Guideline for Anticoagulation and Prophylaxis Using Low Molecular Weight Heparin (LMWH) in Adult Inpatients

1. Purpose
This Guideline provides recommendations regarding best practice for anticoagulation treatment and prophylaxis of venous thromboembolism for adult inpatients in Queensland Health facilities using low molecular weight heparins.

2. Scope
This Guideline provides information for all Queensland Health employees (permanent, temporary and casual) and all organisations and individuals acting as its agents (including Visiting Medical Officers and other partners, contractors, consultants and volunteers).

This Guideline takes into account the medication restrictions outlined in the Queensland Health List of Approved Medicines.

Some Hospital and Health Services may have local guidelines where differing medication restrictions are in place. These are beyond the scope of this Guideline.

3. Related documents

Authorising Policy and Standard/s:
- Queensland Health List of Approved Medicines

Procedures, Guidelines and Protocols:
- Guidelines for Anticoagulation Using Warfarin
- Guidelines for Managing Patients on Dabigatran (Pradaxa®)
- Guideline for managing patients on a factor Xa inhibitor – Apixaban (Eliquis®) or Rivaroxaban (Xarelto®)

Forms and templates:
- Statewide Heparin Intravenous Infusion Order and Administration – Adult form
4. **Guideline**

4.1 **Indications**

The low molecular weight heparins (LMWH), dalteparin and enoxaparin, are approved for use in Australia through the Therapeutic Goods Administration (TGA) and are listed on the Pharmaceutical Benefits Scheme (PBS) (see Table A).

**Table A**: TGA approvals and indications on the PBS for dalteparin and enoxaparin*

<table>
<thead>
<tr>
<th>Dalteparin</th>
<th>Enoxaparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis against thromboembolic complications in the perioperative or</td>
<td>Prevention of thromboembolic disorders of venous origin in patients</td>
</tr>
<tr>
<td>postoperative period of surgery.</td>
<td>undergoing orthopaedic and general surgery.</td>
</tr>
<tr>
<td>Prophylaxis against thrombotic complications during haemodialysis and</td>
<td>Prophylaxis of venous thromboembolism (VTE) in medical patients bedridden</td>
</tr>
<tr>
<td>treatment of acute deep vein thrombosis (DVT).</td>
<td>due to acute illness.</td>
</tr>
<tr>
<td>Extended treatment of symptomatic venous thromboembolism (VTE) (proximal</td>
<td>Prevention of thrombosis in extracorporeal circulation</td>
</tr>
<tr>
<td>deep vein thrombosis and/or pulmonary embolism) to reduce the recurrence</td>
<td>during haemodialysis.</td>
</tr>
<tr>
<td>of VTE in patients with solid tumour cancers.</td>
<td>Treatment of established deep vein thrombosis (DVT).</td>
</tr>
<tr>
<td>Treatment of unstable coronary artery disease, i.e. unstable angina and</td>
<td>Treatment of unstable angina and non-Q-wave myocardial infarction (also</td>
</tr>
<tr>
<td>non-ST-elevation myocardial infarction (also known as non-Q-wave</td>
<td>known as non-Q-wave myocardial infarction).</td>
</tr>
<tr>
<td>myocardial infarction).</td>
<td>Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI) as</td>
</tr>
<tr>
<td></td>
<td>an adjunctive to thrombolytic treatment, including patients to be managed</td>
</tr>
<tr>
<td></td>
<td>medically or with subsequent Percutaneous Coronary Intervention (PCI).</td>
</tr>
</tbody>
</table>

* Information correct as at 28 May 2014. Refer to TGA website or PBS schedule for current indications


Note: Dalteparin prefilled syringe 15,000 international units in 0.6 mL (10) and 18,000 international units in 0.72 mL (10) are only on the PBS for management of symptomatic venous thromboembolism in a patient with a solid tumour(s).

There is good evidence that LMWHs are at least as safe and effective as unfractionated heparin (UFH) for the management of VTE and acute coronary syndrome (ACS) when used appropriately. LMWHs have more predictable anticoagulant activity than UFH, and therapeutic drug monitoring is not routinely necessary.

