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SAFE PRESCRIBING OF HEPARINS FOR VENOUS THROMBOEMBOLISM PROPHYLAXIS

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

This document outlines the principles for safe prescribing of heparins for venous thromboembolism (VTE) prophylaxis. "Heparin" or "heparins" refers to the following medications registered for use in Australia: dalteparin, danaparoid, enoxaparin, fondaparinux and unfractionated heparin. Some recommendations in this document will not apply when patients are prescribed heparins for treatment of VTE or other indications as the balance of expected benefits versus risks may differ. Nevertheless, the general principles of safe prescribing apply whenever heparins are prescribed. There are six steps to safe heparin prescribing for VTE prophylaxis.

Step 1: Assess patient risk of VTE

All adult patients should be assessed for risk of VTE prior to or on admission to hospital. For patients in whom the evidence for starting VTE prophylaxis seems inconclusive, senior medical staff should be consulted or reference made to an approved Drug and Therapeutics Committee hospital policy.

Step 2: Assess for contraindications and bleeding risk

Prior to prescribing heparin, all patients should be asked about contraindications and bleeding risks. Coagulation tests have a poor predictive value and are more likely to be useful when there are clinical indications for performing the tests.

Step 3: Assess for special precautions

3.1 Renal function should be assessed prior to prescription of enoxaparin or fondaparinux for VTE prophylaxis as drug-dose adjustment is required in patients with reduced renal function (creatinine clearance < 30 mL/minute). In these patients enoxaparin dose should be limited to 20 mg daily and fondaparinux should not be given. Unfractionated heparin can be given without dose adjustment. When assessing renal function it is not known which estimating formula provides a better guide to drug-dose adjustments. The Cockcroft-Gault formula is generally recommended for informing drug-dose adjustments especially for critical dose drugs with a narrow therapeutic index. Results of renal function testing should be interpreted with caution taking into account the limitations of the formulae used.

3.2 Many medications including anticoagulants, antiplatelet agents, selective and non-selective non-steroidal anti-inflammatory drugs, and thrombolytic agents may increase the risk of bleeding when used in combination with heparins. Decisions about appropriate concomitant use of these medications for VTE prophylaxis should be made on an individual patient basis in consultation with appropriate senior staff. Low dose aspirin required for prevention or treatment of cardiovascular disease may be continued. Potassium levels should be monitored when unfractionated heparin is prescribed with other medications that can raise potassium.

3.3 When heparins are prescribed for VTE prophylaxis 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 neuraxial 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 and surgeon taking into account patient preferences.

Step 4: Select the most appropriate medication

Different heparins have different risk/benefit ratios. Heparins are not clinically interchangeable (unit for unit), but there is usually more than one option for each clinical indication. The choice of heparin 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; drug specific factors such as dosing schedule, risk of heparin induced thrombocytopenia (HIT), reversibility and cost.

Step 5: Determine appropriate timing of heparin administration

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. For neurosurgery, heparins should be started postoperatively. For trauma patients, heparins should not be started until primary haemostasis has been established.

Step 6: Monitor the patient for adverse events

Patients should be assessed for signs of bleeding while prescribed a heparin. Platelets should be assessed at baseline and intermittently in patients prescribed unfractionated heparin or low molecular weight heparin and at baseline in patients prescribed fondaparinux. Heparin induced thrombocytopenia (HIT) is a clinicopathological diagnosis. Where HIT 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 and incident reporting mechanisms in each institution.

Introduction

The risk of developing venous thromboembolism (VTE) is spread evenly across medical and surgical patients.¹ The risk of VTE in hospitalised patients can be reduced through judicious use of VTE prophylaxis.²⁻⁷ VTE prophylaxis most commonly consists of low dose heparin in combination with mechanical methods such as intermittent pneumatic compression or graduated compression stockings. 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 heparins for VTE prophylaxis. However, heparins, even in low doses, carry a risk of causing bleeding from any site, especially in patients at increased risk of bleeding. Factors reported to increase the risk of bleeding in patients prescribed heparin include: concurrent administration of some drugs, certain clinical conditions and certain surgical and anaesthetic procedures.⁸ Careful clinical management of patients at risk of bleeding is required to minimise the risk and severity of heparin-related bleeding.^{8,9} Thus it is imperative to consider the safety of heparin prescribing.

