Dalteparin sodium in the management of thromboembolic disorders

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Low molecular weight heparins have largely replaced unfractionated heparin for the prevention and treatment of venous and arterial thromboembolic disease since they are efficacious, safe and more convenient. Dalteparin sodium (Fragmin®, Pfizer Inc.) is a low molecular weight heparin produced by controlled nitrous acid depolymerization of unfractionated heparin. Although specific indications and usage vary across countries, dalteparin has received regulatory approval for use in preventing venous thromboembolism following major abdominal and orthopedic surgery, treating acute deep vein thrombosis, and preventing recurrent venous thromboembolism in cancer patients. It is also used for the treatment of unstable coronary arterial disease and prevention of clotting of the extracorporeal system during hemodialysis. More recent research efforts have examined the potential role of dalteparin as an antineoplastic agent. Dalteparin has significantly improved and simplified the management of venous thromboembolism and will remain a very useful anticoagulant of choice, particularly in the oncology population.

Anticoagulants are the mainstay therapy for the prevention and treatment of acute arterial and venous thrombotic disorders. Unfractionated and low molecular weight heparins (LMWHs) are the standard agents for acute treatment or short-term prophylaxis, while vitamin K antagonists, such as warfarin, are used almost exclusively for long-term therapy. Although these agents are highly efficacious and have reasonable safety profiles, LMWHs are superior due to ease of use and minimal adverse effects. Consequently, this class of drugs has largely replaced unfractionated heparin (UFH) in most clinical settings and has recently been recommended as the first-line therapy over warfarin for long-term prevention of recurrent venous thromboembolism (VTE) in patients with cancer.

Overview of the market

Although LMWHs are effective and safe, their pharmacological and clinical limitations have prompted the ongoing search for the ideal anticoagulant. In contrast to traditional anticoagulants that are relatively nonspecific, novel agents are being developed to specifically target critical steps in the coagulation cascade (**Figure 1**) [1]. This approach is based on the hypothesis that specific or selective agents will reduce the risk of bleeding while preserving antithrombotic efficacy. Drugs that inhibit activated factor X (Xa) or thrombin have the most advanced clinical data.

Fondaparinux (Arixtra®, GlaxoSmithKline) is a parental synthetic pentasaccharide with potent inhibitory activity against Xa [2]. It has been shown to reduce the risk of deep vein thrombosis (DVT) by 50% compared with the LMWH enoxaparin (Lovenox®, Clexane®, Sanofi Aventis) in major arthroplasty surgery [3]. It is marketed for this indication but its use is not widespread because of a concern over a higher risk of bleeding compared with LMWH. This drug is comparable to enoxaparin for the initial treatment of DVT and to intravenous UFH for initial treatment of pulmonary embolism (PE) [4,5]. The major advantage of fondaparinux over heparins is that it does not cause drug-related thrombocytopenia. A long-acting derivative, idraparinux, is currently being investigated for long-term use [6]. The advantage offered by idraparinux is once-weekly subcutaneous injection but it lacks a specific antidote for rapidly reversing its anticoagulant activity.

Ximelagatran (Exanta®, AstraZeneca) is an oral direct thrombin inhibitor that had received approval in some countries for short-term prophylaxis in orthopedic surgery [7]. It was extensively investigated for extended use in atrial fibrillation [8] and for treatment of DVT [9,10]. These trials found an unexpected increased risk of hepatotoxicity with prolonged exposure to ximelagatran. The drug has now been withdrawn from the

Keywords: dalteparin, low molecular weight heparin, thromboprophylaxis, venous thromboembolism

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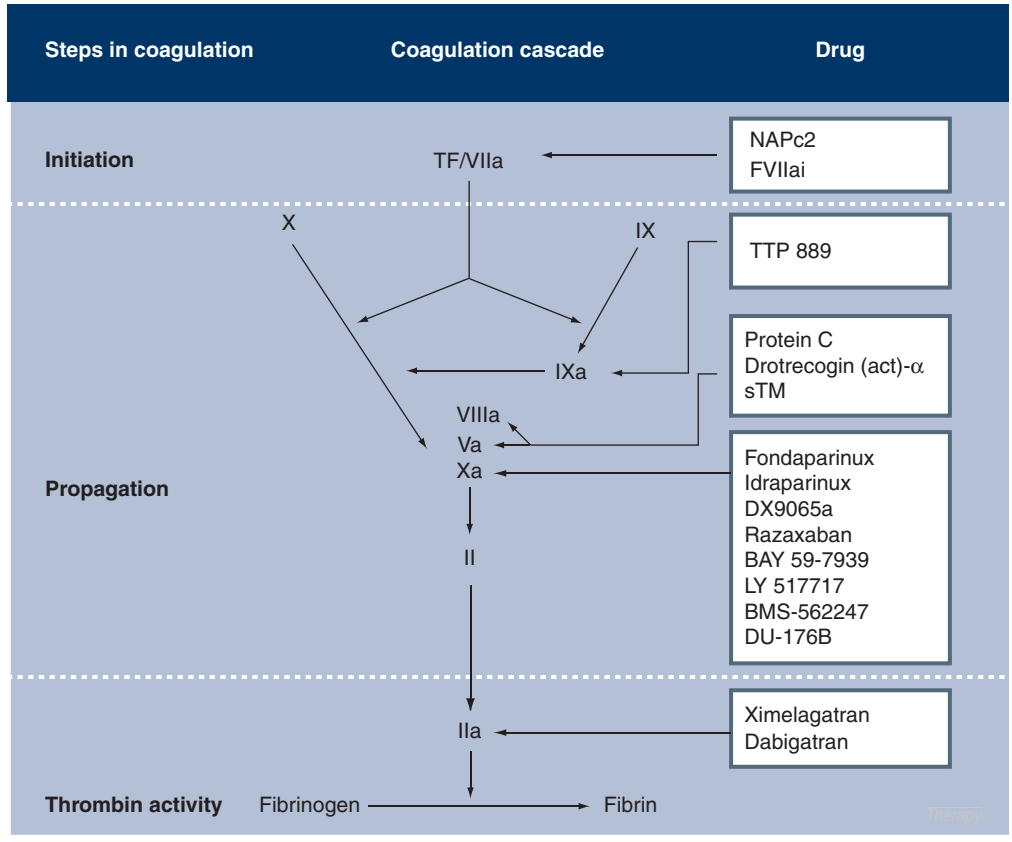
Figure 1. Sample of new antithrombotic agents in development.



