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Safe Use of Heparins and Oral Anticoagulants for Venous Thromboembolism Prophylaxis in Adults

**A position statement of the
NSW Therapeutic Advisory Group Inc.
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Executive Summary

This document outlines the principles for safe use of heparins and oral anticoagulants for venous thromboembolism (VTE) prophylaxis in adult patients. This updated document aligns with the National Health and Medical Research Council 2009 Clinical Practice Guideline for the prevention of venous thromboembolism in patients admitted to Australian hospitals and includes updated information on oral anticoagulants approved for VTE prophylaxis and assessing renal function. Text and tables have been simplified. Many decisions for VTE prophylaxis need to be made on an individual patient basis. These are highlighted clearly in the text.

Definitions used are as follows:

- “Heparin” or “heparins” refers to the following medicines registered for use in Australia:
 - Unfractionated heparin
 - Low molecular weight heparins - dalteparin, enoxaparin
 - Synthetic selective inhibitor of activated factor X - fondaparinux
 - Heparinoid - danaparoid
- “Oral anticoagulants” refers to the following medicines registered for use in Australia:
 - Thrombin inhibitor - dabigatran
 - Selective factor Xa inhibitor - rivaroxaban.

There are six steps to safe use of VTE prophylaxis.

Step 1: Identify patients requiring VTE prophylaxis

- All adult patients should be assessed for need for VTE prophylaxis prior to or on admission to hospital.
- Identification of patients who require VTE prophylaxis should be aligned with current guidelines.
- If unsure whether individual patients require VTE prophylaxis, consult Drug and Therapeutics Committee approved hospital policies or senior medical staff.

Step 2: Assess for bleeding risk & contraindications

- Prior to prescribing heparin or oral anticoagulants, all patients should be asked about bleeding risks and contraindications (eg hypersensitivity, heparin induced thrombocytopenia, renal and hepatic disease, concomitant medications and other conditions that may increase bleeding risk).
- Where these conditions exist, the decision to prescribe VTE prophylaxis should be made on an individual patient basis balancing risks and benefits.
- Coagulation tests are not helpful in predicting postoperative bleeding and are more likely to be useful when there are clinical indications for performing the tests.

Step 3: Assess for special precautions

- Patients should be assessed for special precautions including renal impairment, use of concomitant medicines and planned use of spinal or epidural anaesthesia.
- Decisions should be made on an individual patient basis.

3.1 Assess for renal impairment:

- Renal function should be assessed prior to prescription of enoxaparin, fondaparinux, dabigatran or rivaroxaban as there may need to be dose adjustment or the medicine may need to be withheld.
- Unfractionated heparin can be given in renal impairment without dose adjustment.
- An estimating formula can be used to assess renal function such as the Cockcroft-Gault formula or the Modification of Diet in Renal Disease formula.
- The Cockcroft-Gault formula is generally recommended for informing drug-dose adjustments especially for critical dose drugs with a narrow therapeutic index. The British National Formulary recommends estimated glomerular filtration rate using the Modification of Diet in Renal Disease formula can be used to determine dosage adjustments for most medicines in most patients.
- Results of renal function testing should be interpreted with caution, taking into account the limitations of the formulae used.

Executive Summary (cont)

3.2 Assess for concomitant medicines:

- Medicines that may increase the risk of bleeding when used in combination with heparins or oral anticoagulants include anticoagulants, antiplatelet agents, non-steroidal anti-inflammatory drugs, and thrombolytic agents.
- Decisions about appropriate concomitant use of these medicines for VTE prophylaxis should be made on an individual patient basis. Low dose aspirin used in cardiovascular disease may be continued.
- Unfractionated heparin can raise potassium levels and may lead to hyperkalemia when co-prescribed with another medicine that can raise potassium.
- Potassium levels should be monitored when unfractionated heparin is prescribed with other medicines that can raise potassium.

3.3 Determine if neuraxial (spinal/epidural) anaesthesia is planned:

- When VTE prophylaxis is prescribed for patients having neuraxial anaesthesia:
 - Insertion and removal of regional anaesthesia needles and catheters should take place when the anticoagulant effect is lowest
 - If bleeding is present during needle/catheter placement then subsequent dosing should be delayed for 24 hours
 - If in doubt, the decision to prescribe heparin for VTE prophylaxis should be made on an individual patient basis in consultation with the anaesthetist, surgeon and other relevant specialists.

3.4 Assess for obesity

- Evidence is unclear about adjustments required to VTE prophylaxis dosing in obese patients but there is some indication that adjustments to low-molecular weight heparin dosing may be required.
- Decisions to vary fixed dosing of VTE prophylaxis in obese individuals should be made on individual patient basis in consultation with senior clinical staff.

Step 4: Select the most appropriate heparin or anticoagulant agent

- Different agents have different risk/benefit ratios and there is usually more than one option for each clinical indication.
- The choice of agent depends on factors such as:
 - indication for VTE prophylaxis
 - patient specific factors (such as presence of renal impairment)
 - procedure specific considerations such as type of surgery and/or type of anaesthesia planned
 - medicine specific factors such as dosing schedule, risk of heparin induced thrombocytopenia, reversibility and cost.

Step 5: Determine appropriate timing of VTE prophylaxis

- The timing of peri-operative heparin administration is dependent on the drug chosen, the dose chosen and type of procedure and anaesthesia planned.
- There is no advantage with starting VTE prophylaxis preoperatively versus postoperatively.
- In neurosurgery, heparins should be started postoperatively with extreme caution.
- In trauma, heparins should not be started until primary haemostasis has been established.