In addition to the TGA approved indications and PBS listings, the Queensland Health List of Approved Medicines (LAM) outlines the indications and restrictions for use of dalteparin and enoxaparin in Queensland Health facilities (see Table B).
### Table B: Queensland Health List of Approved Medicines (LAM) LMWH restrictions effective 1 April 2014†

<table>
<thead>
<tr>
<th>LMWH product</th>
<th>LAM restriction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalteparin</td>
<td></td>
</tr>
<tr>
<td>prefilled syringe 2500 international units in 0.2 mL (10)</td>
<td>Specialist Staff and Country Medical Superintendents for adult use: for prophylaxis of venous thromboembolism (VTE)* and during haemodialysis.</td>
</tr>
<tr>
<td>prefilled syringe 5000 international units in 0.2 mL (10)</td>
<td>Specialist Staff and Country Medical Superintendents for adult use: for prophylaxis of venous thromboembolism (VTE)* and during haemodialysis; and treatment of VTE.</td>
</tr>
<tr>
<td>prefilled syringe 7500 international units in 0.75 mL (10) 10,000 international units in 1 mL (10) 12,500 international units in 0.5 mL (10)</td>
<td>Specialist Staff and Country Medical Superintendents for adult use: during haemodialysis; and treatment of venous thromboembolism (VTE).</td>
</tr>
<tr>
<td>prefilled syringe 15,000 international units in 0.6 mL (10) 18,000 international units in 0.72 mL (10)</td>
<td>Specialist Staff and Country Medical Superintendents for adult use for treatment of venous thromboembolism (VTE).</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td></td>
</tr>
<tr>
<td>prefilled syringe 20 mg in 0.2 mL (10)</td>
<td>Specialist Staff and Country Medical Superintendents for use in children (prophylaxis and treatment).</td>
</tr>
<tr>
<td>prefilled syringe 40 mg in 0.4 mL (10)</td>
<td>Specialist Staff and Country Medical Superintendents for prophylaxis in children and for treatment of venous thromboembolism (VTE) and acute coronary syndrome.</td>
</tr>
<tr>
<td>ampoule for IV administration 40 mg in 0.4 mL</td>
<td>Specialist Staff and Country Medical Superintendents for acute coronary syndrome and use in children.</td>
</tr>
<tr>
<td>prefilled syringe 60 mg in 1.0 mL (10) 80 mg in 0.8 mL (10) 100 mg in 1.0 mL (10)</td>
<td>Specialist Staff and Country Medical Superintendents for prophylaxis during haemodialysis in children and for the treatment of venous thromboembolism (VTE) and acute coronary syndrome.</td>
</tr>
</tbody>
</table>

† Information correct as at 1 April 2014. Refer to latest edition of LAM for current restrictions.

* Dalteparin is approved for VTE prophylaxis in surgical patients in Australia by the Therapeutic Goods Administration (TGA). Use of dalteparin for VTE prophylaxis in medical patients is currently off-label; however, its LAM listing for this indication is supported by its registration in the United States and the United Kingdom for VTE prophylaxis in medical patients, as well as its registration for VTE prophylaxis in surgical patients in Australia.

### 4.2 Contraindications

LMWH should not be used in the following patients:

- Previous heparin-induced thrombocytopenia / thrombosis (HITT).
- Known hypersensitivity or adverse reaction to LMWH (dalteparin or enoxaparin).
- Severe renal impairment [Creatinine clearance (CrCl) less than 30 mL/min] except when used as an anticoagulant during haemodialysis or for VTE prophylaxis.

- Conditions in which anticoagulation is contraindicated:
  - active bleeding
  - severe, uncontrolled hypertension (e.g. systolic blood pressure above 180 mmHg and/or diastolic blood pressure above 110 mmHg)
  - active peptic ulceration
  - abnormalities of haemostasis (e.g. thrombocytopenia, haemophilia)
  - severe liver disease.
4.3 Patients at risk of bleeding

For patients at risk of bleeding, unfractionated heparin (UFH) is recommended instead of LMWH. UFH has a much shorter half-life than LMWH and its anticoagulant effect can be reversed rapidly and completely (as opposed to only partially reversed) with protamine (section 4.3.2). UFH may also be a better choice in situations where the diagnosis or potential contraindications are unclear and where the effect may need to be reversed later.

