ADIS DRUG EVALUATION

Drugs 2000 Jul: 60 (1): 203-237
0012-6667/00/0007-0203/$25.00/0

Dalteparin

An Update of its Pharmacological Properties and Clinical Efficacy in the Prophylaxis and Treatment of Thromboembolic Disease

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Data Selection

Sources: Medical literature published in any language since 1996 on dalteparin, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International, Auckland, New Zealand). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'dalteparin' or 'tedelparin' or 'dalteparin sodium'. EMBASE search terms were 'dalteparin' or 'dalteparin sodium' or 'FR 860' or 'KABI 2165' or 'tedelparin'. AdisBase search terms were 'dalteparin' or 'dalteparin sodium' or 'FR-860' or 'KABI 2165' or 'tedelparin'. Searches were last updated on 19th June 2000.

Selection: Studies in patients with or at risk of thromboembolic disease or on haemodialysis/haemofiltration who received dalteparin. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Dalteparin, thromboprophylaxis, orthopaedic surgery, general surgery, pregnancy, deep vein thrombosis, pulmonary embolism, outpatient treatment, unstable coronary artery disease, myocardial infarction, haemodialysis, haemofiltration, pharmacodynamics, pharmacokinetics, pharmacoeconomics, tolerability, dosage and administration, therapeutic use.

Contents

Summary

Abstract

Dalteparin is a low molecular weight heparin (LMWH) with a mean molecular weight of 5000. Compared with unfractionated heparin (UFH), the drug has markedly improved bioavailability and increased plasma elimination half-life, and exerts a greater inhibitory effect on plasma activity of coagulation factor Xa relative to its effects on other coagulation parameters. Dalteparin also has less lipolytic activity than UFH.

Dalteparin 2500U once daily subcutaneously is of similar antithrombotic efficacy to UFH 5000IU twice daily, and 2 studies have shown superiority over UFH 2 or 3 times daily of dalteparin 5000U once daily in patients requiring surgical thromboprophylaxis. After total hip arthroplasty, dalteparin was superior to adjusted-dosage warfarin and was of greater thromboprophylactic efficacy when given for 35 than for 7 days.

Intravenous or subcutaneous dalteparin is as effective as intravenous UFH when given once or twice daily in the initial management of established deep vein thrombosis (DVT). The drug is also effective in long term home treatment.

Dalteparin has been shown to be effective in combination with aspirin in the management of unstable coronary artery disease (CAD), with composite end-point data from 1 study suggesting benefit for up to 3 months. Current data indicate potential of the drug in the management of acute myocardial infarction (MI). Dalteparin is also of similar efficacy to UFH, with a single bolus dose being sufficient in some patients, in the prevention of clotting in haemodialysis and haemofiltration circuits.

Pharmacoeconomic data indicate that overall costs relative to UFH from a hospital perspective can be reduced through the use of dalteparin in patients receiving treatment for venous thromboembolism. Dalteparin has also been shown to be cost effective when used for surgical thromboprophylaxis.

Overall, rates of haemorrhagic complications in patients receiving dalteparin are low and are similar to those seen with UFH.

Conclusions: Dalteparin is effective and well tolerated when given subcutaneously once daily in the prophylaxis and treatment of thromboembolic disease. The simplicity of the administration regimens used and the lack of necessity for laboratory monitoring facilitate home or outpatient treatment and appear to translate into cost advantages from a hospital perspective over UFH or warfarin. Dalteparin also maintains the patency of haemodialysis and haemofiltration circuits, with beneficial effects on blood lipid profiles and the potential for prophylaxis with a single bolus injection in some patients. Data are also accumulating

to show dalteparin to be an effective and easily administered alternative to UFH in patients with CAD.

Pharmacological Properties

Dalteparin inhibits coagulation factor Xa in human plasma in a dose-dependent manner, with anti-factor Xa activities 2 and 5 times those seen after an intravenous dose of UFH 5000IU being reported after intravenous doses of dalteparin 5000 and 10 000U, respectively. In contrast to UFH, anti-factor Xa activity exceeds anti-factor IIa activity in plasma of individuals who have received dalteparin. The drug also exerts significantly greater effects than UFH on plasma anti-factor Xa activity relative to its effects on other coagulation parameters [including activated partial thromboplastin time (aPTT) and thrombin time]. Dalteparin does not have any clinically relevant effects on plasma antithrombin levels, platelet counts or on the fibrinolytic system, although recent studies show inhibition of thrombin formation in patients with activated haemostatic systems.

Data from healthy volunteers and patients undergoing haemodialysis show less lipolytic activity with dalteparin than with UFH, with reductions in blood levels of total and low density lipoprotein cholesterol and triglycerides being shown with the LMWH.

Dalteparin has monoexponential, first order and dose-independent pharmacokinetic characteristics. Absorption is rate-limiting after subcutaneous administration: peak plasma concentrations (as measured by plasma anti-factor Xa activity) are attained after 2.8 to 4 hours, and the drug undergoes substantially less hepatic and renal deposition than UFH. Bioavailability is 87% and plasma elimination half-life ($t_{1/2}\beta$) 2.4 to 4 hours. $t_{1/2}\beta$ after intravenous administration is approximately 2 hours. Elimination takes place predominantly via the kidneys.

The anticoagulant effects of a number of agents (e.g. aspirin, dipyridamole, vitamin K antagonists and non-steroidal anti-inflammatory drugs) may be enhanced by coadministration with dalteparin. The anticoagulant effect of dalteparin may be reduced by the presence of antihistamines, cardiac glycosides, tetracyclines or ascorbic acid.

Therapeutic Use

Surgical Thromboprophylaxis. Randomised and double-blind studies have shown consistently that dalteparin 2500U given subcutaneously once daily for 5 to 13 days is of similar thromboprophylactic efficacy to UFH 5000IU subcutaneously twice daily in patients undergoing general or orthopaedic surgery. Two studies, one in over 800 patients undergoing general surgery and the other with a 6- to 8-week follow-up in 122 patients undergoing orthopaedic surgery, showed dalteparin 5000U once daily subcutaneously to be superior to UFH 5000IU 2 or 3 times daily.

Recent studies have shown that dalteparin 5000U once daily subcutaneously reduces the frequency of venographically evident thromboembolism to a greater extent when given for 35 days than for 7 days in patients undergoing total hip arthroplasty. In 2 double-blind studies (each involving around 200 patients), reductions in incidence of DVT relative to 7-day prophylaxis of 54 and 63% were reported after 35 days' administration. Dalteparin was also of superior thromboprophylactic efficacy to adjusted-dosage warfarin in patients undergoing total hip arthroplasty.

Two small single-blind studies have been carried out to compare dalteparin with the other LMWHs enoxaparin and nadroparin, but the results of these trials were inconclusive.

Thromboprophylaxis in Pregnancy. Dalteparin has been used successfully

with no evidence of any adverse fetal effects in pregnant women at high risk of thromboembolic complications. Dosages were adjusted according to plasma anti-factor Xa activity in these patients. There was an apparently lower risk of bleeding with dalteparin than with UFH in a nonblind comparative study in 105 patients.

Treatment of Established Thromboembolic Disease. Comparative studies have shown intravenous or subcutaneous dalteparin (given once or twice daily) to be of equivalent efficacy in terms of Marder scores and venographic findings to aPTT-adjusted intravenous UFH in patients receiving initial heparin treatment for established DVT. Six-month follow-up data from 1 study showed no significant difference in Marder scores, symptoms or thrombus evolution between patients who received dalteparin 200 U/kg once daily subcutaneously or recipients of continuously infused aPTT-adjusted UFH for 5 to 10 days. Similar conclusions were reported after up to 14 years' follow-up in patients from 3 Swedish clinical studies in which subcutaneous dalteparin adjusted according to anti-factor Xa activity had been compared with aPTT-adjusted intravenous UFH (either given for at least 5 days pending dosage titration of warfarin).

Noncomparative studies have demonstrated feasibility of initial outpatient treatment of established thromboembolic disease with dalteparin 200 U/kg once daily subcutaneously for at least 4 to 5 days. The drug was also effective and well tolerated when self-administered for 3 months at a dosage of 5000U once daily by patients not eligible for warfarin therapy. In a 3-month nonblind comparison, there was no statistically significant difference in efficacy between long term dalteparin 5000U once daily subcutaneously and warfarin in 86 patients with thromboembolic disease.

Coronary Artery Disease. Dalteparin 7500U once daily subcutaneously plus aspirin (n = 562) was of similar efficacy to aspirin alone (n = 561) in terms of a composite end-point of death, MI or recurrence of angina over 39 days of double-blind placebo-controlled treatment in a study in patients with unstable CAD. Equivalence of dalteparin 120 U/kg twice daily subcutaneously and aPTT-adjusted UFH infusion (in terms of rates of death or MI, need for coronary revascularisation or recurrence of angina) was suggested by the results of an initial 6-day nonblind phase in 1482 patients.

In the first of 2 randomised double-blind studies carried out by the Swedish Fragmin and Fast Revascularisation in Coronary Artery Disease (FRISC) study group, significantly lower rates of death and new MI and reduced need for revascularisation or intravenous heparin were reported after 6 days' treatment with dalteparin 120 U/kg subcutaneously twice daily (n = 746) than with placebo (n = 760). Subgroup analyses suggested maintenance of benefit at 40 days with dalteparin 7500 U/day in non-smokers, patients with non–Q-wave MI and those with body mass index below 26 kg/m^2. There was no significant difference from placebo after 4 to 5 months.

A second study carried out by the FRISC group in 2267 patients with unstable CAD showed a 47% decrease ($p = 0.002$) relative to placebo in a combined end-point of death and MI after the first month of a 3-month period of double-blind treatment with dalteparin 5000 or 7500U twice daily. When a triple end-point of death, MI and need for revascularisation was considered for both the 3-month double-blind treatment period and an initial 5- to 7-day nonblind phase (in which all patients received dalteparin), there were significant differences in favour of dalteparin after 1 month and 3 months. Subgroup analyses have sug-

gested a link between efficacy of dalteparin in the longer term and raised levels of the cardiac marker troponin-T.

Outcomes were not affected by dalteparin therapy in a further comparative study in which percutaneous coronary intervention was shown to be superior to non-invasive therapy in 2457 patients with unstable CAD.

In a randomised double-blind study in 517 patients with acute anterior MI, there was a statistically significant 35% reduction versus placebo in a combined end-point of left ventricular thrombus formation or arterial thromboembolism with dalteparin 150 U/kg twice daily subcutaneously for 7 to 11 days after thrombolysis with streptokinase. In another double-blind study in 101 patients with acute MI, dalteparin 100 U/kg before and 12 hours after streptokinase thrombolysis had no effect on rates of death or reinfarction or other cardiac events, although significantly fewer dalteparin than placebo recipients had ECG evidence of ischaemia from 6 to 24 hours after starting treatment. Preliminary results from a study in 1128 patients with acute MI who were not eligible for thrombolysis indicate short term (3-day) but not long term (30- or 90-day) benefit of subcutaneous dalteparin 120 U/kg twice daily.