TF: Tissue factor; Xa: Activated factor X.

market worldwide by the manufacturer [11]. Other promising oral direct thrombin inhibitors are in Phase II/III development.

Introduction to the compound

Dalteparin sodium is one of several LMWHs that are commercially available worldwide (**Figure 2**). Similar to all LMWHs, dalteparin is a potent anticoagulant that acts through indirect inhibition of thrombin, the key procoagulant that converts fibrinogen to fibrin [12]. Each commercially available LMWH is prepared from unique chemical or enzymatic depolymerization of porcine or bovine mucosal heparin and these manufacturing methods are considered proprietary (**Table 1**). Consequently, these agents are biologically distinct. They differ in their oligosaccharide composition and they vary considerably in their molecular weight distribution and degree of sulfation [13,14]. Such biological differences result in physiologic variability among LMWHs in their:

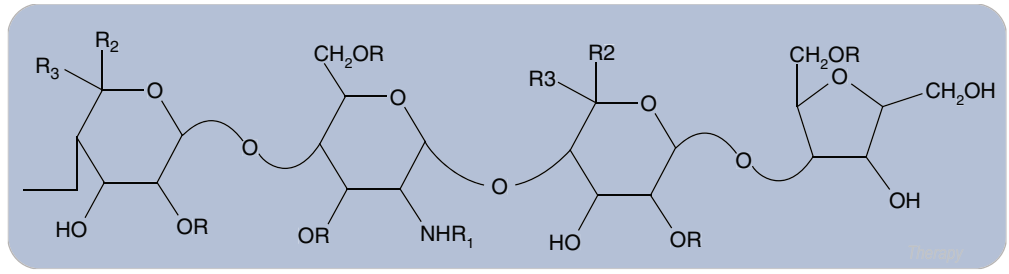
- Affinity to bind to antithrombin, heparin cofactor II, and platelet factor 4, as well as other plasma proteins
- Ability to release various mediators from the vascular endothelium
- Degree of neutralization by protamine sulfate

However, whether these differences are important clinically remains debated and large clinical trials that would be needed to compare the efficacy and safety of these agents directly are not feasible [15]. Regulatory agencies do not consider these agents to be interchangeable and country-specific indications differ for the various LMWH preparations.

Chemistry & pharmacology

Dalteparin sodium is a fractionated derivative of UFH prepared by controlled nitrous acid depolymerization of sodium heparin from porcine intestinal mucosal [16,17]. While UFH is a heterogeneous mixture of large glycosaminoglycan molecules with a mean molecular weight of 15,000 Da (with a range of 3000–30,000 Da), dalteparin is composed of strongly acidic sulfated polysaccharide chains with an average molecular weight of 5000 Da. Approximately 90% of the material, however, ranges in weight from 2000 to 9000 Da.

Figure 2. Dalteparin sodium.



The glycoaminoglycan structure is composed of alternating polymers of D-glucosamine and either gluconic or iduronic acid. The sulfur content is approximately 11% with approximately 2% sulfation/disaccharide unit [17].

Similar to UFH, dalteparin exerts its anticoagulant activity by accelerating the inhibition of activated coagulation factors by antithrombin, the major physiological anticoagulant in plasma. By binding to antithrombin via a unique, high affinity pentasaccharide sequence that is found randomly distributed along approximately 20% of the polysaccharide chains, dalteparin induces a conformational change in antithrombin that accelerates its inactivation of Xa and thrombin (factor IIa) [12]. However, since inactivation of thrombin by antithrombin requires a heparin chain of at least 18 saccharide units long to form a ternary complex between the heparin molecule, antithrombin and thrombin, dalteparin has a lower inhibitory activity against thrombin compared with UFH because of its shorter chain length (**Figure 3**). Consequently, dalteparin (like other LMWHs) predominantly inhibits Xa over thrombin. This differential inhibition of Xa and thrombin is expressed as the anti-Xa:anti-IIa ratio, which is defined as 1:1 for UFH. The anticoagulant potency of LMWHs is also described in international anti-Xa units (IU) referenced against a WHO standard [18]. This standard is currently used only for pharmaceutical purposes to assign an international unit of potency to each batch of LMWH; its clinical usefulness and correlation with pharmacologic activity remain uncertain. The specific activity of dalteparin on Xa is 130 IU/μg and its specific activity on thrombin is 58 IU/μg. This produces an anti-Xa:anti-IIa ratio of 2.2:1 for dalteparin (**Table 1**) [17]. The relative importance of inhibition of Xa and inhibition of thrombin in mediating the antithrombotic effect is unclear, but clinical studies show that specific inhibitors of Xa are comparable in efficacy to UFH and LMWH.

