the Royal Australian and New Zealand College of Obstetrics and Gynaecology
A/Prof Christopher Ward	Physician	Department of Haematology Transfusion Medicine Royal North Shore Hospital Nominee of the Royal Australasian College of Physicians
A/Prof Nicholas Wickham	Oncologist	Consultant Haematologist Adelaide Cancer Centre Nominee of the Medical Oncology Group of Australia
Mr Simon Williams	Orthopaedic Surgeon	Orthopaedic Surgeon, VMO Geelong Hospital, St John of God Hospital & Geelong Private Hospital Nominee of the Royal Australasian College of Surgeons
Dr Agnes Wilson	VTE ADAPTE Project Support	Research Scientist, Research Implementation Program National Institute of Clinical Studies (NICS)

A.2 Declarations of interest of the VTE Prevention Guideline Adaptation Committee

1. Professor Michael Frommer

- undertook a review of literature on VTE prevention and prepared a short report for the NSW Health Department in 2000
- current member of the Pharmaceutical Benefits Advisory Committee and its Economic Sub-committee.

2. Professor Barry Baker

- participated in the development and endorsement of a guideline for the use of surgical prophylaxis for departmental use at the Department of Anaesthetics, Royal Prince Alfred Hospital Sydney (North American published guidelines used as a source for the Royal Prince Alfred guideline).

3. Professor Alex Gallus

- Member of an independent data safety monitoring board for a heparin-like synthetic angiogenesis inhibitor
- Chair of the guideline development and publication committee of the Australasian Society of Thrombosis and Haemostasis (guidelines for warfarin)
- Member of a guidelines committee which prepared OMGA guidelines for antithrombotics in pregnancy
- Member of international steering committee for clinical trials in VTE prevention of an orally active Factor Xa inhibitor under development by Bristol-Myers Squibb and an orally active Factor Xa inhibitor under development by Astellas
- prior Member of a steering committee for two phase II venous thrombosis treatment trials using rivaroxaban, the ODIXa trial, and the EINSTEIN trials
- 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.

4. 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.

5. Professor John Fletcher

- Member of an advisory board for PharmaLink (for drugs not relevant to VTE)
- Prior member of the following advisory panels: Astra-Zeneca, Sanofi-Aventis and Pharmacia
- Current member of advisory board for Bayer
- In 2008, research funding was received by Westmead Hospital from Sanofi-Aventis for VTE Nurse for six months

Professor John Fletcher (cont.)

- travel costs and honorarium received from Bayer for invited presentation on “VTE prevention in orthopaedic surgery – an Australian perspective” at the Asia-Pacific Advisory Board meeting of Bayer Schering Pharma, Hong Kong, August 24 2008 and travel costs to attend the American Society of Hematology meeting, San Francisco 5-9 December 2008
- travel costs and honorarium from Glaxo Smith Kline for invited presentation on “Prevention of VTE: current perspectives” at the 70th annual meeting of the Japanese Surgical Association, Tokyo, 27-29 November 2008 and participation in a VTE expert panel meeting
- Advisor to Executive Board of International Union of Angiology (IUA), contributor to “Consensus statement, Prevention of venous thromboembolism, *Int Angiol* 1997; 16:3-38”, “Prevention of venous thromboembolism, International consensus statement, Guidelines compiled in accordance with the scientific evidence, *Int Angiol* 2001; 20:1-37” and “Prevention of venous thromboembolism, International consensus statement (Guidelines according to scientific evidence), *Int Angiol* 2006; 25:101-161”
- Chairman of the Australia and New Zealand Working Group for VTE Prevention
- President, International Surgical Thrombosis Forum (ISTF) 2008.

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 2008, received three months of funding for a research nurse from an organisation that has a commercial interest in VTE prevention
- in 2008, participated in one meeting as a member of panel/committee for Sanofi-Aventis (in a consultant capacity).

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.

9. A/Professor Nicholas Wickham

- participated in the revision of “*Anticoagulant Guidelines*” for The Queen Elizabeth Hospital North West Adelaide Health Service 1997 (for the Department of Haematology and The Queen Elizabeth Hospital Drug Committee).

10. Mr Simon Williams

- Principal Investigator for Sanofi-Aventis trials of fondaparinux versus clexane in total hip replacement (Pentathlon) and fractured neck of femurs (pentifra and pentifra plus) in 2000. Research department received funding for this involvement. In 2000, received direct financial assistance in attending meetings in Queensland and London based on Sanofi-Aventis trials.
- Member of the Geelong Hospital Orthopaedic Unit which was involved in the Glaxo-Smith Kline trial (TOPVENT) in 2006 and the Bayer RECORD trial in 2007 which investigated oral anticoagulation following total knee replacement. Funding towards research nurse received from both companies. No direct financial funding received.

11. Dr Agnes Wilson

- employed by the NHMRC to produce the VTE prevention guideline.

The other members of the VTE Prevention Guideline Adaptation Committee did not report any competing interests.

A.3 Terms of reference of the VTE Prevention Guideline Adaptation Committee

Purpose

To produce an evidence-based, usable guideline for the prevention of venous thromboembolism in adult surgical and medical patients admitted to Australian metropolitan, regional and rural hospital settings through adaptation of suitable existing international guidelines.

