Low molecular weight heparins and heparinoids

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ABSTRACT

- Several low molecular weight (LMW) heparin preparations, including dalteparin, enoxaparin and nadroparin, as well as the heparinoid danaparoid sodium, are approved for use in Australia.
- LMW heparins are replacing unfractionated heparin for the prevention and treatment of venous thromboembolism and the treatment of non-ST-segment-elevation acute coronary syndromes.
- The advantages of LMW heparins over unfractionated heparin include a longer half-life (allowing once-daily or twice-daily subcutaneous dosing), high bioavailability and predictable anticoagulant response (avoiding the need for dose adjustment or laboratory monitoring in most patients), and a low risk of heparin-induced thrombocytopenia and osteoporosis.
- Laboratory monitoring of LMW heparin therapy should be considered in newborns and children, patients with renal impairment, those who are pregnant, and those at the extremes of bodyweight (eg, < 40 kg or > 100 kg).
- LMW heparins should:
  - be avoided or used with caution in patients undergoing neuraxial anaesthesia, owing to the potential for epidural haematoma formation;
  - not be used (ie, are contraindicated) in patients with immune heparin-induced thrombocytopenia, as they may cross-react with anti-heparin antibodies.
- Conventional unfractionated heparin retains a role in the management of patients at high risk of bleeding, undergoing invasive procedures, and patients with renal failure owing to its shorter half-life, reversibility with protamine sulfate, and extrarenal metabolism.
- The heparinoid danaparoid sodium is effective for the treatment of heparin-induced thrombocytopenia.

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UNFRACTIONATED HEPARIN has been used in clinical practice for more than 50 years and is established as an effective parenteral anticoagulant for the prevention and treatment of various thrombotic disorders. However, low molecular weight (LMW) heparins have recently emerged as more convenient, safe and effective alternatives to unfractionated heparin (Box 1).[1] In Australia, LMW heparins are replacing unfractionated heparin for preventing and treating venous thromboembolism and for the initial treatment of unstable acute coronary syndromes. The LMW heparinoid danaparoid sodium is widely used to treat immune heparin-induced thrombocytopenia.

Limitations of unfractionated heparin

Most of the limitations of unfractionated heparin are explained by its non-specific binding to cell surfaces and plasma proteins.[2]

Unpredictable anticoagulant response: Unfractionated heparin binds non-specifically to macrophages, endothelial cells and plasma proteins, which causes it to have complex dose-dependent pharmacokinetics and an unpredictable anticoagulant effect. Further, the bioavailability of unfractionated heparin is reduced when it is given by subcutaneous compared with intravenous injection. Therefore, therapeutic doses of unfractionated heparin must be closely monitored, with dose adjustment according to the results of the activated partial thromboplastin time (APTT).[2]

Heparin resistance: Non-specific binding of unfractionated heparin to plasma proteins is the most common cause of "heparin resistance", defined as requiring a dose in excess of 35 000 IU over 24 hours to prolong the APTT into the therapeutic range.[3]

Heparin-induced thrombocytopenia: Immune heparin-induced thrombocytopenia occurs in 1%–3% of patients treated with unfractionated heparin, and is caused by binding of unfractionated heparin to platelet factor-4, which induces the formation of an antibody to the heparin–platelet factor-4 complex.[4] The antibody-bound heparin–platelet factor-4 complex activates platelets, causing thrombocytopenia and paradoxical thrombus extension or new venous or arterial thrombosis, usually between five and 15 days after heparin treatment is started. In some patients who develop immune heparin-induced thrombocytopenia, the platelet count may not fall until after the onset of thrombosis.