LMWHs also inhibit Xa activity indirectly through the induction of tissue-factor pathway inhibitor (TFPI) release from endothelial cells [13]. TFPI is an endogenous modulator of the tissue factor-VIIa complex that also binds and inactivates Xa. The degree of TFPI release varies among the different LMWHs but whether this contributes to differences in the antithrombotic potency of these agents is unknown.

In addition to stimulating the release of TFPI, dalteparin also enhances the release of prostacyclin, tissue plasminogen activator, and von Willebrand factor from vascular endothelium [13]. Dalteparin does not appear to have an effect on the fibrinolytic system and it has less lipolytic activity than UFH. It does not affect plasma antithrombin levels and release of platelet factor (PF)4.

The pharmacologic properties of dalteparin are more specific in comparison with those of UFH and are attributable to the lower affinity of dalteparin to bind to endogenous plasma proteins, endothelial cells, and macrophages. Dalteparin also binds less avidly to PF4, high-molecular-weight multimers of von Willebrand factor and osteoclasts. These differences in non-specific binding also lead to the lower risk of heparin-induced thrombocytopenia (HIT) and osteoporosis for dalteparin compared with UFH.

Pharmacokinetics, pharmacodynamics & metabolism

As for all LMWHs, the pharmacokinetic and pharmacodynamics parameters of dalteparin are conventionally expressed as the inhibitory activity on exogenous Xa rather than by the actual concentration of dalteparin in blood or target tissues. The pharmacodynamics of dalteparin can also be measured as the inhibition of factor IIa or TFPI, or the prolongation of the clotting time as determined by the Heptest. These various activities have been shown to correlate with

Table 1. Commercially available low molecular weight heparins.

Product	Company	Preparation	Molecular weight (Da) mean	$T_{½}$ (h)*‡	Anti-Xa:Anti-IIa ratio‡	Bioavailability (%)§
Ardeparin (Normiflo)	Wyeth-Ayerst	Peroxidase cleavage	6000	3.3	1.9	92
Certoparin	Novartis	Isoamyl nitrate depolymerization				
Dalteparin (Fragmin)	Pfizer	Nitrous acid digestion, chromatographic purification	5000	3–5	2.2	87
Enoxaparin (Lovenox)	Sanofi-Aventis	Benzylation and alkaline hydrolysis	4200	4.5	3.9	91
Nadroparin (Fraxiparin)	Sanofi-Aventis	Optimized nitrous acid depolymerization	4500	3.3	3.5	98
Reviparin (Clivarin)	Knoll AG	Nitrous acid digestion, chromatographic purification	4000	3.0	3.5	
Tinzaparin (Innohep)	Leo Pharma	Heparinase digestion using *Flavobacterium heparinicum*	4500	3.3	1.5	90
Heparin	Leo Pharma		11,400	1	1.0	30 (range 10–40)

**Apparent elimination half-life subcutaneously; ‡Amidolytic; §Based on anti-Xa activity*

blood concentrations of LMWHs and anti-Xa activity has become the accepted standard for measuring the anticoagulant activity of all LMWHs. It is important to emphasize, however, that this activity reflects only one of the many different physiological effects of dalteparin and other LMWHs. Consequently, true bioequivalence is not achieved even when the same anti-Xa activity is obtained with different LMWHs. In contrast to UFH, the prothrombin time (PT), activated partial thromboplastin time (APTT) and thrombin time (TT) are not affected by therapeutic doses of dalteparin and are therefore not useful for monitoring.