Haemodialysis and Haemofiltration. Dalteparin was of similar efficacy to UFH in the maintenance of patency of haemodialysis and haemofiltration circuits in studies in which heparin was administered as an intravenous bolus followed by continuous infusion. Initial doses of dalteparin ranged from 2500 to 5000U; those of UFH ranged from 2000 to 5000IU. Infusions were given at fixed hourly rates or were adjusted according to bodyweight or whole blood activated clotting times. Dalteparin prevented blood clot formation in dialysers to a similar extent to tinzaparin, and was associated with similar haemofilter survival times to nadroparin, in comparative studies. Data are also available to show equivalent efficacy of a single bolus of dalteparin (given at the start of haemodialysis) and continuously infused UFH.

Ischaemic Stroke. Dalteparin has not been shown to have any significant advantage over aspirin on cerebral end-points in patients with acute ischaemic stroke. Outcomes were similar in patients treated with dalteparin 100 U/kg twice daily subcutaneously and in those receiving aspirin 160mg daily (orally or rectally) in a recent placebo-controlled double-blind trial in 449 patients with atrial fibrillation and ischaemic stroke.

Pharmacoeconomic Considerations

A retrospective comparison using results from 434 patients, 80.2% of whom received home treatment with subcutaneous dalteparin 200 U/kg once daily for initial management of established DVT, showed a 34.5% reduction relative to inpatient treatment in Swedish mean hospital and treatment costs (1996 values). Australian researchers estimated overall per-patient treatment costs (year not stated) to be reduced by $A1239 when initial DVT treatment with dalteparin 200 U/kg once daily was given at home rather than in hospital.

Canadian and Spanish data indicate overall institutional cost savings when dalteparin is used in place of UFH in the initial management of DVT in hospital. In addition, a brief pharmacoeconomic report from a UK study in 105 patients showed a £900 per-patient overall cost saving when subcutaneous dalteparin 5000U once daily rather than laboratory-adjusted warfarin therapy was given for 3 months for the prevention of recurrence of DVT.

Significantly lower rates of DVT with subcutaneous dalteparin 5000U once daily than with laboratory-adjusted warfarin for a mean 7 days translated into

similar average cost effectiveness of dalteparin and warfarin in terms of cost per event-free patient in a pharmacoeconomic analysis of 382 individuals receiving thromboprophylaxis after total hip arthroplasty. Overall costs per patient from a hospital perspective were similar under different treatment scenarios (short term (6-day) and long term (35-day) treatment started before or after surgery) for dalteparin and warfarin in a North American study in which 1130 patients were randomised to prophylaxis with either drug after total hip arthroplasty. Incremental cost effectiveness of dalteparin ranged from $US1799 to $US4661 per patient (year of costing not stated) in this analysis.

Economic data from a 9-week time and motion study in 116 patients receiving aPTT-adjusted UFH infusion for acute CAD showed costs from a hospital perspective of $Can25.68 for UFH and $Can28.82 for dalteparin 120 U/kg twice daily subcutaneously. In this analysis, costs for dalteparin therapy were estimated using a projection based on assumptions regarding resource utilisation, staff activity and acquisition cost.

Tolerability

Overall, rates of haemorrhagic complications appear similar for dalteparin and UFH in patients receiving thromboprophylaxis and those undergoing treatment for established thromboembolic disease. Collated data from studies in surgical patients receiving subcutaneous thromboprophylaxis with dalteparin 2500 or 5000U or UFH 10 000IU daily show similar rates of bleeding with either heparin. Increased frequency of bleeding complications relative to placebo has been reported in patients undergoing treatment with dalteparin for up to 3 months for unstable CAD; in patients receiving acute treatment for MI in 1 study, major haemorrhage was reported in 2.9% of dalteparin recipients and 0.3% of those receiving placebo ($p = 0.006$). There have been no reports of excess bleeding relative to placebo in patients receiving extended (35-day) thromboprophylaxis with dalteparin after orthopaedic surgery, and the drug has not been associated with clinically significant haemorrhagic complications or adverse fetal or maternal outcomes in pregnant women.

The exact incidence of thrombocytopenia with dalteparin is not known, but has been reported to be less than 1% in patients receiving the drug for thromboprophylaxis.

Dosage and Administration

Patients at moderate risk of venous thromboembolism after surgery should receive dalteparin subcutaneously at a dosage of 2500U once daily; patients at high risk should receive 5000U once daily. A dosage of 200 U/kg once daily or 100 U/kg twice daily is recommended for the initial treatment of established thromboembolic disease, and 120 U/kg every 12 hours in addition to aspirin is indicated for patients with unstable CAD. An intravenous weight-adjusted bolus followed by continuous infusion is recommended for haemodialysis or haemofiltration procedures lasting 4 hours or more; a single intravenous bolus may be suitable where sessions are of less than 4 hours' duration. Subcutaneous administration of dalteparin should be via the abdomen or the lateral portion of the thigh.

Laboratory monitoring of the coagulation response is not necessary in most patients receiving dalteparin therapy. Plasma anti-factor Xa activity should be monitored in certain groups of individuals, however; these include those with acute or chronic renal failure, and those at high risk of bleeding who require treatment for established thromboembolic disease.

Heparin is a naturally occurring glycosaminoglycan with anticoagulant properties that consists of chains of alternating residues of D-glucosamine and a uronic acid. The characteristics and properties of this agent have been reviewed in numerous publications, and the following introduction is a brief summary based on information collated from a number of such sources.[1-4]

Standard unfractionated heparin (UFH) is heterogeneous with respect to molecular weight distribution, anticoagulant activity and pharmacokinetic properties. Its molecular weight ranges from 3000 to 30 000 (mean approximately 15 000, equivalent to around 50 monosaccharide units), and its anticoagulant effect is mediated largely by a pentasaccharide sequence (present in about a third of UFH molecules) with high affinity for the plasma protease inhibitor antithrombin. This sequence binds to and causes a conformational change in antithrombin that enhances its ability to inhibit the activated clotting factors IIa (thrombin), IXa, Xa, XIa and XIIa (fig. 1).

To inhibit the autocatalytic activity of thrombin in the coagulation cascade, heparin must bind to thrombin and antithrombin simultaneously via the formation of a ternary complex (n.b. the term heparin is used throughout this review as a general descriptor for all forms of this anticoagulant). This process requires the participation of both antithrombin and thrombin binding sites and is limited to heparin molecules of about 18 saccharides or more in length. In contrast, the inactivation of factor Xa by antithrombin/heparin does not require the formation of such a complex. Thus, as heparin molecules consisting of fewer than 18 saccharides (molecular weight below approximately 5000) are unable to form the ternary complex with antithrombin and thrombin, a decrease in the mean molecular weight of a mixture of heparin fractions leads to an increase in the ratio of anti-factor Xa to anti-factor IIa activities. Inhibition of thrombin is reflected by prolongation of the activated partial thromboplastin time (aPTT); as the mean molecular weight of heparin decreases, its influence on the aPTT diminishes but anti-factor Xa activity is retained.

Over the past 15 years, a number of low molecular weight derivatives of UFH, prepared by controlled chemical or enzymatic depolymerisation, have become available from commercial sources. These low molecular weight heparins (LMWHs) have mean molecular weights of 4000 to 6000, with 60% of the polysaccharide chains being within the range 2000 to 8000. The rationale behind their development lay in the apparent retention of anticoagulant (anti-factor Xa) activity with reduced haemorrhagic (anti-factor IIa) properties seen with heparin chains of molecular weight below approximately 5000. Although clinical experience with these agents has shown this rationale to be over-simplistic, the LMWHs have nevertheless been shown to have various pharmacological and practical features that are potentially advantageous in patients requiring antithrombotic therapy. It has also become clear that the various LMWHs are distinguished by differing biochemical and physicochemical characteristics. There is therefore a need to consider each product individually, despite the large number of reviews and meta-analyses that compare UFH with LMWHs as a group.

Dalteparin (fig. 2) is a LMWH derived from standard porcine UFH by partial nitrous acid depolymerisation.[5] It has a mean molecular weight of 5000, with 90% of chains falling within the range 2000 to 9000.[5,6] The pharmacological properties and therapeutic use of this LMWH were originally reviewed in *Drugs* in 1996.[3] This updated article reassesses the drug and its place in the management of thromboembolic disease in the light of new data, the most notable of which have been obtained in the settings of coronary artery disease (CAD), home treatment of thromboembolism and pharmacoeconomics.

1. Pharmacological Properties

The following discussion summarises briefly information on the pharmacodynamic and pharmacokinetic properties of dalteparin that has been reviewed previously in more detail,[3] together with additional material that has become available since that time.