The role of the VTE Prevention Guideline Adaptation Committee is to:

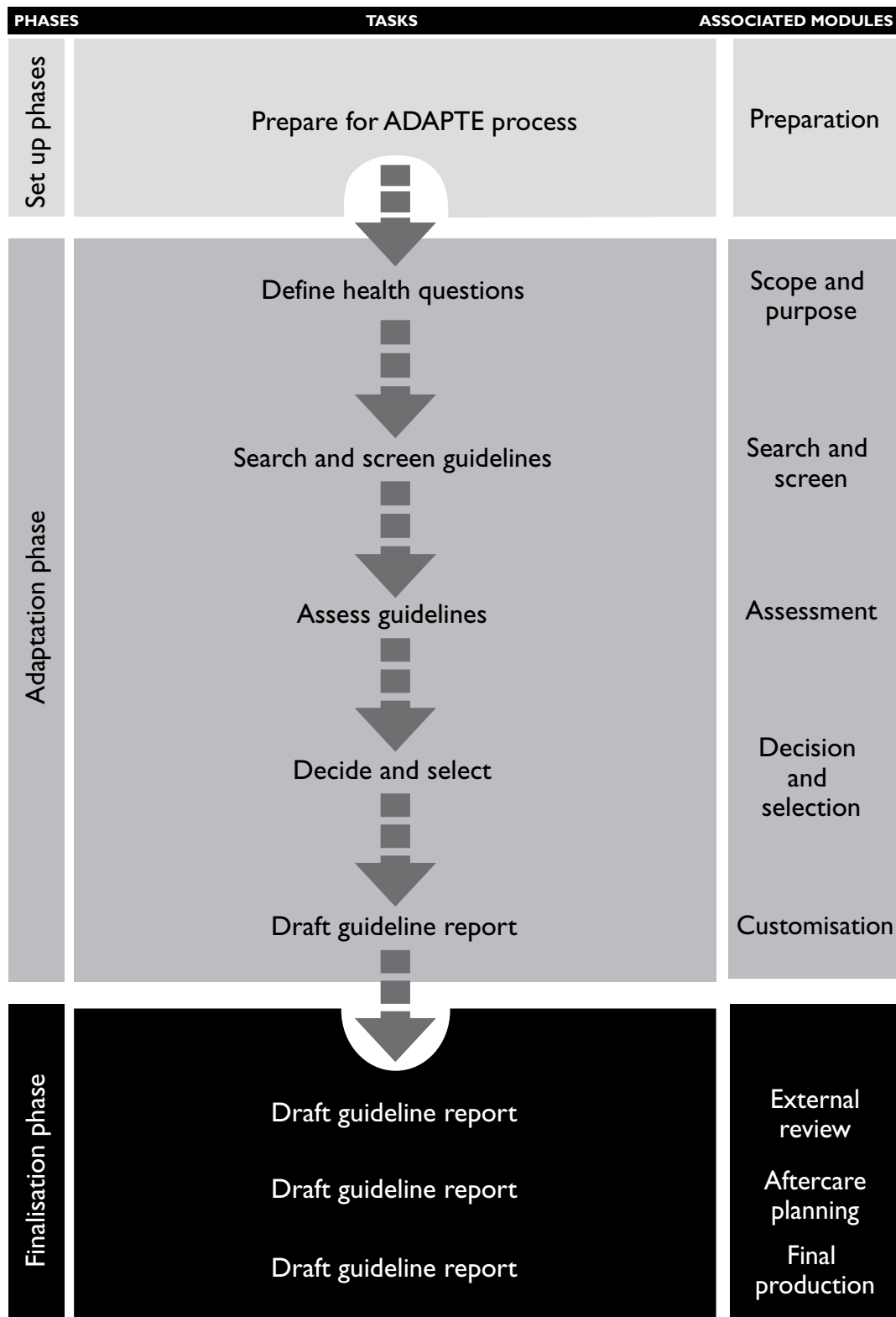
- determine the clinical questions to be addressed in the guideline
- identify and consider the evidence from suitable existing international guidelines
- translate the evidence into broad findings
- use a formal consensus process for decision making where there is disagreement
- identify health outcomes and outcome measures
- develop the recommendations
- formulate the guideline, including implementation plans and plans for review and update
- ensure that the guideline is a useful and implementable resource for clinicians, managers and patients, and that the guideline is relevant to the Australian healthcare context.

Summary of the Adaptation Process

The VTE Prevention Guideline Adaptation Committee will adapt existing high quality international VTE prevention guidelines using the ADAPTE methodology for guideline adaptation. A summary of the steps in the process can be found in the figure on the next page¹.

¹ Manual for Guideline Adaptation. ADAPTE Collaboration Version 1.0. 2007

The ADAPTE Methodology



Membership of guideline adaptation committee

The VTE Prevention Guideline Adaptation Committee will ideally comprise 13–15 members.

Membership of guideline groups should be multi-disciplinary, comprising clinicians (both content area specialists and generalists), patients and technical experts (methodologists and individuals with expertise in guideline appraisal).

The VTE Prevention Guideline Adaptation Committee will ideally have members with expertise in:

- general surgery (or vascular specialist)
- orthopaedic surgery
- obstetrics and gynaecology
- haematology
- medicine (general, respiratory or cardiac medicine)
- nursing
- hospital pharmacy
- oncology
- anaesthesiology
- guideline appraisal methodology
- guideline implementation
- consumer experience.

Frequency of meetings

There will be approximately five meetings between June 2008 and June 2009. The guideline adaptation committee will meet every six weeks for the first three meetings (early June to late August 2008). There will be quarterly meetings thereafter until June 2009.

It is anticipated that the guideline adaptation committee will be a working committee and their clinical expertise will be sought in determining the clinical questions and formulating the recommendations.

Deliverables

By the projected project completion date of June 2009, it is expected that there will be an adapted guideline suitable for use in Australian hospital settings.

The types of documents to be produced include a long version of the guideline, a short version and a patient information guide. Implementation resources will also be considered.

Appendix B: Overview of the guideline development process

In early 2008, the NHMRC undertook to develop this Guideline for the “Prevention of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to Australian hospitals”. This Guideline has been developed by the NHMRC’s National Institute of Clinical Studies (NICS) in accordance with the NHMRC toolkit series,¹⁷⁻¹⁹ under the direction of a multi-disciplinary guideline adaptation committee (refer to [Appendix A](#)).