Osteopenia: Unfractionated heparin causes osteopenia by binding to osteoblasts, which stimulates osteoclast activation and results in bone breakdown. This is particularly relevant in patients requiring long-term anticoagulation therapy, who cannot be treated with oral anticoagulants, such as during pregnancy.[5]

Advantages of low molecular weight heparins over unfractionated heparin

The advantages of LMW heparins over unfractionated heparin are largely attributable to their lower molecular

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1: Profile of low molecular weight (LMW) heparins

Source	■ Derived from unfractionated heparin by chemical or enzymatic methods
	■ LMW heparin preparations may not be clinically interchangeable owing to differences in their pharmacokinetic properties and anticoagulant profiles
Action	■ Binding of LMW heparins to antithrombin accelerates the inhibition of coagulation factor Xa and thrombin about 1000-fold
	■ Unlike unfractionated heparin, which blocks thrombin and factor Xa equally well, LMW heparins primarily block coagulation factor Xa
Administration	■ Given by subcutaneous injection in a fixed, weight-adjusted dose (see Box 4 for approved indications and dosing schedules)
	■ Pregnancy category C*
Contraindications	■ Active bleeding or increased risk of bleeding
	■ Allergy (eg, pruritus, rash, urticaria) or previous immune heparin-induced thrombocytopenia
	■ Use with caution in patients undergoing neuraxial anaesthesia
Metabolism	■ Excreted by the kidneys
Laboratory monitoring	■ Routine laboratory monitoring is not necessary in most patients
	■ Patients for whom laboratory monitoring should be considered include newborns, children, patients with renal impairment, those who are pregnant, those weighing < 40 kg or > 100 kg
	■ Laboratory assays for LMW heparin (antifactor Xa activity) are generally available only in specialised coagulation study laboratories
	■ The anticoagulant activity of LMW heparins cannot be monitored using the activated partial thromboplastin time
Adverse effects	■ Bleeding
	■ Allergy
	■ Thrombocytopenia (rare)

*Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations.

weight and shorter polysaccharide chain length, which causes them to have less non-specific binding to cell surfaces and plasma proteins while retaining their ability to catalyse the inhibition of coagulation enzymes. As a result, LMW heparins can be given once or twice daily in fixed weight-adjusted subcutaneous doses without laboratory monitoring in most patients (see discussion below). They also have high bioavailability after subcutaneous injection and cause fewer adverse effects compared with unfractionated heparin — in particular, a much lower risk of heparin-induced thrombocytopenia and osteoporosis (Box 2).[2,5]

2: Advantages of low molecular weight heparins over unfractionated heparin

Reduced binding to	Clinical relevance
Macrophages, endothelial cells	Longer half-life; can be given by once- or twice-daily subcutaneous injection
Plasma proteins	Predictable anticoagulant response; avoids need for laboratory monitoring in most patients (see Box 1)
Platelets/ platelet factor-4	Lower incidence of immune heparin-induced thrombocytopenia
Osteoblasts	Lower risk of osteoporosis

Remaining advantages of unfractionated heparin

Unfractionated heparin retains a role in the treatment of patients at high risk of bleeding, or in whom rapid reversal of anticoagulation may be required. Unlike LMW heparin, unfractionated heparin has a short half-life after intravenous injection (1–2 hours), can be reversed by protamine sulfate, and plasma clearance is not dependent on renal excretion. Therefore, unfractionated heparin remains the parenteral anticoagulant of choice in intensive care units, operating theatres, and for patients with renal impairment.[6]

Clinical studies

Prevention of venous thromboembolism

Most randomised trials examining the efficacy of LMW heparins for the prevention of venous thromboembolism have used asymptomatic deep vein thrombosis as their primary outcome, as these events are much more common than symptomatic events. No thromboprophylaxis studies have shown a differential benefit of LMW heparin on fatal thromboembolism, or have examined an effect of LMW heparins on the incidence of postphlebitic syndrome.