The antithrombotic effect of UFH is usually as-

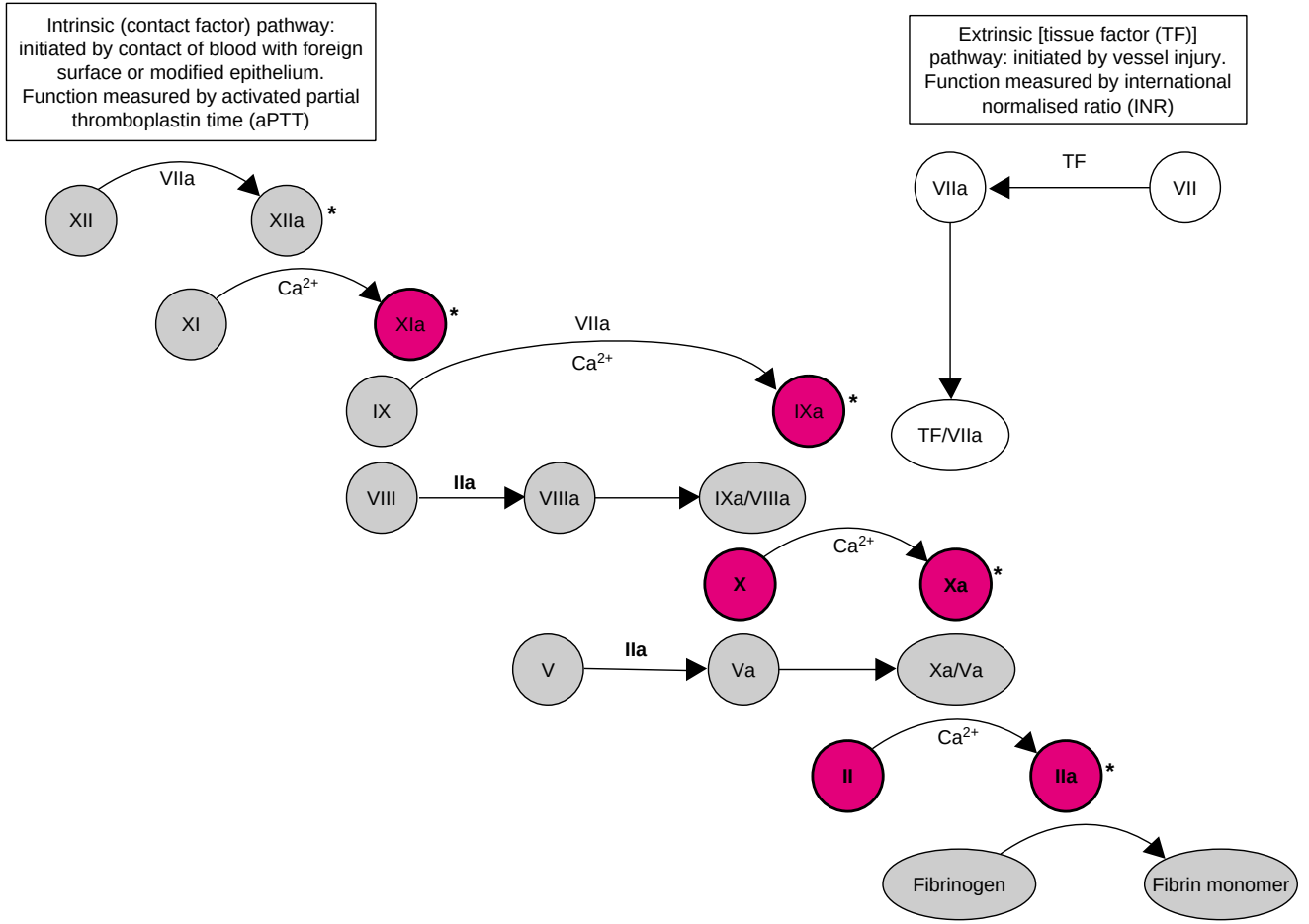

Fig. 1. Simplified representation of the coagulation cascade. Clotting is initiated by activation of either the intrinsic (contact factor) or extrinsic (tissue factor) pathway. These pathways activate factor X to form factor Xa, which in turn activates the rest of the cascade and leads to the formation of thrombin (factor IIa) and the fibrin clot. Note the inhibition of various factors by antithrombin (denoted by *). Note also that antithrombin prevents the cleavage of fibrinogen, and that a number of other antithrombotic regulatory mechanisms (not shown here) also act at various points in the cascade.

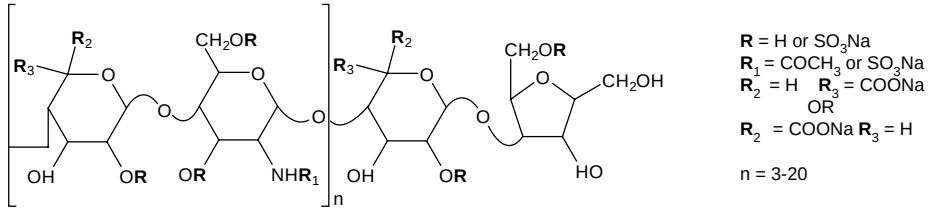

Fig. 2. Structural formula of dalteparin.

sessed by its ability to prolong the clotting time of blood (expressed in terms of aPTT), although it has been suggested that this parameter reflects the undesirable haemorrhage-inducing properties of heparin.[7] Because of the reduced anti-factor IIa effects of LMWHs relative to UFH, the antithrombotic efficacy of dalteparin (in common with other LMWHs) is measured in terms of its ability to inhibit factor Xa. Thus, doses of dalteparin are expressed throughout this review in units (U) of anti-factor Xa activity relative to the First International Standard for Low Molecular Weight Heparins,[8] the reference standard adopted for the LMWHs by the World Health Organization in 1988. Doses of UFH are given in international standard units (IU).

1.1 Effects on Clotting Factor Activities and Other Coagulation Parameters

Pharmacodynamic studies in humans have shown dose-dependent inhibition of factor Xa by dalteparin.[4,7,9-11] Anti-factor Xa activities of 600, 1500 and 300 U/L were reported in 1 study after single intravenous doses of dalteparin 5000 and 10 000U and UFH 5000IU, respectively, with no changes in patients who received placebo.[9]

Anti-factor Xa activity exceeded anti-factor IIa activity in plasma from surgical patients receiving dalteparin, in contrast to patients receiving UFH, who showed similar plasma activity against both coagulation factors.[11,12] Single subcutaneous doses of dalteparin 5000U, enoxaparin 40mg, tinzaparin 50 U/kg and UFH 5000IU have been compared in a randomised crossover study in 12 healthy volunteers which showed dalteparin and enoxaparin to confer the highest peak plasma anti-factor Xa activities (480 to 490 U/L and 420 U/L, respectively).[13] Corresponding activities with tinzaparin and UFH were 180 and 90 U/L, respectively. Peak plasma anti-factor IIa activities were 90 U/L with dalteparin, 40 U/L with enoxaparin, and 50 U/L with tinzaparin and UFH.

Results from healthy volunteers and patients undergoing surgery or haemodialysis have shown that dalteparin exerts a significantly greater effect than UFH on plasma anti-factor Xa activity relative to its effects on clotting parameters that include aPTT and thrombin time (TT).[9-19] In 2 studies in a total of 528 patients undergoing abdominal surgery, plasma anti-factor Xa activities were significantly higher with dalteparin 2500 to 5000 U/day than with UFH 10 000 U/day, with no significant differences between heparins in aPTT values.[20,21] Data from patients undergoing haemodialysis have shown significantly greater increases in aPTT and TT with UFH (95.6 and 188.1 seconds, respectively) than with dalteparin (7.5 and 7.4 seconds) at dosages adjusted to ensure similar plasma anti-factor Xa activity in each treatment group.[22]

Dalteparin does not have any clinically significant effect on plasma antithrombin levels or platelet counts, but platelet factor 4 (PF4) has a smaller inhibitory effect on the anticoagulant effect of dalteparin (and other LMWHs) than on that of UFH,[23] and less PF4 is released into the circulation in the presence of dalteparin than with UFH.[24] Dalteparin also does not appear to exert any clinically significant effect on the fibrinolytic system.[9,14,17,22] Data that have become available in the last 5 years, however, indicate that dalteparin and other LMWHs inhibit thrombin formation in patients with activated

haemostatic systems (e.g. after hip surgery[25] or tissue injury,[26] and in unstable CAD[27]).

1.2 Effects on Blood Lipid Profiles

Standard UFH possesses lipolytic properties associated with increased activity of lipoprotein and hepatic lipases that cause elevations in plasma levels of free fatty acids (FFA).[28,29] In addition, long term use of UFH has been associated with decreased plasma triglyceride clearance, due possibly to depletion of lipoprotein lipase stores by heparin.[30] These properties are of particular concern in patients with chronic renal failure because these individuals frequently have disturbed lipid metabolism (involving mainly hypertriglyceridaemia).

Previously reviewed studies in healthy volunteers[30,31] and in patients undergoing hip replacement[28] or haemodialysis[22,29,32] showed consistently lower lipolytic activity and/or mobilisation of FFA with dalteparin than with UFH. In addition, favourable effects of dalteparin on blood cholesterol and triglyceride levels were reported in studies in patients with chronic renal failure undergoing haemodialysis.[29,32]

These findings have been confirmed by data from more recent clinical trials. German patients (number not stated) undergoing haemodialysis for more than 12 months showed reductions of 12.7 and 14.8% (both $p < 0.05$ *vs* UFH), respectively, in blood total and low density lipoprotein cholesterol levels when dalteparin was given in place of UFH for 6 months.[33] During the dalteparin anticoagulation period, there were also no significant changes in blood levels of high density lipoprotein cholesterol or triglycerides. Data from 240 patients with hypertriglyceridaemia who underwent haemodialysis for more than 1 year showed significant reductions relative to baseline in blood triglyceride levels after 6 and 12 months in approximately 40% of patients who received dalteparin, with no such reduction being observed in patients receiving UFH.[34] After 5 years' follow-up in 54 patients, triglyceride levels in blood were approximately 30% lower in patients receiving dalteparin than in UFH recipients. Although cardiovascular mortality was similar between groups, significantly higher triglyceride levels were present in patients who experienced cardio- or cerebrovascular events than in those who did not.[34]

1.3 Pharmacokinetic Properties

Dalteparin exhibits monoexponential first order pharmacokinetics that are dose-independent and are expressed in terms of plasma anti-factor Xa activity.[35-37]

After subcutaneous administration of dalteparin, absorption is the rate-limiting step in the pharmacokinetics of the drug,[36] with peak plasma concentrations being attained after 2.8 to 4 hours.[13,36,38,39] The volume of distribution of dalteparin ranged from 2.9 to 4.3L[35-37] and from 7.7 to 9L,[38,39] respectively, after single intravenous and subcutaneous doses in healthy volunteers. Tissue distribution studies in animals have shown that dalteparin is deposited in the liver and kidneys to a smaller extent than UFH (10 *vs* 60% 3 hours after administration).[40]

The bioavailability of a subcutaneous dose of dalteparin was shown to be 87% (compared with 20 to 30% for UFH) in healthy volunteers,[36] with a plasma elimination half-life ($t_{½\beta}$) of 2.4 to 4 hours.[13,36,38,39] It is now known that the availability at sites of action of some LMWHs is affected by adhesion to erythrocytes, but data obtained with citrated blood from healthy volunteers showed that the availability of dalteparin, unlike tinzaparin, was not affected by erythrocyte binding.[41] The authors suggested that this difference between the 2 compounds may be accounted for by the lower molecular weight distribution of dalteparin.

The $t_{½\beta}$ of a single intravenous dose of dalteparin is approximately 2 hours, around twice as long as that observed with UFH.[35] Total clearance was found in studies in healthy volunteers to be approximately 2 L/h after single subcutaneous or intravenous doses of 2500 or 5000U.[37,38,42] Animal data indicate the principal route of elimination of dalteparin to be renal; this is in contrast to UFH, which is excreted both renally and via the metabolic activity of the reticuloendothelial system.[40]

1.4 Drug Interactions

Enhancement of the anticoagulant effects of a number of agents [e.g. aspirin, dipyridamole, vitamin K antagonists and non-steroidal anti-inflammatory drugs (NSAIDS)] is possible with dalteparin.[6] Results from a recent double-blind, placebo-controlled crossover study in 24 healthy male volunteers have shown an interaction between dalteparin and the NSAID ketorolac.[43] Bleeding times were prolonged by ketorolac administered alone as 2 oral and 1 intramuscular 30mg doses over 2 days ($p < 0.0001$ *vs* placebo). Bleeding times were increased further with the coadministration of dalteparin, although a subcutaneous dose of 5000U had no effect on this end-point when given alone. Calculation of the ratio of geometric mean bleeding times for ketorolac/dalteparin and ketorolac/placebo indicated the presence of an interaction.