At the commencement of the guideline development process, a search revealed that there were a number of existing evidence-based international guidelines in VTE prevention (published between 2002 and 2008).^{6,7,10,39,354,355} NICS opted to take a pragmatic approach to the development of this VTE prevention guideline by choosing to adapt existing international VTE prevention guidelines. A structured guideline adaptation methodology known as ADAPTE was employed for development of this Guideline.²⁰ ADAPTE is a methodology that provides a systematic approach to aid in the adaptation of guidelines produced in one setting for use in a different cultural and/or organisational context.

ADAPTE comprises three phases; set-up, adaptation and finalisation.²⁰ A number of components of guideline development were considered as part of the set-up phase of ADAPTE. These included establishing:

- the scope of the guideline
- the process for dealing with conflicts of interest
- a consensus process for decision making
- the resources required for guideline adaptation (including time, cost and required expertise).

The set-up phase involved convening an organising committee to assist with consideration of these components. As recommended by the ADAPTE methodology, an organising committee was established and comprised:

- NICS staff who were working on development of the guideline (Dr Sue Phillips and Dr Agnes Wilson)
- individuals with guideline development and methodological expertise (Ms Kay Currie and Dr Heather Buchan)
- individuals with clinical expertise in VTE prevention (Professor John Fletcher and Professor Alex Gallus).

It is important to note that this organising committee only considered matters related to the process of guideline adaptation, they did not undertake any direct guideline development.

The organising committee convened for a day-long meeting in late April 2008. Disclosures of interest were obtained from all organising committee members prior to their participation in this committee. At this meeting, a draft scope for the guideline was formulated and the resources required for guideline development were discussed. NICS staff developed the conflict of interest policy and procedure and the consensus process for decision making independent of the organising committee.

B.1 Appointing the committee

Following the organising committee meeting, NICS established a multi-disciplinary VTE Prevention Guideline Adaptation Committee in June 2008 to produce the guideline through adaptation. The following professional organisations involved in the management of patients at risk of VTE were invited to nominate a representative to become a member of the VTE Prevention Guideline Adaptation Committee:

- The Royal Australasian College of Surgeons (RACS)
- The Royal Australasian College of Physicians (RACP)
- The Australian and New Zealand College of Anaesthetists (ANZCA)
- The Royal College of Nursing, Australia (RCNA)
- The Medical Oncology Group of Australia (MOGA)
- The Society of Hospital Pharmacists Australia (SHPA)
- The Royal Australian and New Zealand College of Obstetrics and Gynaecology (RANZCOG).

Each of these professional organisations is represented in the guideline adaptation committee by one of its nominated members. Consumer groups were also invited to nominate representatives for the guideline adaptation committee. Health Issues Centre nominated one patient representative for this work. Two members from the Australia and New Zealand Working Party for the Prevention of Venous Thromboembolism were also invited to become members of the VTE Prevention Guideline Adaptation Committee. The ANZ Working Party had previously independently compiled a short summary document on VTE prevention based on international guidelines.

The 16-member VTE Prevention Guideline Adaptation Committee was established from the nominations received from the key stakeholder organisations (and included a project manager and two contracted methodologists) (refer to [Appendix A1](#)). In total, eight day long, face-to-face meetings were held over the duration of the guideline adaptation process to get to the draft guideline stage.

B.2 Declaration of interest process

Conflict of interest can be categorised as potential, perceived or actual and relate to members' interests as well as the interests of their family relating to the guideline topic. Interests may be direct or indirect, pecuniary or non-pecuniary. A process for dealing with conflict of interest was developed by NICS and was in accordance with the NHMRC's "*Members' Responsibilities regarding Disclosure of Interest and Confidentiality*" which applies to all members of the Council of the NHMRC, Principal Committees and Working Committees (in accordance with the requirements of the *National Health and Medical Research Council Act 1992*). In addition, members of this committee were asked to declare specific interests related to guideline development (as advised in the ADAPTE methodology). Where committee members were identified as having significant real or perceived conflicts of interest, the Chair could request they step out of the room on matters they were conflicted on. Alternatively, the Chair could decide that the member may stay in the room but not participate in the discussion, or decision making on the specific area where they were conflicted. The period of exclusion and the conflict to which it related to was recorded in the meeting minutes.

The VTE Prevention Guideline Adaptation Committee members were required to declare their relevant interests in writing prior to appointment to this committee (interests may have included: consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry). The purpose of declaring conflicts of interest was to avoid any conflict between the private interests of members and their duties as part of the committee (including pecuniary

interest or the possibility of other advantage). Committee members were required to update their information as soon as they become aware of any changes to their interests. There was also a 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 NICS and was made available to the VTE Prevention Guideline Adaptation Committee. The disclosure of the register of interest to all Committee members was important to allow Committee members are able 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):

1. Developed structured clinical questions.
2. Selected high-quality source documents to use for adaptation.
3. Developed a search strategy and searched the literature.
4. Assessed the eligibility of identified studies.
5. Critically appraised the included studies.
6. Summarised and where appropriate statistically pooled included studies.
7. 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 this Guideline, and the clinical questions that this Guideline would address were formulated.

B.3i 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.3ii Selecting high quality source guidelines 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.²⁰

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 an earlier version of a current guideline. Five of the VTE prevention guidelines crossed disciplines and diseases^{6,9,10,39,355} and 14 were either discipline or disease specific VTE prevention guidelines.^{104,356-368}

NICS short-listed the five cross-discipline, cross-disease VTE guidelines as potential source guidelines for adaptation. One of these guidelines was excluded as it was six years old and was not considered current.¹⁰ The ADAPTE methodology advises that an assessment of the quality of potential source guidelines should be undertaken using the AGREE instrument.²¹ The NICE and

American College of Chest Physicians (ACCP) VTE prevention guidelines both rated highly for the quality of the development process of the guideline.^{6,39} However, the AGREE instrument does not evaluate the content of guidelines, and it became apparent as the Committee considered these two guidelines that neither would be entirely suitable for adaptation. The ACCP guidelines did not contain evidence tables and were therefore more difficult to use as a direct source of evidence for this Guideline. On the other hand, evidence tables were readily available from the NICE guideline, making it suitable for adaptation, with cross-checking against the studies referred to in the ACCP guidelines to ensure completeness.