4.3.1 Risk factors for increased sensitivity to LMWH

The following factors can predispose patients to a higher risk of bleeding during LMWH therapy (particularly during therapeutic dosing):

- renal impairment. LMWHs have a large fraction excreted unchanged and therefore the dose needs to be altered for degree of renal failure; UFH is recommended with severe renal impairment (i.e. CrCl less than 30 mL/min)
- advancing age (especially patients older than 75 years)
- conditions that make estimation of renal function unreliable such as:
  - unstable renal function (e.g. sepsis, acute renal failure)
  - dialysis-dependent patients
  - extremes of body weight
    - underweight patients (i.e. less than 50 kg), especially the elderly with low body weight
    - overweight / obese patients (i.e. greater than or equal to 105 kg), especially morbidly obese with body mass index (BMI) over 35 kg/m²
  - diseases of skeletal muscle (e.g. rhabdomyolysis)
- use of concomitant drugs that affect haemostasis (other anticoagulants, antiplatelet agents)
- recent surgery or trauma
- invasive procedures such as spinal injection or puncture (i.e. epidural analgesia or anaesthesia)
- cancer
- conditions in which anticoagulation is contraindicated (see section 4.2).

4.3.2 Management of over-anticoagulation and bleeding

For inpatients, LMWH therapy should be reviewed daily by a medical officer. If any bleeding occurs, LMWH should be withheld or stopped and consideration of the cause (including changed pharmacokinetics, drug interactions or incorrect dose) should be undertaken with appropriate action subsequently taken. If LMWH therapy is to continue, consider anti-factor Xa assay to assist with management (see section 4.7.4).

If bleeding is serious:

- Ensure adequate blood volume support and maintenance of good urine output.
- Consider protamine sulphate 1 mg per 100 units of dalteparin or 1 mg per 1 mg of enoxaparin (maximum 50 mg) by slow IV injection. Although protamine is less effective in reversing the anticoagulant effect of LMWH than UFH, it may be used to partially correct LMWH overdose (achieving up to 60% reversal of anti-factor Xa activity) in addition to supportive measures in critical clinical situations. Repeated doses of protamine sulphate may be required if ongoing bleeding.

Consider other rescue therapy measures. Consult a haematologist regarding other potential measures, such as blood products (platelets, packed red blood cells), recombinant Factor VIIa or desmopressin acetate.
4.4 Drug interactions

Close clinical monitoring is recommended (watch for signs of bleeding or anaemia) during concomitant administration of LMWH and the following agents, especially if risk factors (see section 4.3.1) are present:

- other anticoagulants* (e.g. warfarin, dabigatran, rivaroxaban, apixaban)
- antiplatelet agents (e.g. aspirin, clopidogrel, prasugrel, ticagrelor, ticlopidine, glycoprotein IIb/IIIa receptor inhibitors (e.g. abciximab, tirofiban))
- non-steroidal anti-inflammatory drugs (NSAIDs), especially long half-life agents such as naproxen, piroxicam.

* In general, there is no need to provide prophylactic anticoagulation with LMWH to someone already on anticoagulation therapy (except during initiation).

4.5 Initiating or re-starting

Before initiating or re-starting:

1. Organise baseline pathology tests (serum creatinine, full blood count, coagulation studies).
2. Obtain patient’s weight (kg) and height (cm). **Do not guess.**
3. Calculate patient’s baseline creatinine clearance (CrCl) as per Cockcroft-Gault equation. **Do not use eGFR** for LMWH dosing. However, CrCl can be calculated using the Medication Dosing Calculator available via desktop icon on Queensland Health computers or via QHEPS.
4. Check for contraindications (see section 4.2).
5. Check for co-prescribed or recently administered antiplatelet agents or anticoagulants (e.g. LMWH doses given in emergency department or at a referring hospital, IV heparin infusion, VTE prophylaxis medication, doses in the stat section on the front of the medication chart).
6. Assess risk factors for altered pharmacokinetics and increased risk of bleeding.