It should also be noted that the anticoagulant effect of dalteparin may be attenuated by the concomitant administration of antihistamines, cardiac glycosides, tetracyclines and ascorbic acid.[6]

2. Therapeutic Use

Dalteparin was one of the first LMWHs to become available commercially, and much information pertaining to its use in a number of clinical settings has become available since the development and introduction of this agent. Many of the studies that have been carried out in patients receiving dalteparin were assessed in the previous review in *Drugs*.[3] The majority of these trials were carried out in patients requiring surgical thromboprophylaxis or treatment for established thromboembolic disease. Other studies reviewed at that time were carried out predominantly in patients receiving heparin to prevent clotting in haemodialysis or haemofiltration circuits, and in patients with CAD.

Since the publication of the previous review, studies of the thromboprophylactic efficacy of dalteparin in surgical patients have tended to focus on the issues of optimum duration of thromboprophylaxis, and a number of clinical trials have been carried out in women at risk of thromboembolic disease in pregnancy. There has also been a great deal of interest in treatment with dalteparin in the home rather than in hospital for patients with established thromboembolic disease, and several important studies of the use of dalteparin in patients with CAD have been published.

As stated in section 1, doses of dalteparin in this review are expressed in units of anti-factor Xa activity relative to the First International Standard for Low Molecular Weight Heparins,[8] and those of UFH in international standard units. Heparin was administered subcutaneously unless stated otherwise.

2.1 Use in Surgical Thromboprophylaxis

Patients who have undergone surgery with general anaesthesia experience periods of prolonged immobility that predispose them to venous thromboembolism. Sequelae of deep vein thrombosis (DVT) include superficial thrombophlebitis, deep venous insufficiency, chronic leg ulceration and cellulitis (reviewed by Bergqvist[44]). Episodes of DVT also put patients at risk of pulmonary embolism (PE), a potentially fatal complication.[45]

Patients are conventionally classified into 3 groups according to their risk of DVT [as summarised in 1992 by the Thromboembolic Risk Factors (THRIFT) Consensus Group[45]]. Patients at low risk are associated with incidences of DVT of below 10% in the absence of prophylaxis, and this category includes individuals undergoing minor surgery (duration <30 minutes), those aged under 40 years who undergo major surgery (duration >30 minutes), and those with minor trauma or medical illness. Thereafter, the risk of DVT increases according to the type of procedure involved and the effect of independent risk factors.

Patients at moderate risk are associated with incidences of DVT of between 10 and 40%, and include individuals undergoing major general surgery and those aged 40 years and over. High risk patients (DVT risk 40 to 80%) include those undergoing major orthopaedic surgery and those undergoing major pelvic or abdominal surgery for cancer.[45] Notable factors that increase a patient's risk

of thromboembolic disease include obesity, pregnancy or childbirth, history of previous thromboembolism, malignant disease, heart failure or recent myocardial infarction (MI).[45]

Since the publication of the THRIFT report, data obtained retrospectively from 2070 Swedish patients undergoing elective abdominal surgery who received thromboprophylactic dalteparin have become available. These have confirmed previous thromboembolism, leg fracture or arthroplasty, malignant disease and prolonged operating time (>150 minutes) as independent predictors of major postoperative thromboembolism, although age and bodyweight were not independent risk factors in these patients.[46]

In general, specific thromboprophylaxis is recommended for all surgical patients at moderate to high risk of DVT.[45] Pharmacological treatments used most commonly include low dose subcutaneous heparin, oral anticoagulants or dextran 70 infusion. Mechanical methods, including graduated compression hosiery and intermittent pneumatic compression, may also be effective in patients at moderate risk, and may be combined with pharmacological prophylaxis in high risk patients.[45]

Contrast venography, the preferred identification method for DVT, has been used consistently for the diagnosis of venous thromboembolism in studies carried out since the last review of dalteparin in *Drugs*.[3] ^{125}I-radiolabelled fibrinogen uptake leg scanning (FUT) was used in many of the studies published before 1996, but this method cannot detect proximal thrombi because of high background levels of radioactivity, and is not suitable for patients undergoing orthopaedic surgery.[47,48] It appears now to have fallen out of use. Clinical diagnoses of PE were confirmed predominantly by pulmonary scintigraphy or angiography.

2.1.1 Comparisons With Unfractionated Heparin or Warfarin, and Efficacy of Long Term Prophylaxis

In randomised and double-blind studies reviewed previously,[3] subcutaneous dalteparin, administered once daily for 5 to 13 days after surgery, was generally of similar thromboprophylactic efficacy to UFH in patients undergoing general or orthopaedic surgery. Most investigators compared dalteparin 2500U once daily with UFH 5000IU twice daily, and the majority of trials were carried out in patients undergoing general or gynaecological surgery.

In general, too few patients were recruited for the drawing of definitive conclusions, although 2 studies, one of which involved over 800 patients undergoing general surgery[49] and the other a follow-up period of 6 to 8 weeks in 122 patients undergoing orthopaedic surgery,[50] showed superiority of dalteparin 5000U once daily over UFH 5000IU 2 or 3 times daily. Clinical trials conducted since 1996 in patients requiring thromboprophylaxis have employed this dosage of dalteparin, and are summarised in table I alongside data from the largest randomised and double-blind studies featured in the previous review. The incidences of DVT shown for all trials are those for events detected by venography or FUT. Cited incidences of PE refer to symptomatic events.

Recent clinical studies have been carried out mainly in patients undergoing total hip arthroplasty, and have focused on the use of extended periods of thromboprophylaxis and comparison of dalteparin with warfarin. Results have shown overall that 35 days' prophylaxis reduces the frequency of venographically evident thromboembolic complications to a significantly greater extent than prophylaxis for 7 days, and have indicated dalteparin to be superior to adjusted-dosage warfarin when either was given for up to 1 week or for 35 days after surgery (table I). It is not clear whether other thromboprophylactic measures were used in most studies, although compression hosiery was used in all patients in 1 trial[54] and was allowed in 1 other[55] (both studies of long versus short term prophylaxis). Heparin treatment was started shortly before surgery by the majority of investigators.

As stated above, dalteparin was given at a dosage of 5000U once daily in studies in which regimens were described fully. However, results of the 2 largest recent trials are currently available in preliminary form only, with dosages not specified.[52,53] Both showed statistically significant re-

Table I. Thromboprophylactic efficacy of dalteparin. Results of clinical studies in surgical patients at moderate to high risk of thromboembolic complications in which dalteparin (D) was compared with unfractionated heparin (UFH) or warfarin, or in which long term (L/T) and short term (S/T) prophylactic regimens were compared. Numbers of patients given were those with evaluable venograms, and follow-up periods relate to the time of final clinical assessment (including screening for thromboembolic events). All heparin doses were administered subcutaneously

Reference (study design)	Patient parameters		Regimens (D doses in anti-factor Xa units; UFH in international standard units)	Follow-up period	Procedure used to detect DVT	Incidence of clinical end-points (% of patients)			Overall efficacy
	no. evaluated (mean age in years)	malignant disease/ history of TE (%)				DVT	PE	mortality[a]	
Orthopaedic surgery: comparison with UFH									
Eriksson et al.[50] (r, db)	63 (68)	0/12.5	D 5000 od × 10 days	6–8wks	V	30.2	12.3	0	D > UFH
	59 (69)		UFH 5000 tid × 10 days			42.4	30.9*	0	
Orthopaedic surgery: comparisons with warfarin (W)									
Francis et al.[51] (r, nb)	192 (63)	NR/9.0	D 5000 od	mean 7 days	V	14.6	NR	NR	D > W
	190 (64)	NR/11.0	W od (target INR = 2.5)			25.8**	NR	NR	
Pineo & Hull[52] (r, db) [abstract]	337 (NR)	NR	D od started immediately before surgery	mean 5.7 days	V	10.7	NR	NR	D > W
	336 (NR)	NR	D od started shortly after surgery			13.1	NR	NR	
	338 (NR)	NR	W od started after surgery			24.0***	NR	NR	
Hull & Pineo[53] (r, db) [abstract]	174 (NR)	NR	D od started immediately before surgery × 35 days	35 days	V	17.2	NR	NR	D > W
	171 (NR)	NR	D od started shortly after surgery × 35 days			22.2	NR	NR	
	188 (NR)	NR	W od during hospital stay, then PL to day 35			36.7**	NR	NR	
Orthopaedic surgery: L/T *vs* S/T prophylaxis									
Dahl et al.[54] (r, db, mc)	93 (71[b])	9.4/8.5[b]	D 5000 od × 35 days[c]	35 days	V	11.8	0[d]	0[d]	L/T > S/T
	89 (71[b])	9.1/4.5[b]	D 5000 od × 7 days, then PL to day 35[c]			25.8*	2.8[d]	0.9[d]	
Lassen et al.[55] (r, db, mc)	113 (68)	2.1/7.1	D 5000 od × 35 days	35 days	V	4.4	NR	NR	L/T > S/T
	102 (70)	2.1/3.5	D 5000 × 7 days, then PL to day 35			11.8*	NR	NR	
General or gynaecological surgery: comparisons with UFH									
Bergqvist et al.[49] (r, db, mc)	421 (68)	64.0/6.7	D 5000 od × 5–8 day	30 days	FUT	5.0	0	2.0[e]	D > UFH
	405 (69)		UFH 5000 bid × 5–8 days			9.2*	1.0	2.0[e]	
Caen[19] (r, db, mc)	195 (52)	NR/8.8	D 2500 od × 7 days	30 days	FUT	3.1	0	0	D ≡ UFH
	190 (60)		UFH 5000 bid × 7 days			3.7	0.5	0	
Hartl et al.[56] (r, db)	112 (65)	32.6/2.0	D 2500 od × ≥7 days	NR	FUT/V	4.5	0.9	0.9	D ≡ UFH

Table I (contd)

ductions (approximately 50%) relative to warfarin (details of regimens used not stated) in overall incidence of DVT with short (mean follow-up 5.7 days)[52] and long (35-day) term[53] dalteparin prophylaxis (started either immediately before or shortly after surgery) [table I]. Warfarin was given during the period of hospitalisation only in both studies; in the long term trial,[53] patients randomised to warfarin received a placebo after discharge, whereas patients on dalteparin received active prophylaxis for the full 35 days. In addition, dalteparin 5000U once daily was significantly more effective in the prevention of DVT than warfarin in a 7-day randomised nonblind study in 382 evaluable patients undergoing total hip arthroplasty (table I).[51] Warfarin dosages were adjusted to maintain a target international normalised prothrombin time ratio (INR) of 2.5; the mean INR attained ranged between approximately 1.8 and 2.1 from day 2 to day 7.