This document outlines the principles for safe prescribing of heparins for VTE prophylaxis. Current information on heparin 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 on heparin safety into one place. It is designed to assist clinicians and complements clinical practice guidelines for VTE prophylaxis in hospitalised adult medical and surgical patients.

Information was identified from the following sources:

- Authoritative and systematically developed Australian and international texts on medicine use and management¹⁰⁻¹²
- Clinical practice guidelines that: 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.²⁻⁷ More recent guidelines were given preference over older guidelines
- Manufacturer's product information.

Where recommendations in these sources was unclear due to lack of evidence, further clarifying information was sought from Australian Specialty Colleges as well as MEDLINE, EMBASE and Cochrane Database of Systematic Reviews.

"Heparin" or "heparins" refers to the following heparin and heparinoid medications registered for use in Australia:

- Unfractionated heparin (UFH)
- Low molecular weight heparins (LMWH) - dalteparin, enoxaparin
- Synthetic selective inhibitor of activated factor X - fondaparinux
- Heparinoid - danaparoid

This document does not discuss the following:

- Detailed pharmacology of heparins
- Issues related to mechanical methods of prophylaxis
- In-depth critical analysis of patients or conditions that do or do not merit VTE prophylaxis based on risk assessment
- Longer-term VTE prophylaxis during pregnancy
- VTE prophylaxis in paediatric patients.

Readers are referred to available guidelines²⁻⁷ and/or Drug and Therapeutics Committee (DTC) approved or endorsed local hospital policies for determining patients who do and do not require VTE prophylaxis.

The general principles of safe prescribing apply whenever heparins are prescribed. Nevertheless, some recommendations in this document will not automatically apply when patients are prescribed heparins for treatment of VTE or other clinical indications as the balance of expected benefits versus risks may differ.

NSW Therapeutic Advisory Group (NSW TAG) recommends that adverse events occurring in patients prescribed a heparin for VTE prophylaxis be reported centrally through the appropriate adverse drug event and incident reporting mechanisms in each institution. Safe prescribing of heparin 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

Whilst this document aims to guide clinical practice, it is not intended to replace clinician judgement.

Step 1: Assess patient risk of VTE

There are many different categorisations of risk of VTE in hospitalised patients. The method of determining risk of VTE should be determined by an approved DTC hospital policy. One way to categorise risk of VTE in hospitalised patients is outlined in Table A.⁵ See recent guidelines for further details about patients at risk of VTE.⁵ If unsure whether individual patients require VTE prophylaxis, consult DTC approved hospital policies or senior medical staff.

Table A: VTE Risk categorisation of surgical and medical patients⁵

Surgical patients at high risk of VTE	Surgical patients at moderate risk of VTE	Surgical procedures where VTE prophylaxis is not required unless other risk factors	Medical patients at risk of VTE
Acute spinal cord injury	General surgery for benign conditions	Elective spine surgery*	Congestive heart failure
General surgery for cancer	Open gynaecologic surgery	Knee arthroscopy*	Severe respiratory disease
Hip fracture surgery	Open urologic surgery	Isolated lower extremity injuries [†]	Confined to bed and have one or more of: -active cancer -previous VTE -sepsis -acute neurologic disease -inflammatory bowel disease
Hip / knee arthroplasty		Laparoscopic surgery*	
Major trauma		Transurethral or other low risk urological procedures [†]	
		Vascular surgery*	

*Based on low or moderate level evidence [†] Based on high level evidence

Recommendations:

All adult patients should be assessed for risk of VTE prior to or on admission to hospital. For patients in whom the evidence for starting VTE prophylaxis seems inconclusive, senior medical staff should be consulted or reference made to an approved Drug and Therapeutics Committee hospital policy.