Step 6: Monitor for adverse events

- Patients should be assessed for signs of bleeding while prescribed VTE prophylaxis.
- Platelets should be assessed at baseline and intermittently in those prescribed unfractionated heparin or low molecular weight heparin and at baseline in patients prescribed fondaparinux.
- Heparin induced thrombocytopenia is a clinicopathological diagnosis. Where heparin induced thrombocytopenia is strongly suspected or confirmed then heparin should be stopped and alternative anticoagulation with danaparoid or lepirudin given.
- Adverse events should be reported centrally through the appropriate adverse drug event or incident reporting mechanisms in each institution.

Note: General principles of safety apply whenever heparins or oral anticoagulants are prescribed. Nevertheless, some recommendations in this document will not automatically apply when patients are prescribed medicine for **treatment** of VTE or other clinical indications as the balance of expected benefits versus risks may differ.

Introduction

What has been updated:

- i. This document has been updated as follows:
 - Information has been aligned with the National Health and Medical Research Council 2009 *Clinical Practice Guideline for the prevention of venous thromboembolism in patients admitted to Australian hospitals*.¹
 - Information on new oral anticoagulants approved for venous thromboembolism prophylaxis has been included
 - Information on assessing renal function has been updated
 - The presentation of the text and tables has been simplified to improve readability and usability of the document.

Background:

- ii. Venous thromboembolism (VTE) occurs in hospitalised surgical and medical patients² and can be prevented through judicious use of VTE prophylaxis.^{1, 3-8} VTE prophylaxis traditionally consists of a low dose heparin (dalteparin, danaparoid, enoxaparin, fondaparinux or unfractionated heparin) with or without with mechanical methods such as intermittent pneumatic compression or graduated compression stockings. In 2009 two oral anticoagulants were approved for VTE prophylaxis in patients who have had major orthopaedic surgery – dabigatran and rivaroxaban.⁹
- iii. With growing Australian and international encouragement for instituting VTE prophylaxis systems in hospitals, it can be expected that an increased number of inpatients will be prescribed VTE prophylaxis. However, heparins (even in low doses) and oral anticoagulants carry a risk of causing bleeding from any site, especially in patients at increased risk of bleeding from other causes such as concurrent administration of some medicines, some clinical conditions and some surgical and anaesthetic procedures.¹⁰ Careful clinical management of patients at risk of bleeding is required to minimise the risk and severity of VTE prophylaxis related bleeding.^{10, 11}
- iv. This document outlines the principles for safe use of heparins and oral anticoagulants in VTE prophylaxis. Current information on heparin and oral anticoagulant safety is scattered through a number of sources and is difficult for clinicians to access when making clinical decisions at the point of care. This document collates this information into one place. It is designed to assist clinicians and complements the National Health and Medical Research Council 2009 *Clinical Practice Guideline for the prevention of venous thromboembolism in patients admitted to Australian hospitals*.¹

Method:

- v. Information was identified from the following sources:
 - Authoritative and systematically developed Australian and international texts on medicine use and management.^{9, 12, 13}
 - Clinical practice guidelines that:^{1, 3-8}
 - reported the type of professionals and stakeholders involved in the development process;
 - outlined the strategy to identify primary evidence; and
 - included an explicit grading of recommendations according to the quality of supporting evidence.

More recent guidelines were given preference over older guidelines

- Manufacturer's product information monographs.
- vi. Where recommendations in these sources was unclear due to lack of evidence, further clarifying information was sought from Australian Specialty Colleges as well as medical databases including MEDLINE, EMBASE and Cochrane Database of Systematic Reviews.

Scope:**What is included:**

- vii. This document assesses issues in the safe use of heparins and oral anticoagulants in VTE prophylaxis in adult patients.
- viii. “Heparin” or “heparins” refers to the following heparin and heparinoid medicines registered for use in Australia:
 - Unfractionated heparin
 - Low molecular weight heparins - dalteparin, enoxaparin
 - Synthetic selective inhibitor of activated factor X - fondaparinux
 - Heparinoid - danaparoid
- ix. Oral anticoagulants refer to the following products registered for use in Australia:
 - Thrombin inhibitor - dabigatran
 - Selective factor Xa inhibitor - rivaroxaban.

What is not included:

- x. An assessment of warfarin is not included in this document as Australian guidelines do not recommend warfarin for VTE prophylaxis.¹
- xi. This document does not discuss the following:
 - Detailed pharmacology of agents used in VTE prophylaxis
 - Issues related to mechanical methods of prophylaxis
 - In-depth critical analysis of patients or conditions that do or do not merit VTE prophylaxis
 - Longer-term VTE prophylaxis during pregnancy
 - VTE prophylaxis in paediatric patients.
- xii. Safe use of these medicines in VTE treatment is not explicitly discussed (see note xvi below).

Further information

- xiii. Readers are referred to available guidelines^{1, 3-8} and/or Drug and Therapeutics Committee approved or endorsed local hospital policies for determining patients who do and do not require VTE prophylaxis.
- xiv. NSW Therapeutic Advisory Group (NSW TAG) recommends that adverse events occurring in patients prescribed a heparin or oral anticoagulant for VTE prophylaxis be reported centrally through the appropriate adverse drug event and incident reporting mechanisms in each institution.
- xv. Safe prescribing of enoxaparin can be measured and monitored using the NSW TAG *Indicators for Quality Use of Medicines in Australian Hospitals* – specifically Indicator 1.3 *Percentage of patients prescribed enoxaparin whose dosing schedule is appropriate* - available at www.nswtag.org.au

Notes:

- xvi. General principles apply whenever heparins or oral anticoagulants are prescribed. Nevertheless, some recommendations in this document will not automatically apply when patients are prescribed medicine for treatment of VTE or other clinical indications as the balance of expected benefits versus risks may differ.
- xvii. Whilst this document aims to guide clinical practice, it is not intended to replace clinician judgement. Many decisions for VTE prophylaxis need to be made on an individual patient basis. These are highlighted clearly in the text.