Superior efficacy of long term over short term prophylaxis with dalteparin has been shown in 2 other double-blind studies, both involving around 200 patients with evaluable venograms. Reductions relative to 7-day prophylaxis in incidence of DVT of 54[54] and 63%[55] were reported after dalteparin 5000U was given once daily for 35 days (table I).

Hip surgery is associated in particular with a high risk of DVT in the proximal veins of the leg,[47] and all 5 recent studies in patients undergoing total hip arthroplasty have reported, in addition to total DVT results, incidences of proximal DVT.[51-55] The incidence of proximal DVT was significantly ($p < 0.05$) lower with dalteparin than with warfarin after a mean 5.7-day follow-up in 1 study (0.8% in both dalteparin groups *vs* 3% with warfarin),[52] and there was a significantly ($p < 0.001$) lower incidence of proximal DVT with 35 days' dalteparin (19.7% overall) than with warfarin in hospital followed by placebo after discharge (36.7%) in another.[53] Other studies showed trends towards lower incidences of proximal DVT with dalteparin than with warfarin,[51] and with 35 days of dalteparin prophylaxis than with 7 days.[54,55] The greater apparent efficacy of dalteparin 5000U daily than UFH 5000IU 3 times daily in the earlier study of Eriksson et al.[50] was based

Table I. Contd

Reference (study design)	Patient parameters		Regimens (D doses in anti-factor Xa units; UFH in international standard units)	Follow-up period	Procedure used to detect DVT	Incidence of clinical end-points (% of patients)			Overall efficacy
	no. evaluated (mean age in years)	malignant disease/ history of TE (%)				DVT	PE	mortality[a]	
	115 (63)		UFH 5000 bid × ≥7 days			4.3	0.9	0.9	
Kakkar et al.[57] (r, db, mc)	1894 (≥40)	37.6/4.6	D 2500 od × 5–10 days	4–8wks	V	0.6	0.7	3.3	D ≡ UFH
	1915 (≥40)		UFH 5000 bid × 5–10 days			0.6	0.7	2.5	
Ward & Pradhan[58] (r, sb)	271 (55[b])	79[b]/NR	D 5000 od × 5 days or until full activity	6wks	V	0	1.8	NR	D ≡ UFH
	281 (55[b])	84[b]/NR	UFH 5000 bid × 5 days or until full activity			0.4	0.4	NR	

a Deaths related to thromboembolic events only (unless stated otherwise).
b Values from intention-to-treat population.
c All patients received dextran 70 for 2 days (starting on the day of surgery) and wore compression hosiery.
d 111 and 106 patients in the L/T and S/T groups, respectively, evaluable for this clinical end-point.
e Total deaths (all causes).

bid = twice daily; **db** = double-blind; **DVT** = deep vein thrombosis; **FUT** = ^{125}I-fibrinogen uptake leg scanning; **INR** = international normalised prothrombin time ratio; **mc** = multicentre; **nb** = nonblind; **NR** = not reported; **od** = once daily; **PE** = pulmonary embolism; **PL** = placebo; **r** = randomised; **sb** = single-blind; **TE** = thromboembolism; **tid** = 3 times daily; **V** = contrast venography; **>** indicates greater efficacy; ≡ indicates equivalent efficacy; ***** $p < 0.05$, ****** $p < 0.01$, ******* $p < 0.001$ *vs* D.

Table II. Thromboprophylactic efficacy of dalteparin (D) relative to other low molecular weight heparins. Results of clinical studies in surgical patients at moderate to high risk of thromboembolic complications in which D was compared with enoxaparin (E) or nadroparin (N). Numbers of patients given are those with evaluable venograms, and follow-up periods relate to the time of final clinical assessment (including screening for thromboembolic events). All doses were administered subcutaneously once daily

Reference (study design)	Patient parameters		Regimens (D and N doses in anti-factor Xa units)	Follow-up period	Procedure used to detect DVT	Incidence of clinical end-points (% of patients)	
	no. evaluated	procedure				DVT	PE
Bounameaux et al.[60] (r, sb)	63	Abdominal surgery	D 2500 × 8 days[a]	8 days	V	32.3	NR
	59		N 3075 × 8 days[a]			16.3*	NR
Røise et al.[61] (r, sb) [abstract]	52	Repair of hip fracture	D 5000 × ≤10 days	10 days	V	8.8	0
	57		E 40mg × ≤10 days			15.4	0
	53		Danaparoid sodium 750U × ≤10 days			5.7	0

a All patients issued with compression hosiery.

DVT = deep vein thrombosis; **NR** = not reported; **PE** = pulmonary embolism; **r** = randomised; **sb** = single-blind; **V** = contrast venography; * $p < 0.05$ *vs* D.

on higher incidences of proximal DVT and PE in the UFH group, although the difference between treatments in overall incidence of DVT was not statistically significant (table I).

2.1.2 Comparisons With Other Agents

At the time of the previous review,[3] few studies comparing dalteparin with thromboprophylactic agents other than UFH were available; apart from the comparisons with warfarin described above (section 2.1.1), there have been no new data published since that time. Dalteparin 2500U twice daily showed greater thromboprophylactic efficacy than the plasma expander dextran 70 (used as a 6% solution) in a nonblind study in 98 evaluable patients undergoing elective hip arthroplasty.[15] Similar incidences of DVT and PE between groups were reported in another study after thromboprophylaxis with dalteparin 2500U once daily or sodium pentosan polysulphate 50mg once or twice daily subcutaneously in 749 patients undergoing abdominal surgery.[59]

Dalteparin has been compared with the LMWHs nadroparin and enoxaparin in 2 single-blind studies (table II). The incidence of venographically determined DVT was lower in 52 patients undergoing hip fracture repair who received dalteparin 5000U once daily than in 57 recipients of enoxaparin 40mg once daily, but the overall significance of these findings is unclear.[61] Although there was no statistically significant difference between groups, full details remain unavailable, and the power of the trial to show definitively superiority or equivalence of treatments is doubtful. An additional group of 53 patients received the heparinoid danaparoid sodium in this study (table II).

The comparison with nadroparin showed a higher incidence of DVT in patients who received dalteparin, but there was an unexpectedly high incidence of DVT in both treatment groups in this study, and both the levels and comparability of the dosages used were questionable (dalteparin 2500U was compared with nadroparin 3075U, both given once daily)[60] [table II]. As patients recruited in this study were required to have at least 1 risk factor from a list including obesity, malignant disease, history of previous venous thromboembolism, heart failure, oral contraceptive use or presumed duration of surgery greater than 4 hours, the dosage of dalteparin used may not have been appropriate for the overall risk profile of the patients treated.

2.2 Thromboprophylaxis in Pregnancy

Thromboembolic complications during pregnancy and childbirth are a major cause of maternal mortality. Obstruction of venous return by the growing uterus and prothrombotic haemostatic changes

are implicated, and a history of DVT has been associated with increased risk of recurrent thromboembolism in pregnant women. Other factors increasing the risk of pregnancy-related thrombosis are the presence of an inherited thrombophilia, such as activated protein C resistance or deficiency of antithrombin or protein C or S, or an acquired thrombophilia such as the antiphospholipid syndrome (reviewed by Hunt et al.[62]).

In the past, pregnant women requiring anticoagulants have received UFH or oral coumarin agents, neither of which is ideal. Oral anticoagulants cross the placenta and are associated with fetal abnormalities in the first trimester and intracranial haemorrhage at all stages of gestation, and UFH is associated with maternal adverse effects such as bleeding, thrombocytopenia and osteoporosis.[62] The use of LMWHs in pregnancy and childbirth is not extensively documented, but the results of several studies in pregnant women receiving dalteparin have become available since 1996.

A single randomised comparison of dalteparin with UFH has been carried out in pregnant women.[63] In this nonblind study, 105 women with a history of thromboembolic disease and/or hereditary thrombophilia received dalteparin (mean dosage of 4631U once daily) or UFH (mean dosage 20 569IU daily divided into 2 doses). Dalteparin and UFH dosages were adjusted according to plasma anti-factor Xa activity and aPTT, respectively. Prophylaxis was continued throughout pregnancy and for up to 6 weeks after delivery. No thromboembolic complications were reported with either heparin, but there were 9 bleeding episodes (including injection site haematomas) in the dalteparin group and 55 with UFH ($p < 0.001$). Only 2 haemorrhages were described as serious (i.e. requiring transfusion); both were observed during childbirth in patients receiving UFH. In addition, there were 2 lumbosacral compression fractures, both in UFH recipients. Pregnancy outcomes were similar between groups.

No thromboembolic complications were reported in 3 case series involving a total of 110 women (117 pregnancies) at high risk of venous thromboembolism who received dalteparin throughout pregnancy. In 2 series,[64,65] all 78 patients had a history of thromboembolic disease; however, one excluded patients with hereditary thrombophilia or antiphospholipid syndrome,[64] whereas the other included patients with acquired or hereditary thrombophilia.[65] In the remaining series of 34 pregnancies,[62] a history of thromboembolic disease was present in 26 and acquired or hereditary thrombophilia in 30 (antiphospholipid syndrome was present in 11 pregnancies). The dosage of dalteparin was adjusted according to plasma anti-factor Xa activity, with most patients receiving between 5000 and 10 000U daily. There were no reports of thrombocytopenia or serious bleeding complications in any of the pregnancies included in these 3 series, although 1 osteoporotic fracture was reported[62] (see section 4).

2.3 Treatment of Established Thromboembolic Disease

For many years, UFH has been the standard treatment for acute episodes of thromboembolic disease. Initial heparin therapy is generally given for 1 or 2 weeks, during which time oral anticoagulant therapy is started, and is discontinued 48 hours after the prothrombin time reaches therapeutic levels. Oral anticoagulant treatment is then continued for at least 3 months to prevent any recurrence of DVT or PE (reviewed by Nurmohamed et al.[48] and Charland & Klinter[66]).

In comparative studies reviewed previously in *Drugs*,[3] dalteparin was shown consistently to be of equivalent efficacy in terms of improvements in venographic findings and Marder scores (a 40-point scale used to quantify the degree of venographically evident venous occlusion[67]) to UFH in the acute management of DVT (see Dunn & Sorkin[3]).