Step 2: Assess patient for contraindications and bleeding risk

Absolute contraindications to heparins include:^{10, 13-18}

- Known hypersensitivity to heparins
- History of, or current, heparin induced thrombocytopenia (may use danaparoid)
- Uncontrollable, active bleeding
- Creatinine clearance <30 mL/minute for fondaparinux (see page 5).

Other conditions can increase the risk of bleeding, but they do not absolutely contraindicate treatment with heparin. Where these conditions exist, the decision to prescribe heparin should be made on an individual patient basis taking risk and benefits into account. Conditions that can increase risk of bleeding with heparins include:^{8, 10, 13-18}

- Bleeding disorders eg haemophilia
- Concomitant medication use with certain medications (see page 6)
- Conditions where bleeding would be catastrophic eg focal lesions, haemorrhagic stroke
- Creatinine clearance <30 mL/minute for LMWH (see page 5)
- High risk of uncontrolled haemorrhage eg acute ulcerative conditions
- Recent surgery on eye, brain or spinal cord
- Severe thrombocytopenia (platelets <50 x 10⁹/L)
- Severe liver disease with coagulopathy and / or oesophageal varices
- Spinal needle insertion (spinal tap or spinal anaesthesia) (see page 7)
- Other conditions: acute bacterial endocarditis, arterial sclerosis, dissecting aneurysm, severe uncontrolled hypertension, diverticulitis, threatened abortion.

Bleeding risks should be explicitly asked about prior to prescribing heparins.¹⁹ In the general assessment of bleeding risk, routine coagulation screening tests have poor positive predictive value, sensitivity and specificity in predicting postoperative bleeding.¹⁹ Coagulation tests are more likely to be useful when there are clinical indications for performing the tests.²⁰

Recommendations: Prior to prescribing heparin, all patients should be asked about contraindications and bleeding risks. Coagulation tests have a poor predictive value and are more likely to be useful when there are clinical indications for performing the tests.

Step 3: Assess for special precautions

Some of the patient and procedure factors that can increase the risk of bleeding as noted above may require special precautions to be taken when prescribing heparins.^{10, 13-18} Specialist advice may be required regarding optimal choice of medication and timing of VTE prophylaxis. The following is offered as a guide to safe practice. Where there are options, individual patients circumstances should be taken into account and the DTC endorsed policy at each institution should be followed.

3.1 Renal impairment

Renal function should be assessed prior to prescription of enoxaparin or fondaparinux for VTE prophylaxis as drug-dosage adjustment is required in patients with reduced renal function (creatinine clearance (CrCl) < 30 mL/minute).^{15, 16} In patients with CrCl < 30 mL/minute recommendations for drug-dose adjustments are:

- Enoxaparin dose should be reduced to 20 mg daily¹⁵
- Fondaparinux should not be given¹⁶
- UFH can be given without dose adjustment¹⁴
- Danaparoid dose reduction should be considered¹¹
- There are no available recommendations for adjusting dalteparin doses.

Renal function can be calculated by 24-hour urine collection or by estimating glomerular filtration rate (GFR) with a formula. Commonly used formulae are:

- The Cockcroft-Gault (CG) formula using serum creatinine (SCr), weight, sex, and age. Automated calculators based on the CG formula are available in the electronic versions of the Australian Medicines Handbook (go to 'Calculators') and Therapeutic Guidelines: Antibiotic (go to Appendix 2.6))
- The Modification of Diet in Renal Disease (MDRD) formula' that uses SCr, age, sex, and race (African-American) and is adjusted to the average adult body surface area. Estimated glomerular filtration rate reporting (eGFR) using the MDRD formula is routinely reported with all SCr test results in Australia.^{21, 22} An automated calculator for eGFR is available from <http://www.kidney.org.au/HealthProfessionals/eGFRClinicalTools/tabid/632/Default.aspx>

See Box 1 (page 6) for details of these formulae.