4.5.1 Switching from LMWH to heparin and vice versa

Table C: Switching from LMWH to heparin and vice versa

<table>
<thead>
<tr>
<th>Changing from</th>
<th>Changing to →</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin IV</td>
<td>Dalteparin or enoxaparin subcutaneous</td>
<td>Heparin IV (refer to statewide Heparin Intravenous Infusion Order and Administration Form – Adult) Wait 1 to 2 hours</td>
</tr>
<tr>
<td>Dalteparin or enoxaparin subcutaneous</td>
<td>Start when next dose is due (minimum 10 hours) without bolus</td>
<td></td>
</tr>
<tr>
<td>Heparin subcutaneous</td>
<td>As soon as diagnosis is made</td>
<td>As soon as diagnosis is made</td>
</tr>
<tr>
<td>Dalteparin or enoxaparin subcutaneous</td>
<td>As soon as diagnosis is made</td>
<td>Seek specialist advice*</td>
</tr>
</tbody>
</table>

* Dose adjustment may be needed depending on when last dose of prophylactic LMWH was administered.
4.6 Dosing

4.6.1 Therapeutic anticoagulation

Dose according to actual body weight (rounded down to the nearest 10 kg) and renal function as detailed in Tables D and E (see also the Medication Dosing Calculator available via desktop icon on Queensland Health computers or via QHEPS). Note the product strengths available on the Queensland Health List of Approved Medicines (see Table B, section 4.1).

For patients with extremes of body weight (i.e. less than 50 kg or BMI greater than 35 kg/m²), UFH is recommended instead of LMWH. Obese patients exhibit variable subcutaneous absorption of LMWH and the optimal dosing method for these patients has not been established. The practice of dose ‘capping’ for obese patients may not be appropriate. If LMWH is required for obese patients, anti-factor Xa monitoring is recommended.

For patients being commenced on warfarin for long-term anticoagulation, refer to Guidelines for anticoagulation using warfarin (copies available at end of patient bed chart or on QHEPS). For deep vein thrombosis or pulmonary embolism warfarin should be initiated at the same time as, or shortly after commencement of, LMWH therapy and should overlap for a minimum of five days and until the International Normalised Ratio (INR) has been in target range for at least two consecutive days. Warfarin should not be initiated prior to LMWH therapy.

Treatment of Venous Thromboembolism (VTE)

Dosing recommendations for treatment of VTE with dalteparin or enoxaparin are outlined in Table D taking into account renal function. Caution should be taken if using LMWH with moderate renal impairment (CrCl 30–50 mL/min).
Table D: Treatment of Venous Thromboembolism (VTE)

<table>
<thead>
<tr>
<th>CrCl (Cockcroft-Gault)</th>
<th>Dosing for therapeutic anticoagulation</th>
</tr>
</thead>
</table>
| Greater than 50 mL/min (normal renal function) | Dalteparin 100 units/kg subcut every 12 hours*  
OR  
Enoxaparin 1 mg/kg subcut every 12 hours OR 1.5 mg/kg subcut every 24 hours  
(NB: the 24-hourly regimen is **not recommended** for inpatients or for high risk patients) |
| 30–50 mL/min (moderate renal impairment) Continue monitoring renal function and anti-factor Xa levels* | Dalteparin 100 units/kg subcut every 12 hours*  
OR  
Enoxaparin 1 mg/kg subcut every 12 hours |
| Less than 30 mL/min (severe renal impairment) | **LMWH not recommended.** Use UFH (refer to statewide Heparin Intravenous Infusion Order and Administration Form – Adult). If intravenous access is not possible, discuss with consultant |
| BMI greater than 35 kg/m² and CrCl greater than 30 mL/min | **LMWH not recommended.** Use UFH  
If treatment with LMWH is necessary:  
Dalteparin 100 units/kg subcut every 12 hours (seek specialist advice if calculated dose is greater than 15,000 units). Monitor anti-factor Xa levels as per Section 4.7.4  
OR  
Enoxaparin 1 mg/kg subcut every 12 hours (seek specialist advice if calculated dose is greater than 150 mg). Monitor anti-factor Xa levels as per Section 4.7.4 |

* Refer to section 4.7.2 regarding monitoring with renal impairment. Use intravenous UFH if anti-factor Xa measurements are unavailable or renal function is unstable (e.g. acute kidney failure) and in dialysis-dependent patients. Intravenous UFH should also be strongly considered where eGFR may be inaccurate such as diseases of skeletal muscle, severe liver disease, extremes of body weight (especially the elderly with low body weight).