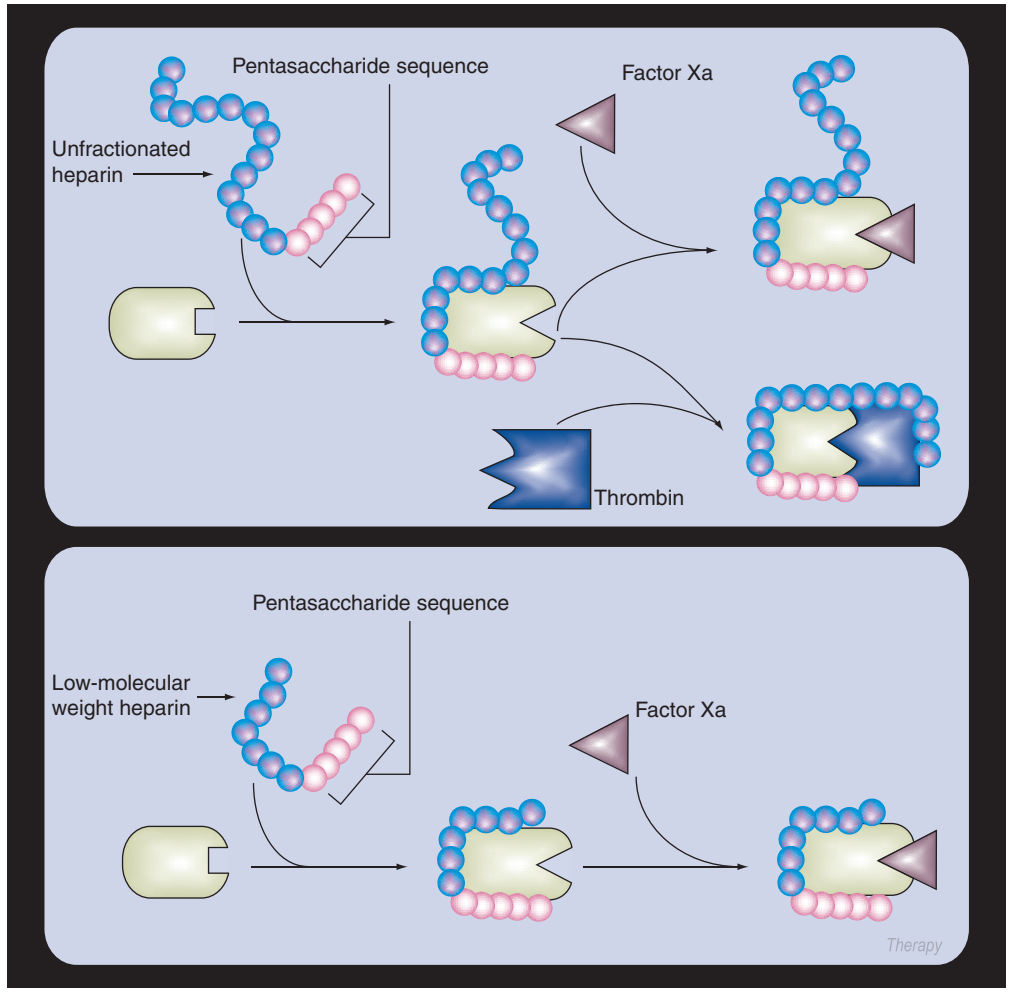
According to anti-Xa activity, dalteparin produces a predictable anticoagulant response when it is given via subcutaneous administration. This reflects its bioavailability, half-life, and dose-independent clearance via non-saturable mechanisms. After subcutaneous administration, the bioavailability of dalteparin is approximately 87%, compared with 20–30% for UFH [16]. The plasma half-life of dalteparin is 2 h after intravenous injection and 3–4 h after subcutaneous injection. The volume of distribution is approximately 40–60 l/kg and a steady-state plasma level is reached after two to four doses, based on twice-daily subcutaneous administration (100 IU/kg every 12 h). Approximately 70% is cleared by renal mechanisms via a first-order process, and the remainder is cleared by the liver [16]. Consequently, dalteparin may accumulate in patients with renal insufficiency.

Clinical efficacy

General surgery

Dalteparin has been extensively investigated for prevention of VTE in major elective abdominal surgery. Compared with placebo, dalteparin 2500 IU once-daily significantly reduces the risk of DVT by 74% (4.2 vs 15.9%; p = 0.008) [19]. Compared with UFH 5000 IU given two or three times a day, dalteparin 2500–5000 IU given once daily appears equally efficacious and safe [20]. Both heparins were usually given 1–2 h prior to surgery and continued for 5–10 days after surgery. With either agent, the incidence of DVT is approximately 4% and that of major bleeding is 3%. Most trials included patients with malignancy but few reported the results

Figure 3. Differential binding of LMWH and UFH to antithrombin and its effect on inhibition of activated factor Xa and thrombin.



LMWH: Low molecular weight heparin; UFH: Unfractionated heparin.

separately for these patients [19,21–23]. The limited data suggest that dalteparin, particularly 5000 IU once-daily, is effective in reducing venous thrombotic events in this high-risk population without increasing the risk of bleeding. In these trials, the incidence of VTE was higher in patients with cancer than those without.

Two studies have evaluated two different dosing regimens of dalteparin [22,24]. Both studies showed that dalteparin 5000 IU (given once-daily or in two equal doses) was more effective in preventing DVT than 2500 IU daily. There was a trend for a dose response in bleeding in patients without malignancy but there was no increase in bleeding in patients with cancer.

One single study has evaluated the use of dalteparin beyond discharge from hospital following major surgery for an abdominal or pelvic malignancy [25]. Following routine prophylaxis with dalteparin 5000 IU given once-daily for the first week while in hospital, patients were randomized to continue with dalteparin or no further prophylaxis. Venography was performed at 28 days after surgery. The trial was conducted in an open-label fashion but the venograms were reviewed by radiologists masked to treatment assignment. Preliminary results showed that prolonging prophylaxis with dalteparin significantly reduced the incidence of overall DVT from 19.6 to 8.8% ($p = 0.03$) and proximal DVT from 10.4 to 2.2% ($p = 0.02$).

In summary, randomized clinical trials have demonstrated that in patients undergoing major elective abdominal surgery, dalteparin given in single daily doses of 2500–5000 IU is superior to placebo and comparable to UFH 5000 IU two

or three times a day. Further studies are needed to evaluate the efficacy and safety of extended prophylaxis in patients with malignancy.