Using renal function estimates for drug-dose adjustment

When assessing renal function it is not known which estimating formula (MDRD or CG) provides a better guide to drug-dose adjustment.²³ Recent Australian advice states MDRD eGFR can be used to guide drug-dosing decisions when no other measure of GFR is known or accessible, but is not suitable for determining drug-dose adjustments for renally cleared critical dose drugs such as LMWHs.²³ The British National Formulary states that, while eGFR using MDRD can be used for drug-dose adjustments for most drugs and patients of average build and height, for drugs with a small safety margin (such as anticoagulants) and for patients at the extremes of weight absolute GFR or CrCl should be used.¹²

Nevertheless, estimating GFR using the CG formula is consistently recommended for drug-dose adjustments, as most studies have used this formula.^{10, 22-25} The requirement for CG calculation for drug-dose adjustment may be impractical at the point of care given the potentially large number of people that require renal function estimation for the purposes of providing safe doses of anticoagulants for VTE prophylaxis.

Both MDRD and CG have limitations and these need to be taken into account when interpreting results. The MDRD and CG equations are less accurate or unreliable in people with a GFR of 60 mL/minute or greater, unusual body habitus (extremes of body size) or 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.^{21, 26} Both formulae may also perform inaccurately in certain 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 accurate.²³

One practical approach to renal function testing prior to VTE prophylaxis could be to assess all patients requiring VTE prophylaxis with the MDRD eGFR that is reported with serum creatinine results. If MDRD eGFR is <60 mL/minute then the CG formula should be used to estimate renal function before heparins are prescribed. This initial assessment with MDRD eGFR can be justified given MDRD tends to underestimate GFR in people with higher levels of renal function.²⁷ Thus a result of >60 mL/minute is likely to mean the actual renal function is greater than this. Data shows it is unlikely when GFR is assessed at > 60 mL/minute using MDRD, the CG formula would result in a GFR of < 30 mL/minute²⁴ which is the cut off for drug-dose adjustments in VTE prophylaxis. This approach may not be appropriate for other drug-dose adjustments in renal impairment.

Box 1: Formulae for estimating renal function

The Cockcroft–Gault (CG) formula

$$\text{CrCl (mL/min)} = [140 - \text{age (years)}] \times \text{bodyweight (kg)} / 0.815 \times \text{SCr (micromol/L)}$$

Weight is ideal or actual weight, whichever is lower

Multiply the value by 0.85 for females.

Ideal weight is calculated as follows:

Females 45.5 kg + 0.9 kg/cm for each cm >152 cm

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 (MDRD) formula

$$\text{MDRD eGFR (mL/min/1.73 m}^2\text{)} = 175 \times ([\text{SCr(micromol/L)/88.4}]^{-1.154}) \times (\text{age in years})^{-0.203}$$

× (0.742 if female) × (1.210 if African- American)

Recommendations:

Renal function should be assessed prior to prescription of enoxaparin or fondaparinux for VTE prophylaxis as drug-dose adjustment is required in patients with reduced renal function (creatinine clearance < 30 mL/minute). In these patients enoxaparin dose should be limited to 20 mg daily and fondaparinux should not be given. Unfractionated heparin can be given without dose adjustment. When assessing renal function it is not known which estimating formula provides a better guide to drug-dose adjustment. The Cockcroft-Gault formula is generally recommended for informing drug-dose adjustments especially for critical dose drugs with a narrow therapeutic index. Results of renal function testing should be interpreted with caution, taking into account the limitations of the formulae used.

3.2 Patients taking concomitant medications

3.2.1 Medications that may increase bleeding

Treatment with medications that may increase the risk of bleeding (see Table B) require careful management when used in combination with heparin. The decision to co-prescribe such medications with heparin should be made on an individual patient basis in consultation with senior staff taking into account patient preference. Careful monitoring is recommended.⁸ Low dose aspirin required for prevention or treatment of cardiovascular disease may be continued.¹⁰

Table B: Medications registered for use in Australia that may increase risk of bleeding.*⁸⁻¹⁰