The NICE guideline framed the clinical questions according to prophylaxis options rather than clinical specialty. The Committee felt that this would not be as useful for clinicians for this Guideline to be organised according to the indication for prophylaxis. It was therefore not possible to adapt the recommendations from the NICE guidelines directly as suggested by the ADAPTE process. Instead, the NICE guideline evidence tables were used as the primary source of evidence with new meta-analysis and recommendations being developed.

NICS approached the lead authors of both the NICE and ACCP VTE prevention guidelines for permission to adapt these guidelines to Australian circumstances. Permission was granted.

B.3iii Developing a search strategy and searching the literature

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” were used as a basis for the evidence, with top-up searches undertaken (from April 2006 to January 2009) to ensure currency and completeness.³⁹ As this Guideline cover all hospitalised patients, a separate search for studies evaluating interventions designed to reduce or prevent VTE in adult hospitalised patients not undergoing surgery was conducted from inception of the databases until January 2009.

A broad search strategy was adopted for both medical and surgical studies, in order to retrieve as many potential relevant citations as possible. This consisted of the MeSH terms (exploded): *venous thrombosis*, *venous thromboembolism*, *pulmonary embolism* and the keywords: *DVT*, *deep vein thrombosis*.

The Cochrane Library was searched for relevant Cochrane reviews, other systematic reviews and RCTs (last searched Issue 1, 2009). PubMed was last searched on January 30, 2009. References of retrieved articles were checked for potentially relevant studies.

B.3iv Assessing the eligibility 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.3v 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 regrouped according to the surgical procedure 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.

For each new 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).²² The methods used to conduct the critical appraisal and summarise the evidence comply with NHMRC requirements¹⁷⁻¹⁹ 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 question²²

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 ⁶	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (ie. 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 ⁶	All or none	All or none	A pseudorandomised controlled trial (ie. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: <ul style="list-style-type: none"> • non-randomised, experimental trial • cohort study • case-control study • interrupted time series with a control group 	A comparison with reference standard that does not meet the criteria required for level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: <ul style="list-style-type: none"> • non-randomised, experimental trial • cohort study • case-control study
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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

B.3vi Critically appraising included studies

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. 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.

B.3vii Summarise and where appropriate statistically pool the relevant data

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 calculated using a fixed effects method unless heterogeneity was high ($I^2 \geq 50\%$) in which case a random effects analysis was used. Forest plots were provided to assist the Committee in discussion of the evidence. In order to examine the possibility that different diagnostic methods for detecting DVT would influence the outcomes, pre-planned subgroup analyses were undertaken by diagnostic method (blinded and unblinded) for all DVT related outcomes. Posthoc subgroup analyses were also undertaken to examine the impact of background method of prophylaxis on the main effects.

B.3viii Assess the body of evidence and formulate recommendations

The body of evidence was assessed by the entire Committee with regard for the volume of evidence, its consistency, the clinical impact, generalisability and applicability. These aspects were graded according to the NHMRC grading criteria.²² Following the grading of the evidence, the committee formulated a recommendation that reflected the summarised body of evidence. The overall recommendations were graded as follows:

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
NA	Not applicable – unable to grade body of evidence
GPP	Good practice point - consensus-based recommendations

The process of formulating recommendations occurred over eight full-day meetings that took place from July to December 2008.

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 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)?

Table 1: Surgical patients

Surgical type	Procedure
Major and minor orthopaedic including:	Total hip replacement
	Total and partial knee replacement
	Hip fracture surgery
	Knee arthroscopy and arthroscopic knee surgery (minor and major)
	Foot fracture
	Pelvic fracture
	Isolated below knee injuries
	Non-operable orthopaedic injury
General	
Cancer	
Gynaecological	
Cardiothoracic	
Urological	
Neurosurgery	
Vascular	
Head and neck	
Plastic and reconstructive*	
Trauma	
Elective spine	
Bariatric*	
Intensive care	
Laparoscopic*	
Gynaecological including:	Obstetrics
	Hysterectomy
Any surgical procedure >45 mins	

Table 2: Medical patients

Type of medical patient	
Acutely ill	
Cancer including:	patients receiving radiotherapy
	patients treated with anti-angiogenic agents
	patients with a central venous catheter
	patients with particular cancer types at higher risk of developing VTE including: head and neck, thoracic, solid tumours, breast cancer, myeloma
	patients receiving chemotherapy
Burns*	
Stroke	
Obstetrics	
Cardiothoracic including:	patients with heart failure taking anti-platelet/anticoagulants (these patients receive arterial thromboprophylaxis not venous)
	patients with decompensated cardiac failure
	haematological patients with decreased platelet count
Renal* including:	patients with renal failure/insufficiency*
Active Infection (i.e. cellulitis, pneumonia)	
Respiratory conditions	
Spinal cord injury	
Intensive care	
Palliative care*	

Patient characteristics

Do the following patient characteristics increase the risk of developing VTE? If so, how should surgical and medical patients with the following patient characteristics be managed with regard to VTE prophylaxis?

- Age
 - is age an independent risk factor for patients with medical conditions (in particular in patients with active cancer or respiratory problems)
 - is this different between surgical and medical patients?
- Obesity (including severely obese patients)
- Previous VTE
- Increased risk of bleeding with medical prophylaxis (including patients with low platelet count; coagulation deficiencies; patients on particular complementary therapies; patients with liver disease)
- Any active inflammatory condition
- Patients with inherited or acquired thrombophilia
- Patients with a family history of VTE
- Pregnant women (including women admitted to hospital during pregnancy; pregnant women undergoing caesarean; pregnant women delivering via vaginal delivery; pregnant women with pre-eclampsia; pregnant women receiving an epidural)
- Patients with chronic venous disease
- Patients with varicose veins

- Patients currently taking oral contraception (OC) or hormone replacement therapy (HRT) – when should OC or HRT be stopped?
- Patients taking low dose aspirin
- Immobilisation including recent prolonged travel prior to surgery

Options for thromboprophylaxis

Consider and review evidence for all of the following options for thromboprophylaxis for each of the surgical or medical categories in Tables 1 and 2.