# For cancer patients -  
Month 1: Dalteparin 200 units/kg subcut once daily for 30 days (max daily dose 18,000 units)  
Months 2–6: Dalteparin 150 units/kg subcut once daily (max daily dose 18,000 units).

**Treatment of Non-ST Elevation Myocardial Infarction (NSTEMI)**

Review current medication list in case patient is already on treatment doses of anticoagulant. If the patient is not already on an anticoagulant, use enoxaparin **plus** dual antiplatelet therapy. Anticoagulation is continued until revascularisation (if performed). For patients treated conservatively anticoagulation should be given for at least 48 hours, or for the duration of hospitalisation up to eight days. Management of anticoagulation at the time of angiogram and vascular access should be guided by local protocols. Anticoagulation is usually discontinued after revascularisation / percutaneous coronary intervention (PCI) unless specified by the operator.

Dosing recommendations for treatment of NSTEMI with enoxaparin is outlined in Table E taking into account renal function. Caution should be taken if using LMWH with moderate renal impairment (CrCl 30–50 mL/min). Current evidence for use of dalteparin in acute coronary syndrome is limited and therefore, enoxaparin is the LMWH of choice.
Department of Health: Anticoagulation and prophylaxis using LMWH in adult inpatients

Table E: Treatment of Non-ST Elevation Myocardial Infarction (NSTEMI)

<table>
<thead>
<tr>
<th>CrCl (Cockcroft-Gault)</th>
<th>Dosing for therapeutic anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than 50 mL/min (normal renal function)</td>
<td>Enoxaparin 1 mg/kg subcut every 12 hours</td>
</tr>
<tr>
<td>30–50 mL/min (moderate renal impairment) Continue monitoring renal function and anti-factor Xa levels.*</td>
<td>Enoxaparin 1 mg/kg subcut every 12 hours</td>
</tr>
<tr>
<td>Less than 30 mL/min (severe renal impairment)</td>
<td>LMWH not recommended. Use UFH (refer to statewide Heparin Intravenous Infusion Order and Administration Form - Adult). If intravenous access is not possible, discuss with consultant</td>
</tr>
</tbody>
</table>

* Refer to section 4.7.2 regarding monitoring with renal impairment. Use intravenous UFH if anti-factor Xa measurements are unavailable or renal function is unstable (e.g. acute kidney failure) and in dialysis-dependent patients. Intravenous UFH should also be strongly considered where eGFR may be inaccurate such as diseases of skeletal muscle, severe liver disease, extremes of body weight (especially the elderly with low body weight).

**Treatment of ST Elevation Myocardial Infarction (STEMI)**

**Thrombolysis (pharmacoinvasive strategy)**

Give enoxaparin between 15 minutes before and 30 minutes after the start of thrombolytic treatment. Anticoagulation is generally given in addition to dual antiplatelet therapy—refer to local protocols. Check renal function prior to starting, then dose enoxaparin according to patient’s age as follows:

- Patients younger than 75 years, 30 mg IV bolus plus 1 mg/kg subcut, then 1 mg/kg subcut every 12 hours. Maximum dose of 100 mg for each of the first two doses (refer to enoxaprin doses in Table D for subsequent doses).
- Patients older than 75 years, 0.75 mg/kg subcut every 12 hours. Maximum dose of 75 mg for each of the first two doses.

Anticoagulation is recommended in STEMI patients treated with thrombolytics until revascularisation (if performed) or for the duration of hospital stay up to eight days.

The majority of patients with STEMI will undergo inpatient coronary angiogram preferably 3–24 hours following thrombolysis (pharmacoinvasive strategy). Management of anticoagulation at the time of coronary angiogram and vascular access should be guided by local protocols and the operating interventional cardiologist. Anticoagulation is usually discontinued after revascularisation / PCI unless specified by the operator.