Step 1: Identify patients requiring VTE prophylaxis

- 1.1. All adult patients should be assessed for need for VTE prophylaxis prior to or on admission to hospital.
- 1.2. Identification of patients who require VTE prophylaxis should be aligned with recent Australian guidelines, although it should be noted that “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.”¹ Surgical and medical patients in whom VTE prophylaxis should be considered are outlined in Table A.

Table A: VTE prophylaxis in surgical procedures and medical conditions¹

Surgical Procedures	Medical Conditions
✓ Total hip replacement	✓ Acute coronary syndrome if not already anti-coagulated
✓ Hip fracture surgery	✓ Cancer patients undergoing a surgical procedure
✓ Total knee replacement	ⓘ Ischaemic Stroke
✓ Lower leg fractures and injuries with immobilisation	ⓘ General medical conditions
✓ General surgery	
✓ Major gynaecological surgery	
✓ Major abdominal surgery	
✓ Cardiac, thoracic or vascular surgery	
✓ Trauma and spinal surgery	
✓ Caesarean section	
ⓘ Urological surgery	
△△ Neurosurgery	
⊗ Knee arthroscopy	
⊗ Head and neck cancer surgery	

Table A key:

✓ VTE prophylaxis should be considered	⊗ Not recommended
ⓘ Base decision on balance of risk of VTE and bleeding	△△ Use with EXTREME CAUTION

- 1.3. Decisions regarding provision of VTE prophylaxis need to take into account factors such as:¹
 - Individual patient risk factors - age, pregnancy, malignancy, previous VTE, varicose veins, obesity, prolonged immobility, oestrogen containing hormone replacement therapy or oral contraceptives, inherited or acquired thrombophilia.
 - Risks related to an acute medical illness.
 - Risks related to an injury or surgical procedure.
 - Bleeding risk.
- 1.4. If unsure whether individual patients require VTE prophylaxis, consult Drug and Therapeutics Committee approved hospital policies or senior medical staff.

Recommendations:

- All adult patients should be assessed for need for VTE prophylaxis prior to or on admission to hospital.
- Identification of patients who require VTE prophylaxis should be aligned with current guidelines.
- If unsure whether individual patients require VTE prophylaxis, consult Drug and Therapeutics Committee approved hospital policies or senior medical staff.

Step 2: Assess for bleeding risk & contraindications

- 2.1 Bleeding risks should be explicitly asked about prior to prescribing VTE prophylaxis.¹⁴
- 2.2 Routine coagulation screening tests are not useful in predicting postoperative bleeding. They have poor positive predictive value, sensitivity and specificity¹⁴ and are more likely to be useful if there are clinical indications for performing the tests.¹⁵
- 2.3 Absolute contraindications to all heparins or oral anticoagulants are known hypersensitivity and uncontrollable, active bleeding. (Table B)
- 2.4 Contraindications applying to some heparins or oral anticoagulants include: history of (or current) heparin induced thrombocytopenia, impaired renal function, hepatic disease, concomitant medications. (Table B)
- 2.5 Other conditions that can increase bleeding risk with VTE prophylaxis include:^{10, 16-24}
 - Bleeding/coagulation disorders eg haemophilia, severe thrombocytopenia (platelets <50 x 10⁹/L), severe liver disease with coagulopathy
 - Conditions where bleeding would be catastrophic eg haemorrhagic stroke
 - High risk of uncontrolled haemorrhage eg acute ulcerative conditions
 - Spinal needle insertion
 - Recent surgery on eye, brain or spinal cord
 - Other eg acute bacterial endocarditis, arterial sclerosis, dissecting aneurysm, severe uncontrolled hypertension, diverticulitis, threatened abortion.
- 2.6 Where these conditions exist, the decision to prescribe VTE prophylaxis should be made on an **individual patient basis** balancing risks and benefits.

Table B: Contraindications to heparins and oral anticoagulants¹⁶⁻²⁴

	Hyper-sensitivity	Uncontrollable active bleeding	History of (or current) heparin induced thrombocytopenia	Hepatic Disease	Concomitant medicines*	Impaired renal function
Unfractionated heparin	⊗	⊗	⊗	—	△ [†]	See Table C
Enoxaparin	⊗	⊗	⊗	—	△ [*]	
Dalteparin	⊗	⊗	⊗	—	△ [*]	
Fondaparinux	⊗	⊗	⊗	—	△ [*]	
Danaparoid	⊗	⊗	—	—	△ [*]	
Dabigatran	⊗	⊗	—	△ Use with caution if liver enzymes > 2x upper limit of normal	⊗ [*] <u>P-glycoprotein inhibitors</u> -quinidine -nelfinavir -amiodarone -ritonavir -clarithromycin -saquinavir -cyclosporine -tacrolimus -itraconazole -verapamil. -ketoconazole <u>P-glycoprotein inducers</u> -rifampicin -St John's Wort	
Rivaroxaban	⊗	⊗	—	⊗ Contraindicated in moderate and severe hepatic impairment with coagulopathy.	⊗ [*] <u>Potent inhibitors of CYP3A4 & p-glycoprotein</u> -ketoconazole -ritonavir -itraconazole -rifampicin -voriconazole <u>Strong CYP3A4 inducers</u> -carbamazepine -phenytoin	

*Caution is required with medicines that may increase bleeding (see 3.2) †Caution is required with medicines that raise potassium (see 3.2)

Table B key:

⊗ Do not use	△ Caution	— No known problems
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Recommendations:

- Prior to prescribing heparin or oral anticoagulants, all patients should be asked about bleeding risks and contraindications (eg hypersensitivity, heparin induced thrombocytopenia, renal and hepatic disease, concomitant medications and other conditions that may increase bleeding risk).
- Where these conditions exist, the decision to prescribe VTE prophylaxis should be made on an individual patient basis balancing risks and benefits.
- Coagulation tests are not helpful in predicting postoperative bleeding and are more likely to be useful when there are clinical indications for performing the tests.