General surgery: Meta-analyses of randomised controlled trials (RCTs) of heparin in patients undergoing general surgery indicate that heparins reduce the risk of venous thromboembolism and fatal pulmonary embolism by 50%–70% compared with controls (E1)[7,8] (for an explanation of level-of-evidence codes, see Box 3). Direct comparisons of daily LMW heparin therapy versus unfractionated heparin therapy indicate that once-daily LMW heparins are at least

as effective and safe as low-dose (eg, 5000IU, three times daily) unfractionated heparin (E1).[7,8]

Orthopaedic surgery: Among patients undergoing surgery for hip fracture or elective hip or knee replacement, LMW heparins reduce the risk of venous thromboembolism by about 50% compared with placebo[7,10-12] (E1). However, LMW heparins should be used with caution in surgical patients undergoing regional anaesthesia with an epidural catheter because of the risk of haematoma formation.

Direct comparisons of LMW heparins with unfractionated heparin in patients undergoing total hip replacement indicate that LMW heparins are more effective than low-dose unfractionated heparin, and at least as effective and safe as adjusted-dose unfractionated heparin or warfarin (E1).[10] In knee-replacement surgery, LMW heparins are superior to both low-dose unfractionated heparin and warfarin (E1).[11] There are insufficient trials directly comparing LMW heparins with unfractionated heparin in patients undergoing hip fracture surgery to be conclusive, but indirect comparisons suggest that LMW heparins and warfarin are most effective (E3).[12]

The optimal duration of thromboprophylaxis following hip or knee replacement surgery is unclear. LMW heparin given for 4–6 weeks is more effective than placebo for preventing venous thromboembolism after hospital discharge (E1), although symptomatic event rates remain low (about 3%) in patients treated with placebo.[13]

Ischaemic stroke and other medical conditions: Compared with placebo, LMW heparins reduce the risk of venous thromboembolism by about 50% in patients with immobility resulting from ischaemic stroke and in other general medical patients with risk factors for venous thromboembolism, including immobility, heart failure, severe lung disease, or malignancy (E2).[14] In patients who have had ischaemic stroke, LMW heparins appear to be more effective than unfractionated heparin for the prevention of venous thromboembolism (E1).[15] However, heparin therapy is associated with a dose-dependent increase in symptomatic haemorrhagic transformation of the cerebral infarct, which, at higher doses, may offset any antithrombotic benefit. Therefore, for patients at increased risk of haemorrhagic transformation (eg, large infarcts, uncontrolled hypertension, or other bleeding conditions), mechanical methods of thromboprophylaxis are recommended during the first two weeks after the stroke.[16] Early anticoagulation therapy should nevertheless be considered in patients with cardioembolic stroke who are at high risk for early recurrent embolism (mechanical heart valves, established intracardiac thrombus, congestive heart failure, and atrial fibrillation with multiple risk factors for thromboembolism[17]) (E3).

Treatment of venous thromboembolism

Meta-analyses of RCTs which have directly compared once-daily or twice-daily LMW heparin therapy with unfractionated heparin therapy as initial treatment for patients with venous thromboembolism, both in the hospital and at home, have shown that LMW heparins are at least as effective and safe as unfractionated heparin (E1).[18-20] LMW heparins may also be considered as an alternative to warfarin for the long-term treatment of venous thromboembolism (given once or twice daily for three to six months) in patients living in geographically isolated places, reluctant to visit the thrombosis service regularly, or with contraindications to vitamin K antagonists (E1).[21]

3: Level-of-evidence codes

Evidence for the statements made in this article is graded according to the NHMRC system[9] for assessing the level of evidence.

- E1 Level I: Evidence obtained from a systematic review of all relevant randomised controlled trials.
- E2 Level II: Evidence obtained from at least one properly designed randomised controlled trial.
- $E3_1$ Level III-1: Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
- $E3_2$ Level III-2: Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case–control studies, or interrupted time series with a parallel control group.
- $E3_3$ Level III-3: Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.
- E4 Level IV: Evidence obtained from case-series, either post-test, or pre-test and post-test.

4: Low molecular weight heparin preparations and heparinoids currently approved in Australia

Preparation (trade name [manufacturer])	Molecular weight (kDa)	Half-life (h)*
Dalteparin sodium (Fragmin [Pharmacia])	5000	3–4
Enoxaparin sodium (Clexane [Aventis])	4200	4–5
Nadroparin calcium (Fraxiparin [Sanofi])†	4500	3–4
Danaparoid sodium (Orgaran [Organon])	5500	~24

*After subcutaneous injection. †Approved for use in Australia but no longer marketed.