**Primary percutaneous coronary intervention (primary PCI)**

For patients presenting with STEMI and referred for urgent primary PCI, a bolus dose of intravenous heparin (typically 70–100 units/kg up to 5000 units) should be administered in combination with loading doses of dual antiplatelet therapy as per local protocols.

Enoxaparin should **not** be administered to patients referred from primary PCI.
4.6.2 Venous thromboembolism (VTE) prophylaxis

Every hospitalised patient should be risk assessed for VTE on admission and at regular intervals. Refer to locally endorsed VTE prophylaxis guidelines or guidelines recommended for use by the Hospital and Health Service (e.g. National Health and Medical Research Council VTE prophylaxis guidelines or Prevention of Venous thromboembolism: Summary of Best Practice Recommendations for Australia and New Zealand) for consideration of appropriate prophylaxis options and duration. Table F outlines VTE prophylaxis dosing and duration for LMWH only. Where LMWH is indicated for VTE prophylaxis, the Queensland Health List of Approved Medicines lists dalteparin, with use of enoxaparin reserved for children.

Table F: LMWH Prophylaxis of Venous Thromboembolism (VTE)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing for VTE prophylaxis</th>
</tr>
</thead>
</table>
| Risk of thrombosis (e.g. surgery, especially procedures associated with high risk of thrombosis such as abdominal, pelvic, thoracic, orthopaedic, major joints or curative surgery for cancer; prolonged surgery and/or immobilisation; previous VTE) | Dalteparin 5000 units subcut once daily for 5–10 days or until mobilised  
May be continued up to five weeks after hip replacement surgery  
OR  
Enoxaparin 40 mg subcut once daily for 7–10 days or until mobilised  
May be continued up to four weeks after total hip replacement |
| Renal impairment (creatinine clearance less than 30 mL/min)               | Dalteparin 2500 units subcut once daily  
OR  
Enoxaparin 20 mg subcut once daily |
| Total body weight less than 50 kg                                        | LMWH not recommended. Use UFH |
| Total body weight greater than 105 kg                                     | If LMWH necessary, consider appropriate dose taking into account body weight and BMI. Seek specialist advice if BMI is greater than 35 kg/m² |

* Dalteparin is the preferred LMWH for VTE prophylaxis due to its lower cost and similar efficacy compared to enoxaparin. Use of dalteparin for VTE prophylaxis in medical patients is currently off-label; however, its LAM listing for this indication is supported by its registration in the United States and the United Kingdom for VTE prophylaxis in medical patients, as well as its registration for VTE prophylaxis in surgical patients in Australia.

Routine anti-factor Xa monitoring is not recommended for patients on LMWH for VTE prophylaxis. If any significant bleeding occurs, LMWH should be stopped and urgent consultant review organised.

4.7 Monitoring

4.7.1 Clinical review

LMWH therapy should be reviewed daily by a medical officer. If any bleeding occurs, the LMWH should be withheld or stopped and urgent consultant review organised (see section 4.3.2). Consider anti-factor Xa assay to assist with management (see section 4.7.4).
4.7.2 Renal function

As it is a significant risk factor for bleeding, renal function should be assessed at baseline and regularly throughout treatment, especially if moderate renal impairment (i.e. CrCl 30–50 mL/min). Consider anti-factor Xa assay to assist with management of patients with renal impairment (see section 4.7.4), especially for prolonged treatment (more than five days). Therapeutic anticoagulation with LMWH is not recommended in patients with unstable renal function or severe renal impairment (i.e. CrCl less than 30 mL/min)—use unfractionated heparin (UFH) instead. Use UFH if anti-factor Xa measurements are unavailable or renal function is unstable (e.g. acute kidney failure) and in dialysis-dependent patients. Intravenous UFH should also be strongly considered where eGFR may be inaccurate such as diseases of skeletal muscle, severe liver disease, extremes of body weight (especially the elderly with low body weight).