Step 3: Assess for special precautions

Patient and procedure factors that require special precautions when prescribing heparins or oral anticoagulants include:¹⁶⁻²²

- Renal impairment
- Use of concomitant medicines
- Planned use of neuraxial (spinal/epidural) anaesthesia.

Specialist advice may be required regarding optimal choice of medicine and timing of VTE prophylaxis in these circumstances. Detailed advice for each circumstance is offered in the following pages.

Where there are options, **individual patient circumstances** should be taken into account and the Drug and Therapeutics Committee endorsed policy at each institution should be followed.

Recommendations

- *Patients should be assessed for special precautions including renal impairment, use of concomitant medicines and planned use of spinal or epidural anaesthesia.*
- *Decisions should be made on an individual patient basis.*

Step 3.1: Assess for renal impairment

When to check renal function:

- 3.1.1 Renal function should be assessed prior to the prescription of enoxaparin, fondaparinux, dabigatran and rivaroxaban.
- 3.1.2 Depending on the level of renal impairment these medicines may need dosage adjustment or be withheld. Table C summarises information regarding dosage adjustments required in renal impairment.

Table C: Dosage adjustments required in renal impairment

	Creatinine clearance 30-50 mL/min	Creatinine clearance 15-29 mL/min	Creatinine clearance <15 mL/min
Unfractionated heparin ¹⁷	↔	↔	↔
Enoxaparin ¹⁸	↔	↓ Reduce dose to 20 mg daily	↓ Reduce dose to 20 mg daily
Dalteparin	No recommendations available		
Fondaparinux ^{20*}	↔	⊗	⊗
Danaparoid ¹³	?	?	?
Dabigatran ²⁴	↓ Reduce dose to 150 mg daily	⊗	⊗
Rivaroxaban ²³	↔	△	⊗

*Fondaparinux should be discontinued if develop labile renal function develops

Table C key:

⊗ Do not use	△ Use with caution	↔ Can be used - no dose adjustment needed
↓ Reduce dose	? Consider dose reduction	

Calculating renal function

- 3.1.3 Renal function can be calculated by 24-hour urine collection or by using a formula to estimate glomerular filtration rate.
- 3.1.4 Commonly used formulae to calculate renal function are:
 - **The Cockcroft-Gault formula:** This formula uses serum creatinine, weight, sex, and age. Automated calculators based on the Cockcroft–Gault formula are available in the electronic versions of the Australian Medicines Handbook (go to ‘Calculators’) and Therapeutic Guidelines: Antibiotic (go to Appendix 2.6)). See Box 1.
 - **The Modification of Diet in Renal Disease formula:** This formula uses serum creatinine, age, sex, and race (African-American) and is adjusted to the average adult body surface area. Estimated glomerular filtration rate reporting using the Modification of Diet in Renal Disease formula is routinely reported with all serum creatinine test results in Australia.^{25, 26} An automated calculator for estimated glomerular filtration rate is available from the Kidney Health Australia website – www.kidney.org.au. See Box 1.

Using renal function estimates for drug-dose adjustment

- 3.1.5 When assessing renal function it is not known which estimating formula (Modification of Diet in Renal Disease or Cockcroft–Gault) provides a better guide to drug-dose adjustment.²⁷
- 3.1.6 Recent Australian advice recommends Modification of Diet in Renal Disease estimated glomerular filtration rate can be used to guide drug-dosing decisions when no other measure of glomerular filtration rate is known or accessible, but is not suitable for determining drug-dose adjustments for renally cleared critical dose drugs such as low molecular weight heparins.²⁷
- 3.1.7 Estimating glomerular filtration rate using the Cockcroft–Gault formula is usually recommended for drug-dose adjustments, as most studies have used this formula.^{19, 26-29}

- 3.1.8 Recent research shows the Modification of Diet in Renal Disease study equation can be used for drug-dose adjustments³⁰ and the British National Formulary now states for most medicines and for most patients (over 18 years) of average build and height, estimated glomerular filtration rate (Modification of Diet in Renal Disease) can be used to determine dosage adjustments in place of creatinine clearance.¹²
- 3.1.9 Absolute glomerular filtration rate can be calculated from estimated glomerular filtration rate using the formula in Figure 1.

Figure 1: Formulae for calculating renal function.

The Cockcroft–Gault formula

Creatinine clearance (mL/min) = $[140 - \text{age (years)}] \times \text{body weight (kg)} / 0.815 \times \text{serum creatinine (micromol/L)}$

Weight – use the lower of actual or ideal body weight

Multiply the value by 0.85 for females.