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

*This list is not comprehensive. Refer to product information¹³⁻¹⁸ for details of other medications that may interact with heparins. [†] Low dose aspirin used for cardiovascular disease does not need to be stopped.¹⁰ [‡]NSAIDs – non-steroidal anti-inflammatory drugs. Includes selective and non-selective agents. [§]Available through Special Access Scheme

Recommendations:

Many medications including anticoagulants, antiplatelet agents, selective and non-selective non steroidal anti-inflammatory drugs, and thrombolytic agents may increase the risk of bleeding when used in combination with heparins. Decisions about appropriate concomitant use of these medications for VTE prophylaxis should be made on an individual patient basis in consultation with appropriate senior staff. Low dose aspirin required for prevention or treatment of cardiovascular disease may be continued.

3.2.2 Medications that raise potassium levels

UFH can raise potassium levels and may lead to hyperkalemia when co-prescribed with another medication that can raise potassium (see Table C). Therefore, potassium levels should be monitored where patients are prescribed UFH in combination with one of these medications.^{9, 10, 14} Raised potassium levels usually resolves when heparin therapy is stopped and treatment for hyperkalemia in this situation is generally not required.⁹

Table C: Medications registered for use in Australia that can raise potassium¹⁰

ACE* inhibitors	Angiotensin II receptor antagonists	Potassium sparing diuretics	Potassium supplements	NSAIDs†	Others
Captopril	Candesartan	Amiloride	Infusions	See Table B	Trimethoprim
Enalapril	Eprosartan	Eplerenone	Injections		
Fosinopril	Irbesartan	Spiroonolactone	Tablets		
Lisinopril	Losartan	Triamterene with hydrochlorothiazide			
Perindopril	Olmesartan				
Quinapril	Telmisartan				
Ramipril					
Trandolapril					

*ACE – Angiotensin converting enzyme †NSAIDs – non-steroidal anti-inflammatory drugs. Includes selective and non-selective agents.

Recommendations:

Potassium levels should be monitored when unfractionated heparin is prescribed with other medications that can raise potassium.

3.3 Patients in whom regional anaesthesia is planned

When heparins are prescribed for VTE prophylaxis in patients having neuraxial (spinal/epidural) anaesthesia, then extra precautions are needed due to the increased risk of epidural/spinal haematoma and associated spinal cord compression.¹⁰

Key strategies for managing anticoagulants in patients having neuraxial anaesthesia in combination with heparins are:^{5, 15, 28}

- Insertion of spinal needle or epidural catheter should occur when preoperative anticoagulation effect is minimal – 8 to 12 hours after UFH or twice daily LMWH, or 18 hours after once daily LMWH
- Needle placement should be avoided less than 2 hours after LMWH dose
- Postoperative LMWH should start 6 to 8 hours postoperatively with the second postoperative dose given no sooner than 24 hours after the first dose
- If bleeding is present during needle/catheter placement then subsequent dosing should be delayed for 24 hours
- Spinal needles or epidural catheters should be removed when anticoagulant effect is lowest
- Subsequent doses of heparins should be delayed for 2 hours after spinal needle or epidural catheter removal
- It is unknown if postoperative continuous epidural anaesthesia is safe in the presence of fondaparinux. Therefore, fondaparinux should not be administered when an epidural catheter remains in place
- 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
- The same cautions should be applied for patients receiving deep peripheral nerve blocks.

If in doubt, the decision to prescribe heparins for VTE prophylaxis should be made on an individual patient basis in consultation with anaesthetist and surgeon and other relevant specialists, taking into account patient preferences.

Recommendations:

When heparins are prescribed for VTE prophylaxis 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 and surgeon, taking into account patient preferences.**

Step 4: Select the most appropriate medication

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:

- All heparins have a similar incidence of bleeding¹⁰
- All heparins 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-Xa levels is not required for any heparin when used for VTE prophylaxis (except for danaparoid)¹⁸
- UFH is a suitable option for all patients requiring VTE prophylaxis except those with hip and knee arthroplasty and trauma.⁵ Activated partial thromboplastin time (APTT) testing is not required when UFH is given in prophylactic doses.¹⁰

Table D (page 10) summarises the key differences between heparins that can help prescribers weigh the risks and benefits for individual patients. Heparin should be prescribed for the duration recommended in clinical guidelines.²⁻⁷ Do not prescribe a heparin for VTE prophylaxis in patients at low risk of VTE (see table A).⁵ Heparin dosing for treatment of VTE or other indications may be different.