Orthopedic surgery

Dalteparin has been evaluated in randomized, controlled trials in patients undergoing major hip surgery. Similar to the regimen in major abdominal surgery, dalteparin is initiated either 2 h or the evening before surgery and then given within 4–8 h after surgery and then once-daily thereafter. The pre-operative and same-day dose is 2500 IU, while 5000 IU is recommended post-operatively. Double-blind, placebo-controlled studies have shown that dalteparin reduces the incidence of DVT by approximately 50% in patients who have undergone fractured hip repair [26] or elective hip arthroplasty [27]. It has been reported to be more efficacious than adjusted-dose warfarin (target internal normalized ratio [INR]: 2.5) but the transfusion requirement was also greater in the dalteparin group [28]. A large, double-blind trial comparing warfarin with pre- and postoperative regimens of dalteparin also found that dalteparin was more efficacious than warfarin in reducing overall and proximal DVT (11.9 vs 24%; $p < 0.001$) but there was no significant difference in efficacy between pre- and post-operative start of dalteparin [29]. Major bleeding was significantly higher for the preoperative dalteparin group compared with warfarin (8.9 vs 4.5%; $p = 0.01$) but there was no difference in bleeding between the postoperative dalteparin and warfarin groups. Also, two trials have shown no difference between dalteparin and adjusted-dose UFH in efficacy or bleeding [30,31]. Based on these studies, dalteparin is approved by the FDA for prevention of DVT in hip replacement surgery and is widely used in Canada and Europe for prophylaxis after other types of major orthopedic surgery as well.

Dalteparin has also been investigated for prevention of VTE following discharge from hospital after total hip replacement. In double-blind, placebo-controlled randomized trials, dalteparin 5000 IU once daily was found to reduce the incidence of DVT by 40–60% [32–34]. Although extended prophylaxis after major hip surgery is recommended by the American College of Clinical Pharmacy (ACCP) guidelines, regulatory approval has not be obtained for this indication [35].

Gynecological oncology surgery

The use of LMWH has also been evaluated in women undergoing surgery for gynecological malignancies in the pelvis because up to 38% of these patients may develop thrombotic complications after surgery [36]. Two randomized trials have studied dalteparin: one comparing once-daily dalteparin with UFH 5000 IU three times a day and the another dalteparin with pneumatic compression [37,38]. In both studies, dalteparin 2500 IU was given 1–2 h before surgery and was repeated at 12 h afterwards. Patients then continued to receive dalteparin 5000 IU once-daily. Both studies were small and there were very few cases of symptomatic thrombotic events. Overall, no difference in efficacy or bleeding complications was observed between treatments.

Other prophylaxis settings

A large, randomized controlled trial has demonstrated that patients hospitalized for medical reasons benefit from dalteparin for routine thromboprophylaxis. Using symptomatic VTE and DVT detected by ultrasonography as the primary outcome, the PRospective EValuation of dalteparin Efficacy for prevention of VTE in immobilized patieNts Trial (PREVENT) showed that once-daily dalteparin 5000 IU for 14 days significantly reduced the incidence of proximal DVT by 45% (5.0 vs 2.8%; $p = 0.002$) [39]. There was a low risk of bleeding (0.49%) with dalteparin. A small trial comparing dalteparin with UFH had suggested that the two agents are comparable [40]. Dalteparin has received regulatory approval in various countries for use in medical inpatients for primary prophylaxis.

Dalteparin has also been investigated in patients with acute ischemic stroke. In a small, double-blind placebo controlled randomized trial, dalteparin 2500 IU twice-daily for 14 days significantly reduced the risk of DVT (20 vs 50%; $p = 0.05$) without increasing bleeding [41].

Finally, dalteparin has been evaluated for prevention of central venous catheter-related thrombosis in patients with cancer. Although an earlier study had suggested that dalteparin 2500 IU once-daily was effective in reducing catheter-related thrombosis [42], a more recent and larger study has failed to show any difference in the incidence of symptomatic catheter-related thrombosis between patients who received dalteparin 5000 IU and those who received placebo [43]. A placebo-controlled study evaluating the efficacy of enoxaparin 40 μg once-daily also failed to show any reduction in catheter-related thrombosis in the same patient population [44], suggesting that standard prophylactic doses of LMWHs do not provide protection against catheter-related thrombosis in cancer patients.

Consequently, the ACCP now recommends that low-dose LMWH should not be used for routine prophylaxis in this setting [35].

Initial treatment of acute venous thromboembolism

A number of randomized, controlled trials have compared the relative efficacy and safety of subcutaneous dalteparin with intravenous UFH for treatment of acute DVT. Most of the studies were small and used improvements in the venographic Marder score as the primary outcome measure. These studies consistently showed that dalteparin, given as 100–120 IU/kg twice-daily or 200 IU/kg once-daily, was comparable to APTT-adjusted UFH infusion in preventing recurrent thrombosis [45–48]. Early studies also showed no significant differences in Marder score values between patients given 100 IU/kg twice-daily and those given a daily dosage adjusted to maintain the plasma anti-Xa activity at 0.5–1.0 IU/ml [49], as well as between patients who received 100 IU/kg twice-daily and those who received 200 IU/kg once-daily [50]. Consequently, the recommended treatment dose is 200 IU/kg subcutaneously once-daily. The expected anti-Xa levels achieved is more than 0.3 IU/ml before injection and less than 1.7 IU/ml 3–4 h after injection. Monitoring, however, is not required for routine treatment but it is recommended in pregnant women, patients with renal insufficiency, and children because relatively little pharmacological and clinical data are available in these populations.