Ideal body weight (females) = 45.5 kg + 0.9 kg/cm for each cm >152 cm

Ideal body weight (males) 50 kg + 0.9 kg/cm for each cm >152 cm

Add 10% for a heavy frame; subtract 10% for a light frame

The Modification of Diet in Renal Disease formula

Estimated glomerular filtration rate (mL/min/1.73 m²) = $175 \times ([\text{Serum creatinine (micromol/L)}] / 88.4)^{-1.154} \times (\text{age in years})^{-0.203}$
 × (0.742 if female) × (1.210 if African- American)

Estimating absolute glomerular filtration rate from estimated glomerular filtration rate

Glomerular filtration rate (absolute) = estimated glomerular filtration rate × (body surface area/1.73)

Body surface area = $\sqrt{([\text{height(cm)}] \times \text{weight (kg)}) / 3600}$

Limitations of estimating renal function using formulae

- 3.1.10 Both Modification of Diet in Renal Disease and Cockcroft–Gault formulae have limitations that need to be taken into account when interpreting results. Both equations are less accurate or unreliable in people with:
- Glomerular filtration rate of 60 mL/minute or greater
 - Extremes of body size
 - Exceptional dietary intake (e.g. high-protein diet)
 - Diseases or conditions affecting skeletal muscle (e.g. paraplegia)
 - Rapidly changing renal function and in patients dependent on dialysis.^{25 31}
 - Populations for which their use has not been validated eg children and Aboriginal and Torres Strait Islander peoples. In these situations, renal function testing using a timed urine collection may be more appropriate.²⁷

Recommendations:

- Renal function should be assessed prior to prescription of enoxaparin, fondaparinux, dabigatran or rivaroxaban as there may need to be dose adjustment or the medicine may need to be withheld.
- Unfractionated heparin can be given in renal impairment without dose adjustment.
- An estimating formula can be used to assess renal function such as the Cockcroft-Gault formula or the Modification of Diet in Renal Disease formula.
- The Cockcroft-Gault formula is generally recommended for informing drug-dose adjustments especially for critical dose drugs with a narrow therapeutic index. The British National Formulary recommends estimated glomerular filtration rate using the Modification of Diet in Renal Disease formula can be used to determine dosage adjustments for most medicines in most patients.
- Results of renal function testing should be interpreted with caution, taking into account the limitations of the formulae used.

Step 3.2: Assess for concomitant medicines

Medicines that may increase bleeding

- 3.2.1 Medicines that may increase the risk of bleeding require careful management when used in combination with heparin or oral anticoagulants (see Table D).
- 3.2.2 The decision to co-prescribe such medicines should be made on an **individual patient basis** in consultation with senior staff taking into account patient preference. Careful monitoring is recommended.¹⁰
- 3.2.3 Low dose aspirin required for prevention or treatment of cardiovascular disease may be continued.¹⁹

Table D: Medicines registered for use in Australia that may increase risk of bleeding:^{*10, 11, 19}

Anticoagulants	Antiplatelets	NSAIDs [†]		Thrombolytics	Others
Bivalirudin	Abciximab	Celecoxib	Meloxicam	Alteplase	Dextran
Lepirudin	Aspirin [†]	Diclofenac	Naproxen	Reteplase	Hydroxychloroquine
Phenindione	Clopidogrel	Ibuprofen	Parecoxib	Streptokinase	
Warfarin	Dipyridamole	Indomethacin	Piroxicam	Tenecteplase	
	Eptifibatide	Ketoprofen	Sulindac	Urokinase [§]	
	Ticlopidine	Ketorolac	Tiaprofenic acid		
	Tirofiban	Mefenamic acid			

*This list is not comprehensive. Refer to product information for details of other medicines that may interact with heparins or oral anticoagulants.^{16-18, 20-24} [†] Low dose aspirin used for cardiovascular disease does not need to be stopped.¹⁹ [‡]NSAIDs – non-steroidal anti-inflammatory drugs, includes selective and non-selective agents. [§]Available through Special Access Scheme

Medicines that raise potassium levels

- 3.2.4 Unfractionated heparin can raise potassium levels and may lead to hyperkalemia when co-prescribed with another medicine that can raise potassium. Medicines registered for use in Australia that can raise potassium include:
- **Angiotensin converting enzyme inhibitors:** captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, trandolapril
 - **Angiotensin II receptor antagonists:** candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan
 - **Potassium sparing diuretics:** amiloride, eplerenone, spironolactone, triamterene with hydrochlorothiazide
 - **Potassium supplements:** infusions, injections, tablets
 - **Non-steroidal anti-inflammatory drugs:** (see table D)
 - **Other:** trimethoprim
- 3.2.5 Potassium levels should be monitored where patients are prescribed unfractionated heparin in combination with one of these medicines.^{11, 17, 19}
- 3.2.6 Raised potassium levels usually resolve when heparin therapy is stopped and treatment for hyperkalemia in this situation is generally not required.¹¹

Recommendations:

- Medicines that may increase the risk of bleeding when used in combination with heparins or oral anticoagulants include anticoagulants, antiplatelet agents, non-steroidal anti-inflammatory drugs, and thrombolytic agents.
- Decisions about appropriate concomitant use of these medicines for VTE prophylaxis should be made on an individual patient basis. Low dose aspirin used in cardiovascular disease may be continued.
- Unfractionated heparin can raise potassium levels and may lead to hyperkalemia when co-prescribed with another medicine that can raise potassium.
- Potassium levels should be monitored when unfractionated heparin is prescribed with other medicines that can raise potassium.