DOSING REGIMENS

Pharmacological

- Unfractionated heparin (UFH) (effects and regimens)
- Low molecular weight heparin (LMWH) (effects, regimens)
- Fondaparinux (effects, regimens)
- Aspirin (effects, regimens)
- Warfarin (effects, regimens)
- Oral thrombin (effects, regimens)
- Factor Xa inhibitors (effects, regimens)

Mechanical

- Graduated compression stockings (GCS) (effects, regimens)
- What are the comparative effects of full length GCS compared with knee length GCS?
- Intermittent pneumatic compression (IPC) (effects, regimens)
- What are the comparative effects of GCS and IPC?
- What are the combined effects of GCS and IPC?
- Foot impulse technology (effects, regimens)

Anaesthesia

- What is the risk of VTE for patients receiving spinal/epidural vs. general anaesthesia?
- What are the risks of complications from anaesthesia such as epidural haematoma in patients receiving VTE pharmacoprophylaxis?
- What is the optimal timing of prophylaxis?
- What should be the timing of epidural for pregnant women on thromboprophylaxis?
- Can delaying systemic pharmacological anticoagulants until after the insertion of the epidural catheter or ensuring that pharmacological anticoagulants agents are not administered within six hours prior to the insertion or six hours following withdrawal of an epidural catheter reduce the rate of complications?

Other

- 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 at <http://www.nhmrc.gov.au/nics/programs/vtp/consultation.htm>

Appendix E: NHMRC Evidence Statement Form

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

<p>Key question(s):</p> <ul style="list-style-type: none"> • 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? 											
<p>1. Evidence base – Number of studies, level of evidence and risk of bias in the included studies</p> <table border="1"> <tbody> <tr> <td>A</td> <td>A level I or several level II studies with low risk of bias</td> </tr> <tr> <td>B</td> <td>One or two Level II studies with low risk of bias or SR/multiple level III studies with low risk of bias</td> </tr> <tr> <td>C</td> <td>Level III studies with low risk of bias or level I or II studies with moderate risk of bias</td> </tr> <tr> <td>D</td> <td>Level IV studies or level I to III studies with high risk of bias</td> </tr> </tbody> </table>		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		
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										
<p>2. Consistency – Comment here on the degree of consistency demonstrated by the available evidence between the studies. Where there are conflicting results, indicate how the group formed a judgment as to the overall direction of the evidence. If only one study was available, rank this component as 'not applicable'.</p> <table border="1"> <tbody> <tr> <td>A</td> <td>All studies consistent</td> </tr> <tr> <td>B</td> <td>Most studies consistent and inconsistency can be explained</td> </tr> <tr> <td>C</td> <td>Some inconsistency, reflecting genuine uncertainty around question</td> </tr> <tr> <td>D</td> <td>Evidence is inconsistent</td> </tr> <tr> <td>NA</td> <td>Not applicable (one study only)</td> </tr> </tbody> </table>		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)
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)										
<p>3. Clinical impact – Comment here on the potential clinical impact that the intervention might have. Factors to consider are: size of patient population, magnitude of effect, relative benefit over other management options, resource implications, and the balance of risk versus benefit. If the intervention is shown to have an effect, does it have the potential to reduce burden of disease?</p> <table border="1"> <tbody> <tr> <td>A</td> <td>Very large</td> </tr> <tr> <td>B</td> <td>Moderate</td> </tr> <tr> <td>C</td> <td>Slight</td> </tr> <tr> <td>D</td> <td>Restricted</td> </tr> </tbody> </table>		A	Very large	B	Moderate	C	Slight	D	Restricted		
A	Very large										
B	Moderate										
C	Slight										
D	Restricted										

NIHMRC Evidence Statement Form (continued)

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 include organisational factors (eg availability of trained staff, clinic time, accessibility of specialised equipment, tests and other resources) and cultural factors (eg attitudes to health 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	
1. Evidence base			
2. Consistency			
3. Clinical impact			
4. Applicability			
Indicate any dissenting opinions			

NHMRC Evidence Statement Form (continued)

RECOMMENDATION What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.	GRADE OF RECOMMENDATION
<p>ANY UNRESOLVED ISSUES?</p>	
<p>IMPLEMENTATION OF RECOMMENDATION Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.</p>	
<p>Will this recommendation result in changes in usual care?</p>	<p>YES</p> <p>NO</p>
<p>Is there any resource implications associated with implementing this recommendation?</p>	<p>YES</p> <p>NO</p>
<p>Will the implementation of this recommendation require changes in the way care is currently organised?</p>	<p>YES</p> <p>NO</p>
<p>Is the guideline development group aware of any barriers to the implementation of this recommendation?</p>	<p>YES</p> <p>NO</p>