Dalteparin has been shown to be efficacious and safe when given on an outpatient basis for treatment of acute DVT in several studies [51,52]. Although dalteparin is more expensive than UFH, the overall cost for treating DVT is less with dalteparin because of the reduction in hospitalization and the elimination of APTT monitoring [53,54].

A single small randomized pilot study has evaluated dalteparin 120 U/kg twice-daily against intravenous UFH for the initial treatment of submassive PE [55]. During the 10-day treatment period, there were no symptomatic recurrent events or new perfusion defects on lung scans in either treatment group.

Adequate studies directly comparing the efficacy and safety of various LMWHs for initial treatment are lacking. The limited data that compare each LMWH with UFH do suggest that LMWHs do not differ significantly in their clinical efficacy and safety [15]. Dalteparin does not have US FDA approval for the treatment of acute VTE, although it is approved and used widely in Canada and Europe for this indication.

Long-term treatment of venous thromboembolism

Although coumarin derivatives are the mainstay of long-term treatment in preventing recurrent VTE, some patients tolerate warfarin poorly. They include patients with malignancy, malabsorption syndromes and those with a high risk of bleeding. Consequently, LMWH has been investigated as an alternative to vitamin K antagonists for long-term therapy.

Three randomized trials have evaluated dalteparin for long-term therapy. The first was a small, open-label study that included patients who were unable to tolerate warfarin [56]. Patients were randomized to twice-daily injections of either dalteparin 5000 IU or UFH 10,000 U. Only 3.3% of patients presented with recurrent VTE during 3 months of follow-up and no difference was observed between the two groups. The second trial primarily included patients without cancer and found no difference in efficacy or safety between dalteparin 5000 IU once-daily and warfarin adjusted to an INR of 2.0–3.0 [57]. The third study is the largest trial investigating the use of LMWH for long-term therapy in cancer patients. The Comparison of Low-molecular-weight heparin versus Oral anticoagulant Therapy for the prevention of recurrent venous thromboembolism (CLOT) trial was a multicenter, randomized, open-label study in which 676 cancer patients with proximal DVT, PE or both were randomized to usual treatment with dalteparin initially followed by coumarin therapy or dalteparin therapy alone for 6 months [58]. In the dalteparin group, patients received therapeutic doses at 200 U/kg once-daily for the first month and then 75–80% of the full dose for the next 5 months. Over the 6-month treatment period, dalteparin significantly reduced the incidence of recurrent VTE from 17 to 9% (risk reduction 52%; $p = 0.002$). There were no differences in bleeding and overall mortality between the groups.

To date, smaller studies have evaluated the use of other LMWHs in the oncology population but none have provided results in favor of the LMWH [59–61]. Similarly, studies in primarily patients without cancer also have not shown any difference between the LMWH and warfarin for

recurrent thrombosis or bleeding evaluating. Meta-analyses of these studies suggest that LMWH is comparable to warfarin in patients without cancer [62,63].

Antineoplastic effects of dalteparin

Experimental studies have suggested that LMWHs may have anticancer effects. The mechanisms being explored include inhibition of angiogenesis, interference with tumor cell adhesion and inhibition of tumor invasion and metastasis [64,65]. Clinical data have shown that LMWHs can improve survival, particularly in patients with limited disease, but whether this benefit arises from anticoagulant or antitumour mechanisms, or both remain uncertain. It is clear, however, that activation of coagulation is criticially involved in tumor growth and progression [66–68].

The Fragmin Advanced Malignancy OUtcome Study (FAMOUS) is the first randomized, placebo-controlled trial to investigate the effect of dalteparin 5000 IU once-daily on overall survival in patients with advanced solid tumors [69]. Therapy was continued for 1 year or until death, if earlier. A trend for survival benefit was observed but it was not statistically significant ($p = 0.29$). In contrast, a small study in patients with newly diagnosed small cell lung cancer has shown a survival benefit with low-dose dalteparin [70]. In this study, patients were randomized to standard chemotherapy with or without dalteparin 5000 IU once-daily. Significant differences were seen in overall, median and progression-free survival, favoring the dalteparin group. The mechanisms for the antineoplastic effects of dalteparin are unknown, but preclinical studies have suggested that dalteparin may have antiangiogenic properties. Another LMWH, nadroparin, has also reported survival benefits in patients with noncurative solid tumors [71], suggesting that antineoplastic effects may be a property of this class of anticoagulants. Further research is needed to confirm these preliminary findings and investigate the mechanisms of action.