Step 3.3: Determine if neuraxial (spinal/epidural) anaesthesia is planned

- 3.3.1 In patients having neuraxial (spinal/epidural) anaesthesia extra precautions are needed in prescribing VTE prophylaxis due to the increased risk of epidural/spinal haematoma and associated spinal cord compression.¹⁹
- 3.3.2 Key strategies for managing VTE prophylaxis in patients having neuraxial anaesthesia in combination with heparins are summarised in Table E:

Table E: Managing VTE prophylaxis in patients having spinal/epidural anaesthesia^{6, 18, 23, 24, 32}

Medicine	Timing of needle/catheter insertion	Timing of needle/catheter removal*	Cautions [†]
Unfractionated heparin	8-12h after last dose	-Just before next scheduled dose. -Then delay next dose for 2h.	-Delay dose for 24h if traumatic
Dalteparin Enoxaparin Danaparoid	-10-12h after prophylactic dosing. -Next dose at least 2h after last dose	-Just before next scheduled dose. -Then delay next dose for 2h.	-Delay dose for 24h if traumatic
Fondaparinux	Only start postoperatively	-Just before next scheduled dose. -Then delay next dose for 2h.	-Delay dose for 24h if traumatic -Not while indwelling epidural catheter in place
Dabigatran		2h before first dose.	-Delay dose for 24h if traumatic -Not while indwelling epidural catheter in place
Rivaroxaban		-Remove at least 18h after last dose. -Next dose at least 6h after catheter removal.	-Delay dose for 24h if traumatic

*Spinal needles or epidural catheters should be removed when anticoagulant effect is lowest. [†]For all medicines delay dose for 24h if bleeding during needle/catheter placement

- 3.3.3 It is important to pay attention to the routine monitoring for symptoms and signs of spinal cord compression required for any patient receiving neuraxial anaesthesia. If spinal haematoma is suspected, diagnostic imaging should be performed without delay
- 3.3.4 The same cautions should be applied for patients receiving deep peripheral nerve blocks.
- 3.3.5 If in doubt, the decision to prescribe heparins for VTE prophylaxis should be made on an **individual patient basis** in consultation with the anaesthetist, surgeon and other relevant specialists.

Recommendations:

- *When VTE prophylaxis is prescribed for patients having neuraxial anaesthesia:*
 - *Insertion and removal of regional anaesthesia needles and catheters should take place when the anticoagulant effect is lowest*
 - *If bleeding is present during needle/catheter placement then subsequent dosing should be delayed for 24 hours*
 - *If in doubt, the decision to prescribe heparin for VTE prophylaxis should be made on an individual patient basis in consultation with the anaesthetist, surgeon and other relevant specialists.*

Step 3.4 Assess for obesity

- 3.4.1 Available evidence is unclear whether dosage adjustment is required in obese patients requiring VTE prophylaxis.
- 3.4.2 Some authors recommend adjustment in low molecular weight heparin dosing may be required in obese patients. Available information is summarised here. Also see Table F.
- The American College of Chest Physicians Evidence-Based Clinical Practice Guidelines recommends weight-based dosing obese patients given low molecular weight heparin for prophylaxis or treatment (Grade 2C). However, the mg/kg dose for prophylaxis is not specified.³³
 - The American College of Chest Physicians Evidence-Based Clinical Practice Guidelines also recommends higher doses of low molecular weight heparin or unfractionated heparin than usual for non-obese patients in patients undergoing inpatient bariatric surgery. (Grade 2C). This guideline does not recommend increasing prophylactic treatment in obese patients in other settings.⁶
 - One small study of 28 morbidly obese medically ill patients showed a weight-based enoxaparin dosing of 0.5 mg/kg once daily was feasible and resulted in no bleeding events, symptomatic VTE, or significant thrombocytopenia. The authors recommended further clinical outcome studies to determine the clinical safety and efficacy of this regimen.³⁴
 - Other evidence extrapolated from literature review suggests increasing doses of low molecular weight heparins by 30% for VTE prophylaxis may be appropriate in morbidly obese patients (body mass index ≥ 40 kg/m²).³⁵
 - For treatment doses of enoxaparin, there is some evidence that obesity (body mass index >30 kg/m²) reduces clearance of chronically dosed enoxaparin and that weight based enoxaparin dosing in obese individuals should be based on lean body weight rather than total body weight.³⁶
- 3.4.3 Dosage adjustment is not required for danaparoid,¹³ otherwise little information is available regarding dosage adjustment required for other heparins or oral anticoagulants in obese patients.
- 3.4.4 Given the uncertainty surrounding dosing of low molecular weight heparins in obese patients, it is recommended decisions to vary fixed dosing of VTE prophylaxis in obese individuals be made on an **individual patient basis** in consultation with senior clinical staff.

Recommendations:

- *Evidence is unclear about adjustments required to VTE prophylaxis dosing in obese patients but there is some indication that adjustments to low molecular weight heparin dosing may be required.*
- *Decisions to vary fixed dosing of VTE prophylaxis in obese individuals should be made on individual patient basis in consultation with senior clinical staff.*

Step 4: Select the most appropriate heparin or anticoagulant agent

- 4.1 Heparins are not clinically interchangeable (unit for unit). However there is usually more than one option for each clinical indication for VTE prophylaxis. Similarities between heparins are:
- There is no single heparin or oral anticoagulant agent that is suitable for all indications. Evidence for each agent and condition is outlined in the NHMRC guidelines.¹
 - In clinical trials, heparins and oral anticoagulants have a similar incidence of major bleeding.¹⁹
 - All heparins and oral anticoagulants have a “C” classification in pregnancy
 - All heparins should be given by deep subcutaneous injection (NOT intramuscular injection) for VTE prophylaxis. Injection near the site of an incision should be avoided.
 - Monitoring of anti-factor Xa levels is not required for any heparin when used for VTE prophylaxis (except for danaparoid).²²
- 4.2 Table F summarises the key differences between heparins and oral anticoagulant agents that can help prescribers weigh the risks and benefits for individual patients.
- 4.3 Each agent should be prescribed for the duration recommended in clinical guidelines based on the indication for prophylaxis.¹
- 4.4 Heparin dosing for treatment of VTE or other indications may be different.