Appendix F: Abbreviations and glossary of terms

ABBREVIATIONS	
ACCP	The American College of Chest Physicians
ADAPTE	The ADAPTE Guideline Adaptation Framework
AGREE	Appraisal of Guidelines Research & Evaluation
ANZCA	The Australian and New Zealand College of Anaesthetists
BMI	Body mass index
CECT	Continuous enhanced circulation therapy
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CR	Cochrane review
DVT	Deep vein thrombosis
FID	Foot impulse device
FIT	Foot impulse technology
FUT	I-Fibrinogen uptake test I 25
GCS	Graduated compression stockings
GP	General practitioner
HIT	Heparin-induced thrombocytopenia
HTA	Health technology assessment report
INR	International normalised ratio
IPC	Intermittent pneumatic compression
IV	Intravenous
LMWH	Low molecular weight heparin
MOGA	The Medical Oncology Group of Australia
NA	Not applicable
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Clinical Excellence, United Kingdom
NICS	National Institute of Clinical Studies
NNTB	Number needed to treat to benefit
NNTH	Number needed to treat to harm
NR	Not reported
OAC	Oral anticoagulant
OR	Odds ratio
PICO	Guidance on the key components of a well formulated clinical question which incorporates Patients, Interventions, Comparisons and Outcomes
PTS	Post-thrombotic limb syndrome
RACS	The Royal Australasian College of Surgeons
RACP	The Royal Australasian College of Physicians
RANZCOG	The Royal Australian and New Zealand College of Obstetrics and Gynaecology
RCT	Randomised controlled trial
RCNA	The Royal College of Nursing, Australia
RR	Risk ratio
SC	Subcutaneous
SHPA	The Society of Hospital Pharmacists Australia
SR	Systematic review
TGA	Therapeutic Goods Administration
UFH	Unfractionated heparin
US	Ultrasound
VFP	Venous foot pump
VTE	Venous thromboembolism
VT	Venous thrombosis

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>).

Absolute risk reduction (risk difference)	The difference in the risk of an event between two groups (one subtracted from the other) in a comparative study.
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Absolute risk reduction	The difference in size of risk between two groups. For example, if one group has a 15 percent risk of contracting a particular disease, and the other has a 10 percent risk of getting the disease, the absolute risk reduction is five percentage points. (Also called risk difference or absolute risk difference).
Acute embolic stroke	Sudden onset of focal neurological deficit of vascular causation with CT or MRI scan confirmation of an ischaemic aetiology associated with a likely embolic source and typically in a large vessel distribution.
Acute ischemic stroke	Sudden onset of focal neurological deficit of vascular causation with CT or MRI scan confirmation of an ischaemic aetiology.
Adverse event	An adverse outcome that occurs during or after the use of a drug or other intervention but is not necessarily caused by it.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in a RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Anticoagulant	Any agent used to prevent the formation of blood clots. These include oral agents, such as warfarin, and others which are injected into a vein or under the skin, such as heparin.
Applicability	The degree to which the results of an observation, study or review are likely to hold true in a particular clinical practice setting.
(AGREE) – Appraisal of Guidelines, Research and Evaluation	An international collaboration of researchers and policy makers whose aim is to improve the quality and effectiveness of clinical practice guidelines (http://www.agreecollaboration.org). The AGREE instrument, developed by the group, is designed to assess the quality of clinical guidelines.
Arm (of a clinical study)	Group of individuals within a study who are allocated to one particular intervention, for example the placebo arm.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Bias	Systematic (as opposed to random) – deviation of the results of a study from the 'true' results that is caused by the way the study is designed or conducted.
Blinding	In a controlled trial – The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. The risk of bias is minimised when as few people as possible know who is receiving the experimental intervention and who the control intervention. Participants, caregivers, outcome assessors, and analysts are all candidates for being blinded. Blinding of certain groups is not always possible, for example surgeons in surgical trials. The terms single blind, double blind and triple blind are in common use, but are not used consistently and so are ambiguous unless the specific people who are blinded are listed. Blinding is also called masking.
Body mass index	A statistical measurement which compares a person's weight and height (body weight in kilograms/height in metres squared).
Carer (caregiver)	Someone other than a health professional who is involved in caring for a person with a medical condition.

Case-control study	A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls), and which seeks to find associations between the outcome and prior exposure to particular risk factors. This design is particularly useful where the outcome is rare and past exposure can be reliably measured. Case-control studies are usually retrospective, but not always.
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Case study	A study reporting observations on a single individual. (Also called anecdote, case history, or single case report.)
Clinical audit	A quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	The extent to which an intervention produces an overall health benefit in routine clinical practice.
Clinical impact	The effect that an intervention is likely to have on the treatment or treatment outcomes of the target population.
Clinical question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Clinical trial	An experiment to compare the effects of two or more healthcare interventions. Clinical trial is an umbrella term for a variety of designs of healthcare trials, including uncontrolled trials, controlled trials, and randomised controlled trials. (Also called intervention study)
Clinician	A healthcare professional providing direct patient care, for example doctor, nurse or physiotherapist.
Cluster	A closely grouped series of events or cases of a disease or other related health phenomenon with well-defined distribution patterns, in relation to time or place or both. Alternatively, a grouped unit for randomisation.
Cochrane Library	A regularly updated electronic collection of evidence-based medicine databases, including the Cochrane Database of Systematic Reviews.
Cochrane Review	A systematic review of the evidence from randomised controlled trials relating to a particular health problem or healthcare intervention, produced by the Cochrane Collaboration. Available electronically as part of the Cochrane Library.
Cohort study	A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study compares groups with different levels of exposure or different exposures.
Co-morbidity	Co-existence of more than one disease or an additional disease (other than that being studied or treated) in an individual.
Compliance	The extent to which a person adheres to the health advice agreed with healthcare professionals. May also be referred to as 'adherence' or 'concordance'.
Confidence interval	A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value.
Confounder	A factor that is associated with both an intervention (and exposure) and the outcome of interest. For example, if people in the experimental group of a controlled trial are younger than those in the control group, it will be difficult to decide whether a lower risk of death in one group is due to the intervention or the difference in ages. Age is then said to be a confounder, or a confounding variable. Randomisation is used to minimise imbalances in confounding variables between experimental and control groups. Confounding is a major concern in non-randomised studies. (See also adjusted analyses.)