Dalteparin was given by either intravenous infusion[68,69] or subcutaneous injection (once or twice daily),[70-75] whereas UFH was given intravenously in all trials but one.[73] Fixed dosages of dalteparin[68] and regimens adjusted according to bodyweight[69,72,74,75] or plasma anti-factor Xa activity[70,71,73] were investigated. UFH dosages were adjusted maintain aPTT at 1.5[74,75] or 2[70,71] to 3

times the control value in the majority of studies,[70-72,74,75] although bodyweight-[69] or anti-factor Xa activity-adjusted[73] or fixed[68] dosages were used by some investigators. One study only was carried out in a double-blind fashion.[68]

Heparin treatment was given for up to 10 days, during which time long term warfarin therapy was started. It should be noted that 2 studies[72,75] that were not available in their finalised form at the time of the last review have since been published in full with no changes in the data presented.[76,77] Dalteparin 120 U/kg twice daily was of similar efficacy to aPTT-adjusted UFH given by continuous intravenous infusion in the only study carried out in patients with acute PE (n = 60).[78]

Since that time, data have continued to show similar efficacy of dalteparin and UFH in the treatment of patients with established DVT. Six-month follow-up of patients randomised to dalteparin 200 U/kg once daily subcutaneously or aPTT-adjusted UFH by continuous intravenous infusion for 5 to 10 days, after which warfarin was continued for at least 3 months, showed no significant differences between groups in Marder scores, symptoms or thrombus evolution.[79] This analysis was an extension of a study reported previously,[74] and the results showed no changes from the initial treatment data.

Retrospective follow-up data covering a period of 5 to 14 years from the original thromboembolic episode in patients in 3 Swedish clinical studies have also been published.[80] Patients were randomised in these nonblind trials to intravenous UFH or intravenous dalteparin infusion, intravenous UFH infusion or subcutaneous dalteparin twice daily, or dalteparin subcutaneously once or twice daily. UFH and dalteparin dosages were adjusted according to aPTT and plasma anti-factor Xa activity, respectively. Initial heparin therapy was given for at least 5 days, during which time long term warfarin treatment was commenced (this was continued for at least 3 months in most patients). The analysis included 180 dalteparin and 85 UFH recipients, of whom 157 were available for clinical examination. Data on the other patients were obtained from clinical notes, questionnaires, or Swedish national statistical or hospital discharge records. Recurrent venous thromboembolism during the extended follow-up period was reported in 29.4 and 23.5% of dalteparin and UFH recipients, respectively (no statistically significant difference). There were no differences between groups in total mortality or mortality from malignant disease.

2.3.1 Outpatient Treatment

Patients with acute thromboembolic disease have traditionally received initial treatment with heparin in hospital. This has been considered necessary because of the need for intravenous administration and laboratory and clinical monitoring of patient responses. However, the ease of subcutaneous administration of LMWH at bodyweight-adjusted dosages raises the possibility that patients with venous thromboembolism might receive acute treatment on an outpatient basis, with potential for savings in hospital costs[81,82] (see section 3.1).

Over the last 5 years, a number of noncomparative trials have been carried out to investigate the feasibility of initial outpatient treatment of established thromboembolic disease with dalteparin.[83-89] In these analyses, dalteparin was given at a dosage of 200 U/kg once daily for at least 5 days (≥4 days in 1 trial[83]), with warfarin treatment being started during initial heparin therapy and continued for a follow-up period of 3 to 6 months (although patients were monitored for up to 3 years in 1 study[88]). Initial treatment with bodyweight-adjusted subcutaneous dalteparin was reported to be effective, well tolerated and readily accepted by patients in all studies. Protocols for administration of dalteparin varied, with injections being administered in the home setting by patients or their caregivers[84,85,89] or by visiting community health staff,[84-86,89] or during outpatient clinic visits.[83,87]

A single report is available from a series of 24 patients with thromboembolic disease for whom warfarin therapy was unsuitable and who received dalteparin on a long term home treatment basis.[90] The drug was reported to be effective and well tolerated when self-administered subcutaneously by

patients for 3 months at a dosage of 5000U once daily (2500U in 1 patient).

Dalteparin was reported to be of equivalent efficacy to warfarin in the only study in which these agents have been compared in patients requiring treatment for thromboembolic disease.[91] Patients were randomised in this 3-month nonblind trial to inject themselves subcutaneously once daily with dalteparin 5000U (44 evaluable patients) or to take warfarin to maintain an INR of 2 to 3 (42 patients) after a 10-day initial treatment period in which all patients received UFH subcutaneously. Venography and ventilation perfusion scans carried out after 12 weeks showed a trend towards greater efficacy of warfarin in the prevention of recurrent DVT (6.8% with dalteparin *vs* 2.4% with warfarin) and PE (4.5 *vs* 2.4%). These differences between groups were not statistically significant, however.

2.4 Use in Coronary Artery Disease

2.4.1 Unstable Coronary Artery Disease

Unstable CAD encompasses both unstable angina and non–Q-wave (non–ST-segment elevation) MI. Patients with these conditions experience ischaemic episodes and are at risk of progression to acute MI and death. The pathological lesion in these individuals is usually a platelet-rich, nonocclusive thrombus overlying fissured or active plaques, unlike the fibrin-rich occlusive thrombus seen in patients with acute MI (reviewed by Campbell et al.[92] and Brieger and Freedman[93]).

Antiplatelet agents form the mainstay of medical therapy in unstable CAD, and aspirin (or an alternative for those unable to tolerate this drug) is normally given to all patients upon presentation. Nitrates are used to control symptoms, and β-blockers and calcium antagonists may be added as necessary.[92] The novel platelet glycoprotein GPIIb/IIIa antagonists, used predominantly at present in conjunction with percutaneous coronary intervention, also show potential in the non-invasive management of unstable angina.[94-97]

The value of heparin (in addition to aspirin) in the prevention of recurrence of symptoms and progression to MI or death has been established in clinical studies, and intravenous infusion of UFH is known to confer antithrombotic benefit in the acute phase of unstable CAD.[98,99] However, the route of administration and the need for laboratory monitoring imposes limits, particularly in terms of duration of use, on UFH therapy. In unstable CAD, patients remain at increased risk of cardiac events for 6 to 12 weeks and in a hypercoagulable state for several months after an acute episode, and the protection offered by the short term UFH treatment received by most patients is lost rapidly after discontinuation of the infusion.[100] The optimum duration of heparin treatment in these patients remains under investigation.

LMWHs are easier to administer than UFH and can be given as bodyweight-adjusted dosages without the need for laboratory monitoring. They are therefore of special interest in the long term protection of patients with CAD.

Subcutaneous dalteparin was compared with UFH and with aspirin therapy alone in a 2-phase multicentre European and North American study in which 1482 patients (all of whom were receiving aspirin 75 to 165 mg/day) with unstable CAD were randomised initially to nonblind treatment with either heparin for 6 days.[101] This was followed by a double-blind phase (days 6 to 45), in which dalteparin 7500U once daily (n = 562) was compared with placebo (n = 561). Between days 6 and 45, the rate of death, MI or recurrence of angina (the composite primary end-point) was 12.3% in both treatment groups. Rates for death or MI were 4.7% with placebo and 4.3% with dalteparin; revascularisation procedures were undertaken in 14.2 and 14.3% of patients, respectively. Eleven patients (2%) in each group died. During the first 6 days, death, MI or recurrence of angina was reported in 7.6% of 731 patients receiving UFH (continuous infusion adjusted to maintain the aPTT at 1.5 times the control value) and 9.3% of 751 patients receiving dalteparin 120 U/kg twice daily. There were 11 deaths (1.5%) in the dalteparin group and 3 (0.4%) in the UFH group ($p = 0.05$). The acute results highlighted subcutaneous dalteparin as an alternative to UFH, although it should be

noted that this phase of the study lacked sufficient statistical power to show conclusively equivalence of the 2 heparins.

The use of dalteparin in the management of patients with CAD has been most extensively investigated by the Swedish Fragmin and Fast Revascularisation during Instability in Coronary Artery Disease (FRISC) study group. The first of 2 large, randomised double-blind studies carried out by this group was reported in 1996[102] and was reviewed in the original evaluation of dalteparin in *Drugs*.[3] This original study showed lower rates of death and new MI over the first 6 days of treatment (the primary end-point) in 746 patients randomised to dalteparin 120 U/kg twice daily for 5 to 8 days followed by 7500U once daily for 35 to 45 days than in 760 placebo recipients (1.8 *vs* 4.8%; $p = 0.001$). Patients were randomised within 72 hours of presentation in this study, and 95% received aspirin 75 mg/day.

During the first 6 days, dalteparin treatment also reduced the need for revascularisation procedures (0.4 *vs* 1.2%; $p < 0.001$) and for intravenous heparin (3.8 *vs* 7.7%; $p < 0.001$). Incidences of a composite end-point of death, MI, or need for revascularisation or intravenous heparin over 6 days were 5.4 and 10.3% ($p < 0.001$) for dalteparin and placebo, respectively. After 40 days, the rates of death, new MI, need for revascularisation and need for intravenous heparin remained lower in the dalteparin than in the placebo group. Subgroup analyses suggested that benefit of dalteparin was confined to non-smokers (80% of patients), those with non–Q-wave MI and those with low body mass index (<26 kg/m^2). There were no significant differences between groups in rates of death, new MI or need for revascularisation 4 to 5 months after the end of treatment.[102]

Since that time, the FRISC group has published the results of a 2-part multicentre study that involved patients from an original population of 3489 with symptoms of acute ischaemia of whom 2267 were either not eligible for coronary revascularisation (n = 1032) or were randomised to non-invasive therapy (n = 1235) [FRISC II].[103] These individuals all received initial treatment with dalteparin 120 U/kg (maximum 10 000U) twice daily for 5 to 7 days, after which 2105 patients received double-blind treatment with either dalteparin 5000 or 7500U (depending on bodyweight) twice daily or placebo for 3 months by self-injection on an outpatient basis. All patients received aspirin (maintenance dosage of 75 to 320 mg/day), and β-blockers unless contraindicated. Nitrates and calcium antagonists were added as required.

There was a statistically significant ($p = 0.002$) 47% decrease relative to placebo in a combined end-point of death and MI with dalteparin after 1 month when the double-blind treatment period only (i.e. from day 5 to 7 onwards) was considered (fig. 3). The difference between groups after 3 months was not statistically significant, however. Results from the total cohort of randomised patients, which included both the nonblind and double-blind treatment periods, also showed a significant decrease relative to placebo in death and MI over the first month, but not after 3 months (fig. 3). Results for the triple end-point of death, MI and need for revascularisation showed significant decreases in the dalteparin group relative to placebo after 1 month (24% reduction; $p = 0.001$) and 3 months (13% reduction; $p = 0.031$) [fig. 3]. There were no statistically significant differences between groups after 6 months for either end-point.

Substudies based on the FRISC[104] and FRISC II[105] cohorts have suggested that longer term (5-week and 3-month, respectively) benefit is confined to patients with raised plasma levels of cardiac troponin-T (a component of cardiac muscle filaments that acts as a marker of cardiac injury[106]).