Recommendations:

Different heparins have different risk/benefit ratios. Heparins are not clinically interchangeable (unit for unit), but there is usually more than one option for each clinical indication. The choice of heparin 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; drug specific factors such as dosing schedule, risk of heparin induced thrombocytopenia (HIT), reversibility and cost.

Step 5: Determine appropriate timing of heparin administration

The timing of peri-operative heparin administration should be decided on an individual patient basis and depends 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,⁵ especially for patients admitted on the day of surgery. However the optimal timing remains unknown.²

Preoperative dosing may be appropriate for at risk patients admitted to hospital before the day of scheduled surgery. Extra caution is needed in administering preoperative VTE prophylaxis to patients undergoing major neurosurgery as bleeding may have catastrophic consequences. For neurosurgery, heparins should be started postoperatively, and for trauma, heparins should not be started until it is considered safe to do so and primary haemostasis has been established.⁵ Table E (page 11) summarises recommendations for timing of peri-operative heparin administration. Consideration should be given to continuing heparin (for those requiring preoperative heparin as per risk assessment) in surgical inpatients whose procedure is postponed while they are waiting for a rescheduled procedure.

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. For neurosurgery, heparins should be started postoperatively. For trauma patients, heparins should not be started until primary haemostasis has been established.

Step 6: Monitor the patient for adverse events

6.1 Bleeding

The main risk of heparins is bleeding, which can occur at any site. The risk and severity of heparin-related bleeding may be minimised with careful clinical management.^{8,9} Easy bruising or petechial haemorrhages may precede frank bleeding, while nose bleeding, haematuria, or melena may be the first sign of bleeding.⁸ Therefore, patients should be assessed periodically for bleeding while on any dose of heparin. Assessment for bleeding should include assessment of vital signs, clinical review of the operative site (where appropriate) and review of surgical drains and urinary, intravenous or epidural catheters. The volume and extent of blood loss should be accurately recorded on the observation chart / and or medical record and reported to the admitting team. Minor bleeding can usually be controlled by stopping heparin. More severe bleeding may require heparin reversal with protamine sulphate depending on the heparin used.⁸ See table D (page 10) for recommendations about heparin reversal.

6.2 Thrombocytopenia

In addition to their anticoagulant effect, heparins (particularly UFH and to a lesser extent LMWH) may also cause thrombocytopenia. Thrombocytopenia does not appear to be dose related.⁹ Primarily two different types of thrombocytopenia may occur:

1. A mild to moderate decrease in platelet count may occur within 1 to 4 days. This often reverses spontaneously. As long as platelet counts are greater than $100 \times 10^9/L$ heparin may be continued.¹⁴
2. Heparin-induced thrombocytopenia (HIT) is an antibody-mediated reaction resulting from irreversible aggregation of platelets. HIT is a potentially life and limb threatening condition that occurs most commonly in patients prescribed UFH and to a lesser degree in patients prescribed LMWH. Neither UFH, LMWH nor fondaparinux should be prescribed for patients who currently have, or have a history of, HIT.

HIT occurs about 4-10 days (sometimes several weeks) after starting heparin therapy. HIT may occur earlier in patients exposed to heparin in the previous 3 months.