Acute coronary syndromes

Dalteparin was first introduced as an alternative to UFH in the late 1990s to reduce the risk of recurrent ischemic events in patients presenting with acute coronary syndrome. The FRagmin during InStability in Coronary artery disease (FRISC) trial randomized patients with unstable angina or non-Q-wave myocardial infarction (MI) in a double-blind fashion to receive placebo or dalteparin 120 IU/kg twice-daily for 6 days followed by 7500 IU once-daily for 35–45 days [72]. All patients also received aspirin 75 µg daily. The primary outcome was the incidence of death or new MI during the first 6 days. Lower rates of death and new MI were seen in the dalteparin group than in the placebo group at day 6 (1.8 vs 4.7%; $p < 0.001$), primarily due to a reduction in MI. Dalteparin also significantly reduced the need for revascularization procedures and intravenous heparin. Differences between groups were maintained at 40 days but were no longer significant at 4–5 months after the end of treatment.

Dalteparin was then compared with UFH in patients with unstable angina or non-Q-wave MI in the FRagmin In Unstable Coronary artery disease (FRIC) Study [73]. Patients were randomized to receive either intravenous UFH (dose adjusted to maintain APTT 1.5 × control) and aspirin or dalteparin (120 IU/kg twice-daily) and aspirin for 6 days. They were then subsequently randomized to treatment with placebo or dalteparin 7500 IU daily. The primary end point was the composite of death, MI or recurrent angina at the end of the acute 6-day period. A significant difference was not observed between dalteparin and UFH. In the prolonged phase, there was also no difference between dalteparin and placebo, suggesting that dalteparin did not confer additional benefit over aspirin alone.

The Fragmin and/or Early Revascularization During Instability in Coronary Artery Disease (FRISC II) study also evaluated dalteparin against placebo in a double-blind design [74]. All patients were treated with dalteparin 120 IU/kg twice-daily and aspirin 75–320 µg/day for at least 5 days and then were randomized to placebo or dalteparin 5000–7500 IU twice-daily for 90 days. The primary end point was a composite of death and MI during the double-blind 90-day treatment period. No significant difference was observed at 90 days but bleeding was increased.

Overall, the evidence from these trials suggest that dalteparin is effective and comparable to UFH in reducing ischemic outcomes in patients with unstable angina or non-Q-wave MI, but that it does not provide any added efficacy over aspirin alone beyond the first week of treatment. These results are similar to those seen in randomized trials comparing enoxaparin and UFH [75], although differences in study design precludes valid comparisons about the relative efficacy and safety of these agents.

Hemodialysis & hemofiltration

Dalteparin is used for prevention of fibrin deposition and clotting of blood in the extracorporeal circulation of patients undergoing hemodialysis and hemofiltration. It appears to be comparable to UFH for this indication [76,77]. Various regimens of dalteparin have been tested. The most common regimen for chronic renal failure is an intravenous bolus of 30–40 IU/kg followed by an infusion of 10–15 IU/kg/h. This normally produces plasma levels of 0.5–1.0 IU/ml.

Use of dalteparin in pregnancy

Dalteparin is frequently used in pregnant women for prevention and treatment of VTE, as well as for improving live birth rates in women with antiphospholipid antibody syndrome and recurrent pregnancy losses [78–80]. Large randomized trials, however, are lacking to identify the optimal regimen in these settings. Pharmacokinetic studies also have provided conflicting information on how dalteparin is metabolized during various pregnancy-related thrombosis settings but suggest that laboratory monitoring of the anti-Xa effect is essential in order to maintain therapeutic levels [81–83]. Laboratory studies also suggest various LMWHs differ in their pharmacodynamic and hemostatic profiles in pregnancy but whether such variation translate to differences in efficacy and safety is unknown [84].

Given the sensitive and difficult population, and the lack of large randomized trials in pregnancy settings, none of the LMWHs have regulatory approval for use in pregnancy.

Safety & tolerability

Dalteparin has few serious adverse effects. Besides the risk of major hemorrhage that can result from the use of any anticoagulant, dalteparin has been associated with HIT, osteoporosis, and rarely hypersensitivity. The risk of major bleeding reported with dalteparin is less than 5% in the postoperative setting and 5–10% when used in therapeutic doses. Its use is contraindicated when there is active bleeding, severe thrombocytopenia (platelet count < 50×10^9/l) and it must be used with extreme caution in conditions that predispose to serious bleeding. The use of dalteparin in patients with renal impairment is not well studied and must be monitored carefully. Prolongation of the anticoagulant effect in such patients may lead to an increased risk of bleeding even at reduced doses. Dalteparin should be used with caution in patients receiving spinal or epidural anesthesia and must be avoided within 2 h of insertion or manipulation of an indwelling epidural catheter.

Heparin-induced thrombocytopenia (HIT) is caused by the formation of antibodies directed against complexes of heparin and PF4 that form on the surface of platelets and activate their Fc receptors [85]. The true incidence of HIT associated with dalteparin and other LMWHs is not known but the incidence is much lower than that with UFH [86]. Patients with a history of HIT should not receive dalteparin.

Osteoporosis has been reported with prolonged LMWH use but the incidence is uncertain. Similar to HIT, osteoporosis with LMWH use is much lower compared with UFH use. [87] The mechanisms of action on bone turnover between LMWHs and UFH are different and favor less bone loss with LMWHs [88,89].