Acute coronary syndromes

Among patients with acute coronary syndromes without persistent ST-segment elevation who are treated with aspirin, adjunctive LMW heparin for the first 5–8 days further reduces the risk of death or myocardial infarction compared with placebo by 50%–60%, and is at least as effective and safe as unfractionated heparin (E1).[22]

Among patients with acute coronary syndromes and persistent ST-segment elevation (acute myocardial infarction) who are treated with aspirin and thrombolysis (tenecteplase, a fibrin-specific thrombolytic agent), adjunctive therapy with LMW heparin (enoxaparin) is superior to intravenous unfractionated heparin for preventing recurrent major ischaemic events and death (E2).[23]

A disadvantage of LMW heparins in patients with acute coronary syndromes undergoing percutaneous coronary interventions is its long half-life and the difficulty in reversing its anticoagulant effects. Unfractionated heparin there-

fore remains the preferred parenteral anticoagulant treatment in such patients because of its short half-life and reversibility with protamine sulfate.

Pregnancy

LMW heparins are being used increasingly in pregnant women with prosthetic heart valves and for the prevention and treatment of venous thromboembolism. Like unfractionated heparin, LMW heparins are safe for the fetus because they do not cross the placenta. However, LMW heparins are more convenient, associated with a lower risk of osteoporosis, and appear to have a similar efficacy and safety profile when compared with unfractionated heparin when used in pregnancy (E3).[5,24]

Postpartum, LMW heparins are safe because they are not secreted into breast milk. However, warfarin also does not induce a measurable anticoagulant effect in breast-fed infants and can be used postpartum.[25] Warfarin is safe to use postpartum.

Temporary discontinuation of oral anticoagulant therapy

LMW heparins have an emerging role for the management of patients receiving long-term oral anticoagulant medication who are undergoing invasive procedures that require temporary cessation of anticoagulation therapy. In the past, patients considered to be at high risk of thromboembolic complications during temporary discontinuation of oral anticoagulants required hospitalisation for several days before and after the procedure for administration of intravenous heparin. However, the availability of LMW heparins has allowed most of these patients to be managed out of hospital.

Which low molecular weight heparin preparation?

Three LMW heparin preparations are currently approved for use in Australia (Box 4). Differences in the chemical composition and anticoagulant effects of different LMW heparin preparations have led major regulatory bodies such as the Food and Drug Administration in the United States to conclude that they should be considered as individual drugs and not clinically interchangeable. However, LMW heparins also share many chemical characteristics and appear to have similar clinical efficacy and safety. The few RCTs that have directly compared the efficacy and safety of different LMW heparin preparations have been underpowered or failed to show clinically meaningful differences between them.[26] In the absence of direct comparisons, conclusions about their relative efficacy and safety rely on indirect comparisons, which are not reliable.

Based on the available evidence from RCTs, LMW heparin preparations approved for use in Australia appear to have comparable efficacy and safety for the prevention of venous thromboembolism in general and orthopaedic surgery and the treatment of deep vein thrombosis. They are also similarly effective in patients with non-ST-segment-elevation acute coronary syndromes, although only dalteparin and enoxaparin are approved for this indication (Box 5). In most other clinical settings, including the prevention of venous thromboembolism in immobilised medical patients, those with multitrauma and treatment of patients with acute myocardial infarction receiving throm-

5: Approved indications and recommended doses of low molecular weight (LMW) heparin preparations currently available in Australia