Consensus methods	Techniques that aim to reach an agreement on a particular issue. Formal consensus methods include Delphi and nominal group techniques, and consensus development conferences. In the development of clinical guidelines, consensus methods may be used where there is a lack of strong research evidence on a particular topic. Expert consensus methods will aim to reach agreement between experts in a particular field.
Continuous enhanced circulation therapy	Pneumatic compression devices that create pressure and apply it to the patient's limbs. Battery-operated compression devices that can be used continuously.
Control group	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) – in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Controlled clinical trial	A study testing a specific drug or other treatment involving two (or more) groups of patients with the same disease. One (the experimental group) receives the treatment that is being tested, and the other (the comparison or control group) receives an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. A controlled clinical trial where patients are randomly allocated to treatment and comparison groups is called a randomised controlled trial.
Cost benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost-effectiveness analysis	An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (For example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
Deep vein thrombosis	A blood clot that occurs in the "deep veins" in the legs, thighs or pelvis. Asymptomatic deep vein thrombosis is defined as painless DVT detected only by screening with fibrinogen scanning, ultrasound, or ascending venography and is often confined to the distal veins and, when it involves the proximal veins, the thrombi usually are smaller than in symptomatic patients with proximal thrombosis. Symptomatic deep vein thrombosis results from occlusion of a major leg vein and results in leg pain or swelling. It requires specific investigation and treatment which in hospitalised patients may delay discharge, or require readmission to hospital.
Distal	Refers to a part of the body that is farther away from the centre of the body than another part.
Dosage	The prescribed amount of a drug to be taken, including the size and timing of the doses.
Double blind study	A study in which neither the subject (patient) nor the observer (investigator/clinician) is aware of which treatment nor intervention the subject is receiving. The purpose of blinding is to protect against bias.
Drop-out	The loss of participants during the course of a study. (Also called loss to follow up). The loss of participants during the study can also be referred to as attrition.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association.
Elective	Name for clinical procedures that are planned and booked in advance as opposed to emergency procedures which may take precedence.
Electrical stimulation	Designed to caused muscle contractions and thereby increase venous blood flow velocity out of the leg to reduce the incidence of post-surgical venous thrombosis.
Emboli	Material propagated through the circulatory system.
Epidemiological study	The study of a disease or health issue within a population, defining its incidence and/or prevalence and examining the roles of various possible confounding factors (for example: infection, diet) and interventions.
Evidence table	A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.

Exclusion criteria (for a literature review)	Explicit criteria used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (for a clinical study)	Criteria that define who is not eligible to participate in a clinical study.
External validity	The extent to which results provide a correct basis for generalisations to other circumstances. For instance, a meta-analysis of trials of elderly patients may not be generalisable to children. (Also called generalisability or applicability.)
Extrapolation	In data analysis, predicting the value of a parameter outside the range of observed values.
I25I-Fibrinogen uptake test	A fibrinogen uptake test is a test that was formerly used to detect deep vein thrombosis. Radioactive labelled fibrinogen is given which is incorporated in the thrombus. The thrombus can then be detected by scintigraphy.
Follow-up	The observation over a period of time of study/trial participants to measure outcomes under investigation.
Foot impulse device	The foot impulse device is designed to stimulate the leg veins (venous pump) artificially by compressing the venous plexus and mimicking normal walking and reducing stasis in immobilised patients. Other names for this method of mechanical VTE prophylaxis include: foot impulse technology (FIT) or venous foot pump (VFP).
Forest plot	A graphical representation of the individual results of each study included in a meta-analysis together with the combined meta-analysis result. The plot also allows readers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centred on each study's point estimate. A horizontal line runs through each square to show each study's confidence interval – usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are shown at the bottom, represented as a diamond. The centre of the diamond represents the pooled point estimate, and its horizontal tips represent the confidence interval.
Graduated compression stockings	Mechanical method of prophylaxis. Stockings manufactured to provide compression around the legs at gradually increasing pressures. There are different standards for graduated compression stockings so it is suggested that mmHg (mm Mercury) be considered. Also known as anti-embolism stockings.
Haemorrhagic stroke	Sudden onset of focal neurological deficit of vascular causation with CT or MRI scan confirming a haemorrhagic aetiology.
Harms	Adverse effects.
Heparin-induced thrombocytopenia	Low blood platelet count resulting from the administration of heparin (or heparin-like agents). Despite having a low platelet count, patients with this condition are at high risk of their blood clotting.
Heterogeneity	Or lack of homogeneity. Used in a general sense to describe the variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies, or the variation in internal validity of those studies. It can be used specifically, as statistical heterogeneity, to describe the degree of variation in the effect estimates from a set of studies. Also used to indicate the presence of variability among studies beyond the amount expected due solely to the play of chance. The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.
Homogeneity	This means that the results of studies included in a systematic review or meta-analysis are similar and there is no evidence of heterogeneity. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance.
Homogeneous	Used in a general sense to mean that the participants, interventions, and measurement of outcomes are similar across a set of studies. Can also be used specifically to describe the effect estimates from a set of studies where they do not vary more than would be expected by chance.