In the second part of the FRISC II study,[107] the 1235 patients randomised to non-invasive therapy who formed part of the study population referred to above were compared with 1222 patients randomised to percutaneous coronary intervention. From randomisation, all patients received dalteparin 120 U/kg twice daily for at least 5 days in the non-invasive group and until coronary intervention in the invasive therapy group. Thereafter, treatment was continued for 3 months, with patients in both groups

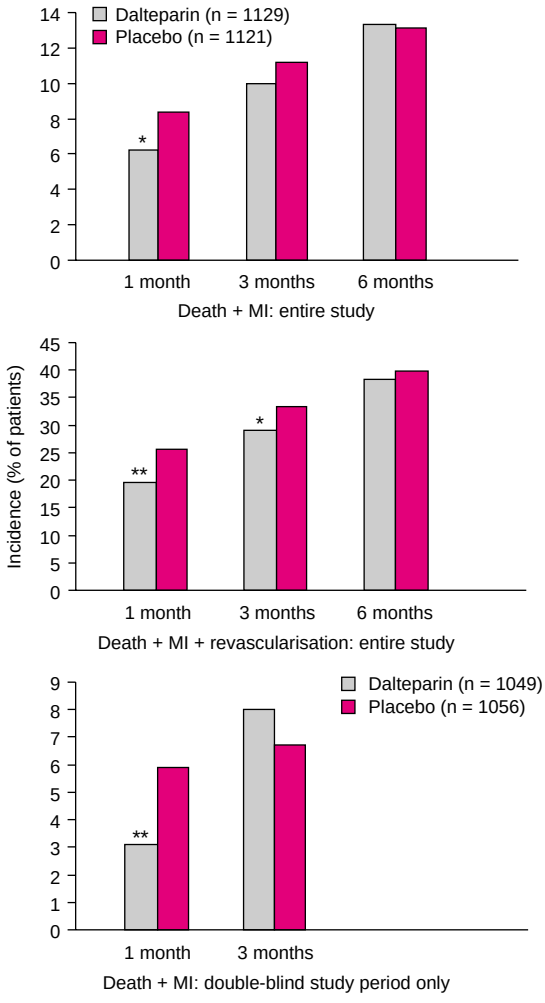

Fig. 3. Effects of dalteparin in patients with unstable coronary artery disease. Rates of death and myocardial infarction (MI) or death, MI and need for revascularisation after 1, 3 and 6 months' treatment with dalteparin or placebo.[103] All patients received initial treatment with dalteparin 120 U/kg twice daily subcutaneously for ≥5 days, after which double-blind treatment with dalteparin 5000 or 7500U (depending on bodyweight) twice daily or placebo was started. Results are shown for up to 6 months for the entire study (non- and double-blind treatment periods), and for death and MI for the 3-month double-blind period only (i.e. from day 5 to 7 onwards). * $p < 0.05$, ** $p < 0.01$ *vs* placebo.

being randomised to dalteparin 5000 or 7500U on the basis of bodyweight twice daily or placebo.

After 6 months, there was a significant 22% decrease relative to non-invasive treatment in the composite end-point of death or MI in the invasive therapy group (relative risk 0.78; $p = 0.031$). The incidence of symptoms of angina and rate of need for re-admission to hospital were approximately halved by the use of invasive therapy. However, outcomes were not affected by the use of dalteparin (fig. 4). It should be noted that coronary angiography was performed within 7 days of presentation in 96 and 10%, and coronary revascularisation within 6 months in 77 and 37%, respectively, of patients in the invasive and non-invasive therapy groups.

2.4.2 Acute Myocardial Infarction

Since 1988, patients with acute MI have undergone routine treatment with intravenous thrombolysis, with the best results being obtained in patients who receive prompt treatment and who have early and complete restoration of blood flow in the affected coronary artery (reviewed by Frostfeldt et al.[108]). The additional effect of aspirin is well established, and infusion of UFH (in addition to initial recombinant tissue plasminogen activator therapy) has been shown to improve arterial patency in the short term.[109] As in patients with unstable CAD, interest has been shown in the LMWHs as easily administered alternatives to UFH in these individuals.

The largest available published study compared dalteparin with placebo in patients with acute anterior MI (diagnosed on the basis of clinical history and ECG changes).[110] In this randomised, double-blind multicentre trial, dalteparin 150 U/kg or placebo twice daily was started either immediately or 8 hours after thrombolysis with streptokinase (given to 91.5% of patients) and was continued for 7 to 11 days. Echocardiographic recordings showed 35 and 37% reductions, respectively, relative to placebo ($n = 270$) in a combined end-point of left ventricular thrombus formation or arterial thromboembolism and in left ventricular thrombus formation alone in 247 patients who received dalteparin (both $p < 0.05$) [fig. 5]. The odds ratio for left ventricular thrombosis for dalteparin versus placebo was 0.49 ($p = 0.009$), but there were no significant differences between groups in rates of mortality or re-infarction.

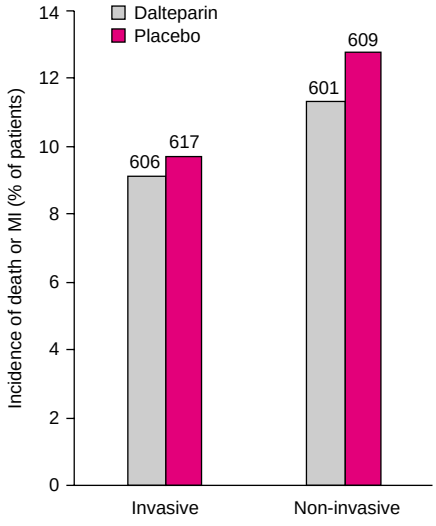

Fig. 4. Effect of dalteparin in patients randomised to invasive or non-invasive treatment of unstable coronary artery disease. A total of 2457 patients were assigned to either treatment approach and then randomised to double-blind therapy with dalteparin 5000 or 7500U (depending on bodyweight) or placebo twice daily for 3 months after nonblind initial treatment with dalteparin 120 U/kg twice daily.[107] Rates of death or myocardial infarction (MI) [combined end-point] are shown. Figures above bars show the numbers of patients available for 3-month assessment.

In this trial, 97.6% of patients received aspirin at a maintenance dosage of 160 mg/day.

In a smaller randomised, double-blind multicentre comparative study,[108] dalteparin 100 U/kg, given just before streptokinase and again after 12 hours in 54 patients, had no significant effect relative to placebo (47 patients) on angiographic signs of coronary reperfusion. There were no significant differences between groups in clinical outcomes, including rates of death or reinfarction, overall numbers of cardiac events or need for revascularisation, over 21 days. However, significantly fewer dalteparin than placebo recipients showed ECG evidence of ischaemic episodes from 6 to 24 hours after the start of treatment (16 *vs* 38%; p = 0.04).

Preliminary results from a study in which 1128 patients with acute MI who were not eligible for thrombolysis received dalteparin 120 U/kg twice daily in addition to aspirin for 3 days have indicated short term benefit of dalteparin.[111] A retrospective comparison with 679 patients treated at the same centres with UFH showed statistically significant (all $p < 0.001$) reductions with dalteparin therapy in incidences of death, revascularisation, left ventricular thrombus and heart failure. However, after randomised and double-blind treatment with dalteparin 7500U (n = 519) or placebo (n = 518) once daily for 1 month, there was no significant difference between groups in the composite end-point of death, re-infarction or infarct extension, revascularisation, post-infarction angina and heart failure at either day 30 or day 90.

2.5 Use in Haemodialysis and Haemofiltration

Blood flowing through haemodialysis circuits is in continuous contact with the surfaces of synthetic channels that lack the endothelial cell lining necessary for the prevention of blood coagula-

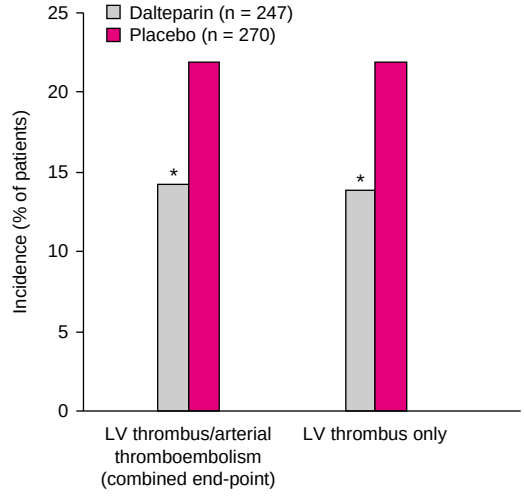

Fig. 5. Effect of dalteparin on clinical end-points in patients with acute anterior myocardial infarction. In a randomised, double-blind multicentre study, 517 evaluable patients received dalteparin 150 U/kg twice daily or placebo for 7 to 11 days (started after thrombolysis with streptokinase in 91.5% of patients).[110] Incidences of left ventricular (LV) thrombus or arterial thromboembolism and LV thrombus only are shown. * $p < 0.05$ *vs* placebo.

tion.[112] Pharmacological anticoagulation is therefore required to maintain circulation during haemodialysis or haemofiltration, and heparin is used widely in this setting.

LMWHs are of interest in the prevention of blood coagulation in extracorporeal circuits because they interact with platelets to a smaller extent than UFH (section 1) and have potential advantages in terms of bleeding complications. It may also be possible with these agents to maintain the patency of haemodialysis and haemofiltration circuits with a single loading dose, rather than the loading dose followed by continuous infusion that is conventionally used.

Studies previously reviewed in *Drugs*[3] showed consistent equivalent clinical efficacy of dalteparin and UFH in patients undergoing haemodialysis or haemofiltration.[22,113-117] In all studies, both types of heparin were administered as an initial bolus dose followed by continuous infusion (either intravenously or into the arterial side of the dialyser); initial doses of dalteparin typically ranged from 2500 to 5000U in these studies; subsequent infusions were administered at a fixed hourly rate, or were adjusted on the basis of bodyweight or whole blood activated clotting times. UFH was most commonly given in these studies as an initial bolus of 2000 to 5000IU, with subsequent infusion rates set in a manner similar to dalteparin. Generally, small numbers of patients were evaluated, but numbers of dialysis or filtration sessions assessed ranged from 20 to over 10 000, and sessions of both under and over 4 hours' duration were assessed. The efficacy of each heparin was most commonly expressed in terms of visual evidence of clot formation in the extracorporeal circuit, although the volume of occluded dialyser fibres was used as an end-point in 1 study,[115] and levels of fibrinopeptide A (a physiological indicator of coagulant activity) were measured in 2 others.[113,116]

Studies carried out since 1996 have continued to show similar efficacy of dalteparin and UFH in patients undergoing haemodialysis or haemofiltration,[118,119] and comparisons of dalteparin with other LMWHs (tinzaparin and nadroparin) have been undertaken.[120,121] Available details from these trials are summarised in table III.