Recommendations:

- *Different agents have different risk/benefit ratios and there is usually more than one option for each clinical indication.*
- *The choice of agent depends on factors such as:*
 - *indication for VTE prophylaxis*
 - *patient specific factors (such as presence of renal impairment)*
 - *procedure specific considerations such as type of surgery and/or type of anaesthesia planned*
 - *medicine specific factors such as dosing schedule, risk of heparin induced thrombocytopenia, reversibility and cost.*

Table F: Differences between heparins and oral anticoagulants when used for VTE prophylaxis^{9, 11, 13, 17, 18, 20-24, 33-39}

	Unfractionated heparin	Dalteparin	Enoxaparin	Danaparoid	Fondaparinux	Dabigatran	Rivaroxaban	
Pharmacology	Approved indication for VTE prophylaxis	-Surgical patients -High risk medical patients.	-Surgical patients.	-Surgical patients -Medical patients bedridden with acute illness.	-General or orthopaedic surgery	-Hip fracture, hip/knee replacement -Abdominal surgery.	-Adults elective total hip/ knee replacement	-Adults elective total hip/ knee replacement
	Route of administration	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Oral	Oral
	Dosing in VTE prophylaxis	5000 units 2-3x daily depending on risk	2500 – 5000 units once daily.	20-40 mg once daily.	750 anti-factor Xa units twice daily	2.5 mg once daily. Use with caution if weight < 50 kg.	110 mg 1-4 hours post-operatively then 220 mg once daily.	10 mg once daily 6-10 hours post-operatively when haemostasis established.
	Elimination	Liver & reticuloendothelial system	Primarily renal	Primarily renal	Renal	Renal	Primarily renal	Renal and gastrointestinal
	Dosing in renal impairment	See Table C						
	Dosing in obesity	Information unclear or not available	Consider increase in dose	Consider increase in dose	Nil change required	Information unclear or not available	Information unclear or not available	Information unclear or not available
	Reversibility	Complete with protamine.	60-75% with protamine.	60% with protamine.	Non-reversible.	Non-reversible.	Non-reversible	Non-reversible
Risk of HIT	Highest incidence	Lower incidence	Lower incidence	Can be used to treat HIT	No information	No information	No information	
Monitoring	Renal function	Not required	At baseline	At baseline	Not required	At baseline and periodically.	At baseline	At baseline
	Liver function	Not required	Not required	Not required	Not required	Not required	Required	Required
	Baseline platelet count	Yes.	Yes.	Yes.	Not required	Yes	No information	No information
	Repeat platelet count	Repeat after 24 hours in patients who had unfractionated heparin in past 100 days. Then every 2-4 days in postoperative and medical patients up to 14 days or heparin stopped (whichever is earlier). *†	Repeat after 24 hours in patients who had unfractionated heparin in past 100 days. Then every 2-4 days in postoperative and medical patients up to 14 days or heparin stopped (whichever is earlier). *† Not required in medical or obstetric patients.	-Repeat after 24 hours in patients who had unfractionated heparin in past 100 days. -Then every 2-4 days in postoperative and medical patients up to 14 days or heparin stopped (whichever is earlier). *†	Not required	When treatment ceased	No information	No information
	Other coagulation parameters	Not required.	Not required	Not required.	Functional anti-factor Xa (if renal impairment or weight > 90 kg).	Not required	Not required	Not required
	Assess for bleeding	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Approximate daily cost / patient	< \$5	< \$5	< \$5	> \$70	\$10-\$15	\$5-\$10	\$5-\$10	

*Based on low-level supporting evidence.^{37, 38} †Frequency of monitoring depends on risk of heparin induced thrombocytopenia.^{37, 38}

Step 5: Determine appropriate timing of VTE prophylaxis

- 5.1 The timing of peri-operative VTE prophylaxis administration should be decided on an **individual patient basis** and depends on the agent, dose, type of procedure and type of anaesthesia planned. Recommendations are given in Table G.
- 5.2 The optimal timing of heparin use perioperatively remains unknown. In general there is no advantage to starting heparin preoperatively compared to starting postoperatively,⁶ especially for patients admitted on the day of surgery. Preoperative dosing may be appropriate for at risk patients admitted to hospital before the day of scheduled surgery. Consider continuing heparin (for those starting preoperatively) in patients whose procedure is postponed.
- 5.3 Dabigatran and rivaroxaban should only be started postoperatively.
- 5.4 For neurosurgery, only start heparin postoperatively with **EXTREME CAUTION**.¹
- 5.5 For trauma, heparins should not be started until it is considered safe to do so and primary haemostasis has been established.¹

Table G: Recommendations for timing of peri-operative VTE prophylaxis^{3, 6, 18, 20-24, 32}

	Starting time (hours BEFORE surgery)		Starting time (hours AFTER surgery)	
	General anaesthesia	Regional anaesthesia	General anaesthesia	Regional anaesthesia
Unfractionated heparin	⌚ 2h			⌚ 6-8h
Dalteparin	⌚ Evening before (5000 units) ⌚ 1-2h (2500 units)	⌚ 8-12h prior to needle placement.	⌚ Timing unspecified.	⌚ 6-8h ⚠ Caution: Delay for 24h if bleeding during needle/catheter placement.
Enoxaparin	⌚ 12h (40 mg) ⌚ 2h (20 mg)			
Danaparoid	⌚ 1-4h			
Fondaparinux	⊠	⊠	⌚ At least 6h postoperatively. ⚠ Caution: Do not start until haemostasis established.	⌚ At least 6h ⚠ Caution: Do not start until haemostasis established. ⚠ Caution: Not recommended while epidural catheter in place.
Dabigatran	⊠	⊠	⌚ Start 1-4h post operatively.	⌚ At least 2h after removal of catheter. ⚠ Caution: Not recommended while epidural catheter in place.
Rivaroxaban	⊠	⊠	⌚ Start 6-10 hours postoperatively when haemostasis established.	⚠ Caution: Delay for 24h if bleeding during needle/catheter placement.