4.7.3 Platelets

Platelet count should be measured during LMWH treatment to monitor for heparin-induced thrombocytopenia / thrombosis (HITT). HITT is a rare (less than 1%) but well-recognised and potentially fatal complication of heparin therapy, usually occurring within 5–10 days after the start of therapy (may occur earlier if patient has been exposed to heparin within the last three months). Although the frequency of HITT is three-fold less with LMWHs than with UFH, monitoring is still recommended. Platelet count should be measured at baseline and then three times weekly from day 4 through to day 14, or until LMWH therapy is stopped (whichever occurs sooner). A platelet count drop of 30%–50% below baseline may indicate HITT. The diagnosis is confirmed with a positive serological test for specific heparin-associated antiplatelet antibodies. If HITT is suspected, cease LMWH and substitute an alternative anticoagulant agent (e.g. danaparoid) in consultation with a haematologist. If HITT is confirmed, this should be carefully documented and future use of UFH or LMWH avoided.

4.7.4 Anti-factor Xa assay for therapeutic anticoagulation

To assist with management of therapeutic anticoagulation, LMWH therapy may be monitored using an anti-factor Xa assay (reported as *Clexane assay* or *Fragmin assay* in AUSLAB / AUSCARE). Anti-factor Xa monitoring is not routinely necessary, but should be considered to guide dosing for certain patient groups including:

- pregnancy (NB: LMWH are Category C)
- renal impairment (CrCl less than 50 mL/min)—start monitoring within 48 hours
- extremes of body weight (as CrCl may be inaccurate)
  - underweight patients (less than 50 kg, especially the elderly with low body weight)
  - obese patients (greater than or equal to 105 kg, especially the morbidly obese [BMI over 35 kg/m²])
- prolonged treatment (more than five days), especially in patients with moderate renal impairment (i.e. CrCl 30–50 mL/min)
- thromboembolic event despite therapeutic anticoagulation (consider HITT)
- paediatrics (NB: safety and efficacy of LMWH in children has not been established).
Anti-factor Xa monitoring process

Steps for organising anti-factor Xa levels are:
- wait until the patient has received at least two doses of LMWH before collecting blood for anti-factor Xa monitoring
- blood should be collected four hours after a subcutaneous dose for a peak level
- use blue top (citrate) blood collection tubes
- arrange for levels during normal haematology laboratory hours (e.g. for a patient receiving doses at 0800 hours and 2000 hours, arrange a level for 1200 hours rather than 2400 hours)

Therapeutic ranges for anti-factor Xa monitoring are shown in Table G.

Table G: Therapeutic ranges for anti-factor Xa monitoring*

<table>
<thead>
<tr>
<th>LMWH</th>
<th>Therapeutic range</th>
<th>Target level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalteparin</td>
<td>0.5 to 1 units/mL peak level for 100 units/kg twice daily dosing</td>
<td>0.75 units/mL</td>
</tr>
<tr>
<td></td>
<td>1 to 2 units/mL peak level for once daily dosing (cancer patients)</td>
<td>1.5 units/mL</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>0.5 to 1 units/mL peak level for 1 mg/kg twice daily dosing</td>
<td>0.75 units/mL</td>
</tr>
<tr>
<td></td>
<td>1 to 2 units/mL peak level for 1.5 mg/kg once daily dosing in patients with normal renal function</td>
<td>1.5 units/mL</td>
</tr>
</tbody>
</table>

* These therapeutic ranges and target levels are not clearly defined in literature. They have been based on expert clinical consensus following review of available literature at the time of last review.

Dosing adjustments are based on the following equation:

\[
\text{New dose (mg)} = \frac{\text{current dose (mg) × target level}}{\text{current peak level}}
\]

Therapeutic range depends on indication, in addition to which LMWH and dosing regimen is used. Further advice on dose adjustment can be sought by discussion with consultant, haematologist or clinical pharmacist.

4.8 Peri-operative management

LMWH should be ceased before procedures associated with high risk of bleeding including cardiac surgery, neurosurgery, abdominal surgery, surgery involving a major organ, or in major surgery where complete haemostasis is required. Other procedures such as spinal / epidural anaesthesia may require complete haemostasis. Consult local guidelines or seek specialist advice (e.g. surgical, haematology, cardiology). Patient factors associated with an increased risk of bleeding are detailed in section 4.3.1.