Indication	Approved preparations and doses (by subcutaneous injection)	Duration*
Prevention of venous thromboembolism		
■ General surgery		
Moderate risk†	Dalteparin, 2500 IU 1–2 h before surgery, and once daily after surgery Enoxaparin, 20 mg 2 h before surgery, and once daily after surgery	5–10 days
High risk‡	Dalteparin, 5000 IU the evening before surgery, and once daily after surgery Enoxaparin, 40 mg. Initial dose 12 h preoperatively, and once daily after surgery	5–10 days
■ Orthopaedic surgery	Dalteparin, 5000 IU the evening before surgery, and once daily after surgery Enoxaparin, 40 mg. Initial dose 12 h preoperatively, and once daily after surgery	Up to 30–35 days
■ Medical patients§	Enoxaparin 40 mg once daily	6–14 days
■ Haemodialysis¶	Dalteparin, Enoxaparin	
Treatment of venous thromboembolism		
■ Deep vein thrombosis**	Dalteparin, 100 IU/kg twice daily Enoxaparin, 1.5 mg/kg body weight once daily, or 1 mg/kg body weight twice daily	At least 5 days
■ Non-ST-segment-elevation acute coronary syndrome	Dalteparin, 120 IU/kg twice daily Enoxaparin, 1 mg/kg body weight every 12 h	5–7 days

*Approved treatment duration varies according to LMW heparin preparation. Commonly recommended treatment durations are presented. †Minor surgery in patients with additional risk factors (eg, immobility, obesity, cardiac or respiratory disease), non-major surgery in patients aged 40–60 years with no additional risk factors or major surgery in patients aged <40 years. ‡Non-major surgery in patients aged >60 years or with additional risk factors, major surgery in patients aged >40 years or with additional risk factors. §Immobile due to acute illness or physical impairment. ¶For dosing recommendations, see product information. **LMW heparins appear also to be effective and safe for the treatment of acute pulmonary embolism, but are not approved for this indication in Australia.

6: Important messages for patients

- Low molecular weight (LMW) heparins prevent the formation of blood clots in blood vessels (veins and arteries) and on heart valves.
- LMW heparins are given by injection under the skin once or twice daily.
- LMW heparins can cause minor bleeding (eg, easy bruising, gum bleeding after brushing teeth) as an undesirable adverse effect—a soft toothbrush, waxed dental floss and an electric shaver are recommended to minimise bleeding.
- Major bleeding is uncommon and allergic reactions are rare.

bolytic therapy, the best evidence exists for enoxaparin. Important messages for patients are given in Box 6.

Laboratory monitoring of low molecular weight heparins

Randomised trials have demonstrated that a fixed, weight-adjusted dose of LMW heparin can be used in most patients without the need for laboratory monitoring. However, there are limited data on LMW heparin dosing in newborns and children, patients with renal impairment, pregnancy, and those who weigh less than 40 kg or more than 100 kg. Therefore, many haematologists recommend laboratory monitoring of LMW in these patients, although this is still an uncertain area where opinions differ.

Danaparoid sodium

Danaparoid sodium is a mixture of anticoagulant glycosaminoglycans with predominant antifactor Xa anticoagulant activity. It shares many of the pharmacological properties of the LMW heparins, having high bioavailability after subcutaneous injection, a long plasma half-life, predictable anticoagulant response, and renal route of excretion.

Randomised trials have demonstrated that danaparoid sodium is effective and safe for prevention of postoperative venous thromboembolism in patients undergoing general or orthopaedic surgery[27,28] (E2), and it is approved for this indication in Australia. However, because it is substantially more expensive than other LMW heparin preparations, danaparoid sodium is rarely used for this indication. Currently, danaparoid sodium is used mainly to treat immune heparin-induced thrombocytopenia and for prevention and treatment of venous thromboembolism or arterial thrombosis in patients with a past history of immune heparin-induced thrombocytopenia[29] (E3) who cannot be treated with unfractionated or low molecular weight heparin. Although cross-reactivity with heparin antibodies has been reported *in vitro* with danaparoid sodium, the clinical significance of this finding is unclear, as the drug can be successfully used in most of these patients.

Competing interests

John Eikelboom has received honoraria for speaking at symposia sponsored by pharmaceutical companies that market LMW heparins (Pharmacia, Aventis, Sanofi-Synthelabo).

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