Patients who get HIT most frequently (1-5%) include postoperative orthopaedic, cardiac and vascular surgery patients receiving UFH for 1-2 weeks. Patients who get HIT less frequently (0.1-1%) include medical and obstetric patients receiving UFH and postoperative patients receiving LMWH. Patients who get HIT rarely (<0.1%) are medical and obstetric patients receiving LMWH.²⁹

HIT is a clinicopathological diagnosis²⁹ and should be suspected if platelet counts fall below $100 \times 10^9/L$ or fall more than 50% from baseline during heparin treatment or thrombosis occurs in patients treated or recently treated with heparin.^{3, 14, 29}

Where HIT 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 in accordance with dosing protocols.²⁹

Platelets should be assessed at baseline in all patients prescribed a heparin and intermittently in the majority of patients prescribed UFH or LMWH.^{9, 29, 30} See table D (page 10) for recommendations about platelet monitoring.

We recommend that adverse events, in particular bleeding or HIT, occurring in patients prescribed a heparin for VTE prophylaxis 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 a heparin. Platelets should be assessed at baseline and intermittently in patients prescribed unfractionated heparin or low molecular weight heparin and at baseline in patients prescribed fondaparinux. HIT is a clinicopathological diagnosis. Where HIT 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.

Table D: Differences between heparins when used for VTE prophylaxis

	UFH	Dalteparin	Enoxaparin	Fondaparinux	Danaparoid
Marketed indication for VTE prophylaxis¹⁰	Prevention of VTE in surgical and high risk medical patients.	Prevention of VTE in surgical patients.	Prevention of VTE in surgical patients and in medical patients bedridden due to acute illness.	Prevention of VTE in high risk orthopaedic surgery (hip fracture, knee or hip replacement) and abdominal surgery.	Prevention of VTE in patients undergoing general or orthopaedic surgery. ¹⁸
Other accepted indications for VTE prophylaxis¹⁰	N/A	N/A	N/A	N/A	Treatment of VTE in patients with (or history of) heparin-induced thrombocytopenia.
Dosing in VTE prophylaxis	5000 units 2-3x daily depending on risk of VTE. Note: this is not the same dose required for VTE treatment.	2500 – 5000 units daily depending on risk of VTE. Note: this is not the same dose required for VTE treatment.	20-40 mg once daily depending on risk of VTE. Note: this is not the same dose required for VTE treatment.	2.5 mg once daily Use with caution in patients who weigh less than 50 kg. ^{9, 16}	750 anti-factor Xa units twice daily. ¹⁸
Unit cost	Just over \$1 per ampoule.	Approximately 4x cost per syringe compared with UFH.	Approximately 4x cost per syringe compared with UFH.	Up to 9x cost per syringe compared with UFH.	Up to 35x cost per syringe compared with UFH.
Elimination	Liver & reticuloendothelial system	Primarily renal	Primarily renal	Renal	Renal
Dosage adjustment in renal impairment	Nil required. UFH is preferred in patients with unstable or deteriorating renal function. ³¹	Unknown	Dose reduction is recommended when CrCl is <30 mL/min. ¹⁰	Do NOT use in patients with CrCl <30 mL/min. ¹⁶ Use cautiously if CrCl is 30-50 mL/min. ¹⁶	Consider dose reductions in those with a CrCl < 20 mL / min. ¹¹
Required monitoring	a) Platelet counts should be measured at baseline in all patients and repeated after 24 hours in patients who had UFH in past 100 days. ^{9, 10, 29, 30} b) Consensus* suggests monitoring platelet counts intermittently (every 2-4 days [†]) is appropriate in postoperative and medical patients receiving UFH up to 14 days or heparin stopped (whichever is earlier). ^{9, 10, 29, 30} c) Activated partial thromboplastin time (APTT) testing is not required for prophylaxis. (APTT testing is required if therapeutic doses of UFH are given). ¹⁰ d) Assess for signs of bleeding during therapy.	a) Platelet counts should be measured at baseline in all patients and repeated after 24 hours in patients who had UFH in past 100 days. ^{9, 10, 29, 30} b) Consensus* suggests monitoring platelet counts intermittently (every 2-4 days [†]) is appropriate in postoperative patients receiving LMWH up to 14 days or heparin stopped (whichever is earlier). ^{9, 10, 29, 30} c) Medical or obstetric patients receiving LMWH do not require platelet counts. ²⁹ d) Assess renal function at baseline (page 5-6). e) Assess for signs of bleeding during therapy.	a) Platelet counts should be measured at baseline in all patients and repeated after 24 hours in patients who had UFH in past 100 days. ^{9, 10, 29, 30} b) Consensus* suggests monitoring platelet counts intermittently (every 2-4 days [†]) is appropriate in postoperative patients receiving LMWH up to 14 days or heparin stopped (whichever is earlier). ^{9, 10, 29, 30} c) Medical or obstetric patients receiving LMWH do not require platelet counts. ²⁹ d) Assess renal function at baseline (page 5-6). e) Assess for signs of bleeding during therapy.	a) Monitor platelets at beginning and end of treatment. ¹⁶ No further monitoring of platelet counts is required. ²⁹ b) Assess renal function at baseline (page 5-6) and periodically. Discontinue in patients who develop labile renal function or severe renal impairment. ¹⁶ c) Assess for signs of bleeding during therapy.	a) Functional anti-factor Xa. ¹⁸ b) Assess for signs of bleeding during therapy.
Risk of HIT	Highest incidence	Lower incidence	Lower incidence	Unknown	Can be used to treat HIT. ¹⁰
Reversibility	Complete reversal with protamine sulphate. ¹⁴	Incomplete reversal with protamine sulphate – maximum 60-75%. ¹⁷	Incomplete reversal with protamine sulphate – maximum 60%. ¹⁵	Non reversible with protamine sulphate. ¹⁶	Non reversible with protamine sulphate. ¹⁸