Table G key:

⊠ Not indicated	⚠ Caution	⌚ Instructions for timing
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Recommendations:

- The timing of peri-operative heparin administration is dependent on the drug chosen, the dose chosen and type of procedure and anaesthesia planned.
- There is no advantage with starting VTE prophylaxis preoperatively versus postoperatively.
- In neurosurgery, only start heparin postoperatively with **EXTREME CAUTION**.
- In trauma, heparins should not be started until primary haemostasis has been established.

Step 6: Monitor for adverse events

Bleeding

- 6.1 The main risk of heparins is bleeding which can occur at any site. The risk and severity of bleeding may be minimised with careful clinical management.^{10, 11} Easy bruising or petechial haemorrhages may precede frank bleeding, while nose bleeding, haematuria, or melena may be the first sign of bleeding.¹⁰
- 6.2 Bleeding assessment should be conducted periodically in patients receiving any dose of heparin or anticoagulant and should include:
 - Assessment of vital signs
 - Clinical review of the operative site (where appropriate)
 - Review of surgical drains and urinary, intravenous or epidural catheters.
- 6.3 The volume and extent of any blood loss should be accurately recorded on the observation chart and/or medical record and reported to the admitting team.
- 6.4 Minor bleeding is usually controlled by withholding VTE prophylaxis. In more severe bleeding, protamine sulphate can be used to reverse heparinisation in some patients.¹⁰ (Table F)
- 6.5 Bleeding related to VTE prophylaxis should be reported centrally through the appropriate adverse drug event or incident reporting mechanisms in each institution.

Thrombocytopenia

- 6.6 Unfractionated heparin (and to a lesser extent low molecular weight heparin) may also cause thrombocytopenia which does not appear to be dose related.¹⁰
- 6.7 A mild to moderate fall in platelet count may occur within 1-4 days. This often reverses spontaneously. While platelet counts remain $>100 \times 10^9/L$ heparin may be continued.¹⁷
- 6.8 Heparin induced thrombocytopenia is an antibody-mediated reaction resulting from irreversible aggregation of platelets. It is potentially life and limb threatening and occurs most commonly in patients prescribed unfractionated heparin (less commonly in patients prescribed low molecular weight heparin).
- 6.9 Heparin induced thrombocytopenia is a clinicopathological diagnosis³⁷ and should be suspected if:^{4, 17, 37}
 - Platelet counts fall below $100 \times 10^9/L$ or;
 - Platelet counts fall more than 50% from baseline during heparin treatment or;
 - Thrombosis occurs in patients treated or recently treated with heparin.
- 6.10 Heparin induced thrombocytopenia occurs about 4-10 days (sometimes several weeks) after starting heparin therapy. Heparin induced thrombocytopenia may occur earlier in patients exposed to heparin in the previous 3 months.³⁷ Risks for developing heparin induced thrombocytopenia are described in Table H.

Table H: Risk of developing heparin induced thrombocytopenia³⁷

Heparin received	Patient groups affected	Estimated risk of HIT
Unfractionated heparin for 1-2 weeks	Postoperative patients especially: -orthopaedic -cardiac -vascular surgery -likely others	~1-5%
Unfractionated heparin	Medical & obstetric patients	~0.1-1%
Low molecular weight heparin	Postoperative patients	~0.1-1%
Low molecular weight heparin	Medical & obstetric patients	<0.1%

- 6.11 Platelets should be assessed at baseline in all patients prescribed a heparin. Other platelet monitoring requirements are described in Table F.
- 6.12 Unfractionated heparin, low molecular weight heparin and fondaparinux should NOT be prescribed for patients with (or have a history of) heparin induced thrombocytopenia.
- 6.13 Where heparin induced thrombocytopenia is strongly suspected or confirmed then heparin should be stopped and alternative anticoagulation with a heparinoid (danaparoid sodium) or a selective inhibitor of thrombin (lepirudin) given as per dosing protocols.³⁷
- 6.14 Heparin induced thrombocytopenia should be reported centrally through the appropriate adverse drug event or incident reporting mechanisms in each institution.

Recommendations:

- Patients should be assessed for signs of bleeding while prescribed VTE prophylaxis.
- Platelets should be assessed at baseline and intermittently in those prescribed unfractionated heparin or low molecular weight heparin and at baseline in patients prescribed fondaparinux.
- Heparin induced thrombocytopenia is a clinicopathological diagnosis. Where it is strongly suspected or confirmed, heparin should be stopped and alternative anticoagulation with danaparoid or lepirudin given.
- Adverse events should be reported centrally through the appropriate adverse drug event or incident reporting mechanisms in each institution.

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Disclaimers

- Dr Jocelyn Lowinger is an employee of NSW Therapeutic Advisory Group Inc. She has no other interests to declare.
- No other interests declared.

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