4.8.1 Semi-acute, elective or minor procedure / surgery

- Assess the risk of bleeding (according to type of surgery and patient factors) against the risk of thrombosis as LMWH may not need to be discontinued for minor procedures.
- If there is a high risk of thrombosis, consider bridging anticoagulant therapy with UFH.
- If LMWH needs to be withheld, plan ahead. The risk of excessive bleeding during surgery is increased for up to 36 hours after LMWH administration, and protamine can only partially reduce this risk.
4.8.2 Urgent invasive procedure/surgery
- Stop LMWH. Refer to relevant local VTE prophylaxis guidelines if available.
- Consider delaying surgery, if appropriate, for up to 24–36 hours.
- Where surgery cannot be delayed, cross-match blood and consult with haematology regarding measures to control bleeding prior to and during surgery (refer to section 4.3.2 for management of bleeding).

4.8.3 Re-starting LMWH after surgery
- Decision to re-start LMWH after surgery depends on many factors including risk of bleeding versus thrombosis, treatment versus prophylaxis, haemostasis after surgery, type of anaesthetic and epidural.
- For patients undergoing minor procedures associated with a low risk of bleeding, LMWH therapy can usually be resumed 24 hours post-procedure.
- For patients undergoing major surgery or procedures with a high risk of bleeding, treatment doses of LMWH should be delayed for 48–72 hours after haemostasis has been secured.
- If the patient requires treatment doses of LMWH and there is a high risk of thrombosis, consider bridging anticoagulant therapy with UFH.

5. Review
This Guideline is due for review on: 1 July 2017
Date of Last Review: 27 May 2014
Supersedes: Queensland Health Dosing and Monitoring Guidelines for Enoxaparin 2008

6. Business Area Contact
Medicines Regulation and Quality
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Phone: 07 3328 9818
7. **Definitions of terms**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition / Explanation / Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS</td>
<td>Acute coronary syndrome</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>CrCl</td>
<td>Creatinine clearance</td>
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<tr>
<td>DVT</td>
<td>Deep vein thrombosis</td>
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<tr>
<td>HITT</td>
<td>Heparin induced thrombocytopenia / thrombosis</td>
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<tr>
<td>INR</td>
<td>International normalised ratio</td>
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<tr>
<td>LAM</td>
<td>Queensland Health List of Approved Medicines</td>
</tr>
<tr>
<td>LMWH</td>
<td>Low molecular weight heparin</td>
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<tr>
<td>NSAIDs</td>
<td>Non-steroidal anti-inflammatory drugs</td>
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<tr>
<td>NSTEMI</td>
<td>Non-ST elevation myocardial infarction</td>
</tr>
<tr>
<td>PBS</td>
<td>Pharmaceutical Benefits Scheme</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
</tr>
<tr>
<td>STEMI</td>
<td>ST elevation myocardial infarction</td>
</tr>
<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration</td>
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<tr>
<td>UFH</td>
<td>Unfractionated Heparin</td>
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<tr>
<td>VTE</td>
<td>Venous thromboembolism</td>
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</tbody>
</table>

8. **Approval and Implementation**

**Policy Custodian:**
Dr Sue Ballantyne  
Director, Medicines Regulation and Quality

**Approving Officer:**
Dr Jeannette Young  
Chief Health Officer

**Approval date:** 27 May 2014  
**Effective from:** 1 July 2014
Disclaimer
This guideline has been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach.

Information in this guideline is current at time of publication.

The Department of Health, Queensland Government does not accept liability to any person for loss or damage incurred as a result of reliance upon the material contained in this guideline.

Clinical material offered in this guideline does not replace or remove clinical judgement or the professional care and duty necessary for each specific patient case.

Clinical care carried out in accordance with this guideline should be provided within the context of locally available resources and expertise.

This guideline does not address all elements of standard practice and assumes that individual clinicians have the responsibility to:

- Discuss care with consumers in an environment that is culturally appropriate and which enables respectful confidential discussion. This includes the use of interpreter services where necessary.
- Advise consumers of their choice and ensure informed consent is obtained.
- Provide care within scope of practice, meet all legislative requirements and maintain standards of professional conduct.
- Apply standard precautions and additional precautions as necessary, when delivering care.
- Document all care in accordance with mandatory and local requirements.

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