*Based on low-level supporting evidence.^{29, 30} †Frequency of monitoring depends on risk of HIT.^{29, 30}

Table E: Recommendations for timing of peri-operative heparin administration*

	Preoperative		Postoperative		
	General anaesthesia	Regional anaesthesia	General anaesthesia	Regional anaesthesia	Neuraxial catheter removal
UFH	Commence 2 hours preoperatively.	8-12 hours prior to needle placement. ⁵	Can be started postoperatively but timing unspecified. ²	Start 6-8 hours postoperatively. ²⁸ Delay for 24 hours if haemorrhagic tap. ²⁸	Just before next scheduled dose. ⁵ Delay next dose for 2 hours. ^{5,28}
Dalteparin	5000 units: commence evening before surgery. ¹⁷ 2500 units: commence 1-2 hours preoperatively. ¹⁷	8-12 hours prior to needle placement. ⁵	Can be started postoperatively but timing unspecified. ²	Start 6-8 hours postoperatively. ²⁸ Delay for 24 hours if haemorrhagic tap. ²⁸	Just before next scheduled dose. ⁵ Delay next dose for 2 hours. ^{5,28}
Enoxaparin 20-40 mg	40 mg: commence 12 hours preoperatively. ¹⁵ 20 mg: commence 2 hours preoperatively. ¹⁵	8-12 hours prior to needle placement. ⁵	Can be started postoperatively but timing unspecified. ²	Start 6-8 hours postoperatively. ²⁸ Delay for 24 hours if haemorrhagic tap. ²⁸	Just before next scheduled dose. ⁵ Delay next dose for 2 hours. ^{5,28}
Fondaparinux	Not indicated preoperatively.	Not indicated preoperatively.	Start at least 6 hours postoperatively after haemostasis has been established. ^{5, 16}	Start at least 6 hours postoperatively after haemostasis has been established. ¹⁶ Not recommended for use when epidural catheter is in place. ⁵	Just before next scheduled dose. ⁵ Delay next dose for 2 hours. ^{5,28}
Danaparoid	Give the last preoperative dose 1-4 hours before surgery. ¹⁸	8-12 hours prior to needle placement. ⁵	Can be started postoperatively but timing unspecified. ²	Start 6-8 hours postoperatively. ²⁸ Delay for 24 hours if haemorrhagic tap. ²⁸	Just before next scheduled dose. ⁵ Delay next dose for 2 hours. ^{5,28}

* The timing of peri-operative heparin administration should be decided on an individual patient basis.

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