Impedance plethysmography	A non-invasive test that uses electrical monitoring in the form of resistance (impedance) changes to measure blood flow in veins of the leg. Information from this test assists in the detection of DVT.
Incidence	The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.
Inclusion criteria (for a literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
International normalised ratio	A laboratory test used to measure the level of coagulant activity of vitamin-K dependent clotting factors in a plasma sample compared to a normal and standardised control. It is used to monitor the anticoagulant activity of warfarin and is also sensitive to changes in liver function which manufactures these clotting factors.
Intermittent pneumatic compression	A mechanical method of VTE prophylaxis that comprises the use of inflatable garments wrapped around the legs, inflated by a pneumatic pump. The pump provides intermittent cycles of compressed air which alternatively inflates and deflates the chamber garments, enhancing venous return.
Internal validity	The degree to which the results of a study are likely to approximate the 'truth' for the participants recruited in a study (that is, are the results free of bias)? It refers to the integrity of the design and specifically the extent to which the design and conduct of a study are likely to have prevented bias. Variation in quality can explain variation in the results of studies included in a systematic review. More rigorously designed (better quality) trials are more likely to yield results that are closer to the truth. (Also called methodological quality but better thought of as relating to bias prevention).
Intervention	Any action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy.
Intraoperative	The period of time during a surgical procedure.
Length of stay	The total number of days a patient stays in hospital.
Low molecular weight heparin	A low molecular weight fraction of heparin isolated specifically for its ability to bind to clotting factor Xa. Requires subcutaneous administration.
Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.
Multicentre trial	A trial conducted at several geographical sites. Trials are sometimes conducted among several collaborating institutions, rather than at a single institution – particularly when very large numbers of participants are needed.
Narrative summary	Summary of findings given as a written description.
Number needed to treat to benefit	An estimate of how many people need to receive a treatment before one person would experience a beneficial outcome. For example, if you need to give a stroke prevention drug to 20 people before one stroke is prevented, then the number needed to treat to benefit for that stroke prevention drug is 20. The NNTB is estimated as the reciprocal of the absolute risk difference.
Number needed to treat to harm	A number needed to treat to benefit associated with a harmful effect. It is an estimate of how many people need to receive a treatment before one more person would experience a harmful outcome or one fewer person would experience a beneficial outcome.
Observational study	A study in which the investigators do not seek to intervene, and simply observe the course of events. Changes or differences in one characteristic (e.g. whether or not people received the intervention of interest) are studied in relation to changes or differences in other characteristic(s) (e.g. whether or not they died), without action by the investigator. There is a greater risk of selection bias than in experimental studies.
P values	The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than one in 20, the P value is less than 0.05; a result with a P value of less than 0.05 is conventionally considered to be 'statistically significant'.

Peer review	A process where research is scrutinised by experts that have not been involved in the design or execution of the studies. An article submitted for publication in a peer-reviewed journal is reviewed by other experts in the area.
Perioperative	The period from admission through surgery until discharge, encompassing preoperative and postoperative periods.
Pulmonary embolism (plural = pulmonary emboli)	A blood clot that breaks off from the deep veins and travels around the circulation to block the pulmonary arteries (arteries in the lung). Most deaths arising from deep vein thrombosis are caused by pulmonary emboli.
Placebo	An inactive substance or preparation used as a control in an experiment or test to determine the effectiveness of a medicinal drug.
Placebo effect	A beneficial (or adverse) effect produced by a placebo and not due to any property of the placebo itself.
Post-thrombotic limb syndrome	Chronic pain, swelling, and occasional ulceration of the skin of the leg that occur as a consequence of previous venous thrombosis.
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.
Preoperative	Pertaining to the period before surgery commences.
Primary research	Study generating original data rather than analysing data from existing studies (which is called secondary research).
Proximal	Refers to a part of the body that is closer to the centre of the body than another part.
Proximal DVT	A DVT occurring in deep knee or thigh veins, known as proximal DVT. A proximal DVT is likely to involve the same amount of vein whether it is symptomatic or asymptomatic i.e. an asymptomatic proximal DVT is not necessarily smaller than a symptomatic proximal DVT.
Pulmonary embolism	A blood clot that breaks off from the deep veins and travels round the circulation to block the pulmonary arteries (arteries in the lung). Most deaths arising from DVT are caused by PE.
Prophylaxis	A measure taken for the prevention of a disease.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective.
Qualitative research	Research concerned with phenomena that are described rather than measured numerically.
Quantitative research	Research that generates numerical data or data that can be converted into numbers, for example clinical trials or case controlled studies.
Randomisation	Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias.
Randomised controlled trial	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.
Relative risk	The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B). Also called risk ratio.
Resource implication	The likely impact in terms of cost, workforce or other health system resources.
Retrospective study	A retrospective study deals with the present/ past and does not involve studying future events. This contrasts with studies that are prospective.
Risk difference	The difference in size of risk between two groups. For example, if one group has a 15 percent risk of contracting a particular disease, and the other has a 10 percent risk of getting the disease, the risk difference is five percentage points.

Risk ratio	The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of one indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is less than one indicates that the intervention was effective in reducing the risk of that outcome. (Also called relative risk, RR.)
Selection bias	<ol style="list-style-type: none"> 1. Systematic differences between comparison groups in prognosis or responsiveness to treatment. Random allocation with adequate concealment of allocation protects against selection bias. Other means of selecting who receives the intervention are more prone to bias because decisions may be related to prognosis or responsiveness to treatment. 2. A systematic error in reviews due to how studies are selected for inclusion. Reporting bias is an example of this. 3. A systematic difference in characteristics between those who are selected for study and those who are not. This affects external validity but not internal validity.
Selection criteria	Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.
Stakeholder	Those with an interest in the use of a technology under appraisal or a guideline under development. Stakeholders include manufacturers, sponsors, healthcare professionals, and patient and carer groups.
Statistical power	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Systematic review	A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.
Thrombophilia	The genetic or acquired pro-thrombotic states that increase the tendency to venous (or arterial) thromboembolism. It is a condition which leads to a tendency for a person's blood to clot inappropriately.
Thromboprophylaxis	A measure taken to reduce the risk of thrombosis.
Treatment allocation	Assigning a participant to a particular arm of the trial.
Unfractionated heparin	Naturally-occurring polysaccharide anticoagulant isolated for pharmacological use from pig intestine or bovine lung. Usually given as subcutaneous injection as prophylaxis or by continuous infusion as therapy for a thrombosis.
Venous thromboembolism	The blocking of a blood vessel by a blood clot dislodged from its site of origin. It includes both deep vein thrombosis and pulmonary embolism.
Venous thrombosis	A condition in which a blood clot (thrombus) forms in a vein.

Appendix G: Acknowledgements

In addition to the VTE Prevention Guideline Adaptation Committee, the following individuals have contributed significantly in the development of this Guideline using the ADAPTE methodology:

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