Dalteparin has been used successfully in pregnant women for prevention and treatment of VTE, history of recurrent fetal loss, as well as an alternative to warfarin in women with mechanical heart valves [87]. However, the experience is based largely on observational studies and very small randomized trials. LMWHs do not cross the placenta but there have been reports of congenital anomalies in infants born to women who received LMWHs during pregnancy, including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia and cardiac defects [17]. There is, however, no evidence that demonstrates an increased incidence of congenital anomalies compared to the general population or a causal relationship with LMWH exposure. Of note, the multidose vial preparation of dalteparin (25,000 IU/ml) contains benzyl alcohol (14 μg/ml) as a preservative, which has been associated with a potentially fatal 'gasping syndrome' in neonates. This can manifest as metabolic acidosis, respiratory distress, convulsions and intracranial hemorrhages. Due to the fact that benzyl alcohol may cross the placenta, this formulation of dalteparin should not be used in pregnancy women. It is not known whether dalteparin is excreted in human milk.

Like other LMWHs, the efficacy and safety of dalteparin has not been well established in children although it is used in this population for treatment of thrombotic disorders [90].

Expert commentary & outlook

Dalteparin is a LMWH with a 20-year history in the management of thrombotic disorders. It is at least as efficacious as UFH in these settings, and may be safer and more cost effective. It has a solid,

safety profile over extended periods of use and it is convenient and safe to administer on an outpatient basis. Its major limitation remains its parenteral administration and cost. It may have a future role as an antineoplastic agent but further studies are needed to explore this possibility.

The other area of clinical and research interest is the extended treatment of VTE in patients with cancer. Unlike other indications in which it has significant market competition, dalteparin is the only LMWH with strong evidence in this setting. However, it remains unknown whether the regimen identified in the CLOT trial is the optimal approach, or whether a shorter duration of dalteparin administration or a higher long-term dose would provide similar or even better results. Related to this, research is clearly needed to stratify patients with respect to the risk of recurrent VTE or bleeding while on dalteparin therapy or other anticoagulants. According to the CLOT trial, 9% of patients with cancer and VTE will experience recurrent VTE while on dalteparin and the management of such patients has not been studied.

Finally, an oral agent that does not require laboratory monitoring and has few drug interactions and low toxicity will definitely challenge all the available anticoagulants and is one that would be highly welcomed by physicians and patients. Many novel anticoagulants with these putative advantages are in late Phase II/early Phase III development. Whether any of these agents are going to provide clinicians with more options in antithrombotic management will remain unanswered until Phase III trials demonstrate evidence of superiority, or at least comparability, over traditional anticoagulants in efficacy, safety, cost and convenience.

Highlights

- Dalteparin binds to antithrombin and accelerates the inhibition of activated factor X (Xa) and thrombin.
- Its induction of tissue-factor pathway inhibitor (TFPI) release from endothelium may contribute to the antithrombotic effect.
- Dalteparin given subcutaneously has a bioavailability of 87% and achieves a peak plasma level in 2–3 h.
- Half-life is approximately 4 h and is cleared by the kidneys via a first-order dose-independent process.
- Monitoring of its anticoagulant effect can be done using anti-Xa levels taken at 3 h after a subcutaneous injection.
- It does not alter the prothrombin time (PT) or activated partial thromboplastin time (APTT) when administered in prophylactic or therapeutic doses.
- Dalteparin is an efficacious anticoagulant for the prevention and treatment of venous and arterial thromboembolic disorders.
- It is approved for prophylaxis after major surgery, hip replacement surgery, and medical inpatients.
- It is also approved for treatment of acute VTE and long-term treatment to prevent recurrent VTE in patients with cancer.
- It is used commonly for preventing clotting of extracorporeal circulation of patients undergoing hemodialysis and hemofiltration.
- Dalteparin has a good safety profile with few side effects.
- It is associated with a low risk of bleeding when used in the appropriate clinical situations.
- It should be used in caution in patients with renal insufficiency, pregnant women and in children because of limited data in these populations.
- Prophylaxis in general surgery: dalteparin 2500 IU is given 1–2 h before the operation and no sooner than 4 h after surgery, followed by 5000 IU subcutaneously once-daily for 5–7 days starting on the day after surgery. Alternatively, dalteparin 5000 IU is given the evening before surgery and then 5000 IU the following evenings for 5–7 days.
- Prophylaxis in elective hip surgery: dalteparin 2500 IU is given 1–2 h before the operation and no sooner than 4 h after surgery, followed by 5000 IU subcutaneously once-daily for 5–7 days starting on the day after surgery. Alternatively, dalteparin 5000 IU is given the evening before the operation and then 5000 IU the following evenings for 5–7 days.
- Prophylaxis in medical inpatients: dalteparin 5000 IU once-daily for 14 days.
- Treatment of acute deep vein thrombosis: dalteparin 200 IU/kg subcutaneously once-daily or 100 IU/kg subcutaneously twice-daily for a minimum of 5 days. Dose should be individualized in patients with renal insufficiency, pregnant women, and children.
- Unstable coronary artery disease: dalteparin 120 IU/kg twice-daily for up to 6 days.
- Extended treatment for prevention of recurrent VTE in patients with cancer: dalteparin 200 IU/kg once-daily for 30 days then approximately 150 IU/kg for subsequent 5 months.
- Hemodialysis and hemofiltration: For chronic renal failure, 30–40 IU/kg intravenous bolus injection followed by intravenous infusion of 10–15 IU/kg/h.

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