In patients undergoing haemodialysis, anticoagulant efficacy assessments were based on the visual examination of extracorporeal circuits; there were no significant differences between dalteparin and tinzaparin or UFH in this respect in either of the 2 trials published since the last review.[119,120] There was also no significant difference between dalteparin and tinzaparin in the incidence of bleeding complications.[120] Single bolus treatment with dalteparin was compared with continuous infusion of UFH in the other haemodialysis study.[119] Mean venous compression times at the end of each procedure were not significantly different between heparins, and clotting times (as measured by a factor Xa-specific method) were prolonged to a similar extent, although the time spent on dialysis at each session in this crossover study in 18 patients was not stated.

In the haemofiltration study in which dalteparin was compared with UFH,[118] a total of 82 filters (41 in each group), of which 45 were withdrawn from use before failure due to blood clotting, were available for analysis. There was no significant difference between the dalteparin or UFH groups in time to failure of the haemofilter. Mean times to failure were 51.7 hours for UFH and 46.8 hours for dalteparin; corresponding median times were 44.3 and 63.0 hours. There were also no significant differences between groups in reduction in platelet counts or incidence of bleeding complications.

Similarly, filter survival times were similar with dalteparin and nadroparin in the study in which these 2 LMWHs were compared.[121] In the intention-to-treat analysis in 32 patients, 16 patients had filter survival times of more than 18 hours and 16 had filter survival times below 18 hours during the first course of haemofiltration. There was no correlation between the order of drug administration and filter survival time, and no thromboembolic or major bleeding complications were observed during the study.

Preliminary data from Germany[33,34] show benefit of dalteparin treatment in terms of effects on

Table III. Summary of comparative studies of dalteparin (D) in patients (pts) undergoing haemodialysis (HD) or haemofiltration (HF). Treatments were assessed primarily on the basis of their efficacy in the prevention of clotting of blood in extracorporeal circuits in pts receiving HD and in terms of time to failure of haemofilters in pts on HF

Reference	Pt characteristics		Study design	Heparin regimens	Relative overall efficacy
	no. evaluated	details of dialysis or filtration sessions			
Beijering et al.[120] (abstract)	159	40 HD sessions/pt	r, sb, mc	D (mean dose 5546 U/session; range 1875–12 913U)	D ≡ TZ
				TZ (mean dose 5024 U/session; range 700–1200U)	
de Pont et al.[121]	32	HF: flow rate of 200 ml/min and ultrafiltrate volume 100 L/24h. Time on HF not stated	r, db, co	D 2000U bolus, then 320 U/h	D ≡ N
				N 2050U bolus, then 328 U/h	
Kwon et al.[119] (abstract)	18	HD; D used for 2mo for consecutive sessions, then UFH for a further 2mo in all pts	nb; co	D single bolus; mean dose 2552 U/session	D ≡ UFH
				UFH CI; mean dose 3174 U/session	
Reeves et al.[118]	25	Manual and automatic HF systems used, both with circuit blood flow 120 ml/min. Mean total time on HF = 56h for D and 63h for UFH	r, pg	D 20 U/kg bolus, then 10 U/kg/h CI	D ≡ UFH
	22			UFH 2000–5000IU bolus, then 500–2000 IU/h to maintain aPTT at 60–80 sec	

aPTT = activated partial thromboplastin time; **CI** = continuous infusion; **co** = crossover; **db** = double-blind; **mc** = multicentre; **N** = nadroparin; **nb** = nonblind; **pg** = parallel groups; **r** = randomised; **sb** = single-blind; **TZ** = tinzaparin; **UFH** = unfractionated heparin; ≡ indicates equivalent overall efficacy.

blood lipid profiles in patients on haemodialysis. These results are reviewed in section 1.

2.6 Use in Ischaemic Stroke

The levels of mortality and morbidity associated with ischaemic stroke are considerable: approximately 25% of individuals affected die within a month of the event, and 6-month mortality is around 50%.[122] Of patients who survive beyond 6 months, only half remain capable of independent living.[122] The management of ischaemic stroke has until recently involved largely supportive measures, but increased understanding of the disorder and the development of novel therapies such as thrombolytic drugs and LMWHs has led to increased interest in active intervention. In addition, long term aspirin therapy has been shown to be useful in patients at high risk of occlusive vascular disease (including those with a history of stroke).[123]

At the time of the last review in *Drugs*,[3] a single double-blind comparison with placebo had been carried out in 60 patients in the acute phase of ischaemic stroke.[17] Although dalteparin 2500U twice daily for 14 days reduced the incidence of DVT relative to placebo (20 *vs* 50%; $p = 0.05$), there was no statistically significant difference between groups in the incidences of death (cerebral or all causes) or cerebral haemorrhage. Predominantly elderly pa-

tients were enrolled in this study (78% aged over 70 years), and none were receiving aspirin (patients using anticoagulant therapy other than dalteparin were excluded from this trial). Patients were required to start treatment within 72 hours of onset of symptoms.

Since that time, a much larger double-blind placebo-controlled study in which dalteparin 100 U/kg twice daily was compared with aspirin 160mg (orally or rectally) daily in 449 patients with atrial fibrillation and ischaemic stroke has been published [the Heparin in Acute Embolic Stroke Trial (HAEST)].[124] It should be noted that patients receiving oral anticoagulants were excluded from this trial. There were no statistically significant differences between groups in the primary end-point of recurrent ischaemic stroke over 14 days or in any of the secondary end-points (detailed in table IV). Neurological outcomes as measured by Scandinavian Stroke, modified Rankin, Barthel and International Stroke Trial (IST) scales over 14 days were similar between groups. In addition, the IST scale, which measures treatment effects in terms of death or levels of recovery and independence, showed similar outcomes in each treatment group after 3 months. The median age of the patients in this trial was 80 years, and randomisation was required within 30 hours of onset of stroke. The median duration of treatment was 13 days.

3. Pharmacoeconomic Considerations

LMWHs have higher acquisition costs than UFH, which makes their use superficially unattractive in purchase terms to healthcare providers and third party payers. However, economic analyses published in recent years have shown potential cost advantages related to clinical efficacy, ease of administration and the elimination of the need for laboratory monitoring with LMWHs.[125] Furthermore, data are available to show greater cost effectiveness of LMWH than UFH in patients requiring surgical thromboprophylaxis if the costs associated with failed prophylaxis are considered.[125]

The majority of pharmacoeconomic analyses of dalteparin have been carried out in patients requiring treatment for established thromboembolic disease, with an emphasis on the advantages to healthcare providers of home rather than hospital treatment. These analyses, 3 of which were attached to clinical studies reviewed in section 2.3.1,[83,86,91] considered costs associated with treatment only from an institutional perspective. Indirect and societal costs and cost effectiveness in terms of quality of life or years of life gained have not been assessed to date, although cost effectiveness in terms of episodes of DVT avoided has been calculated in 1 study.[126] Dalteparin was administered subcutaneously in all studies discussed in this section.

3.1 Treatment of Established Thromboembolism

In one of the studies reviewed in section 2.3.1,[83] mean hospital and treatment costs were calculated for 434 patients who received home treatment for established DVT with dalteparin 200

Table IV. Comparison of dalteparin (D) with aspirin therapy after ischaemic stroke in patients (pts) with atrial fibrillation[a]. Details and results from the Heparin in Acute Embolic Stroke Trial (HAEST).[124] Pts were randomised to treatment in a double-blind manner within 30 hours of stroke

No. of pts	Treatment	Primary end-point	Secondary end-points		
		recurrence of ischaemic stroke within 14 days (% of pts)	death within 14 days (% of pts)	symptomatic cerebral haemorrhage within 14 days (% of pts)	progression of symptoms within 48h (% of pts)
224	D 100 U/kg bid SC + PL od PO or PR × 14 days	8.5	9.4[b]	2.7	10.7
225	ASP 160mg od PO or PR + PL bid SC × 14 days	7.5	7.1[b]	1.8	7.6

a Confirmed by ECG.

b Causes of death were distributed evenly between groups.

bid = twice daily; **od** = once daily; **PL** = placebo; **PO** = orally; **PR** = rectally; **SC** = subcutaneously.

U/kg once daily for at least 4 days, with long term warfarin therapy being initiated from day 1. Home treatment was used for at least part of the treatment period in 80.2% of participants. Retrospective comparison with medical costs estimated for conventional inpatient treatment with dalteparin showed a reduction in direct cost per patient of 34.5% when the initial treatment was given on an outpatient basis. Costs were expressed in Swedish Kronor for the year 1996 and included staffing, premises, overheads, laboratory and diagnostic tests and drugs, and outpatient clinic costs.

Similarly, an Australian group showed an estimated overall per-patient cost saving of $A1239 (year of costing not stated) when 100 patients received dalteparin 200 U/kg once daily for at least 5 days as outpatients rather than as inpatients for the initial treatment of DVT.[86] Costs considered included full-time–equivalent nursing and medical staffing costs, on-call time, drugs, laboratory and diagnostic tests, and administrative costs associated with the home care programme.

Preliminary data from a retrospective analysis of 126 patient records in which standardised costs [in Canadian dollars ($Can) for 1996] were attached to hospital resource utilisation suggested annual institutional savings per 100 patients of $Can143 910 and $Can63 960 in community and teaching hospital settings, respectively, when dalteparin was used instead of UFH for the initial treatment of DVT (routes of administration not stated).[127]

A Spanish cost-minimisation study based on meta-analytical data showing therapeutic equivalence of subcutaneous dalteparin and continuous infusion of UFH indicated a 38% cost reduction when the former is used in the initial treatment of DVT.[128] Estimated hospital costs associated with dalteparin 200 U/kg/day or UFH 5000IU bolus followed by aPTT-adjusted infusion were applied in this analysis, and showed a cost per patient [in pesetas (Pta) for 1995–1996] of Pta7200 for dalteparin and Pta11 591 for UFH.

Results of a briefly reported cost analysis from the UK suggested that 3-month treatment with dalteparin 5000U once daily cost £900 less per patient (year of costing not stated) than conventional laboratory-adjusted warfarin therapy in 105 patients who presented with acute DVT.[91] Few details were given in this analysis of direct medical costs in which fixed costs were assigned to in- and outpatient care, procedures, investigations, consumables and staffing.

3.2 Surgical Thromboprophylaxis

Dalteparin has been compared in 2 pharmacoeconomic assessments with warfarin[126,129] in patients receiving thromboprophylaxis after total hip arthroplasty.

One of these analyses[129] was based on the results of a clinical study in 382 evaluable patients that was reported in section 2.1.1 and table I in which dalteparin 5000U once daily for a mean 7 days was compared with laboratory-adjusted warfarin.[51] The economic analysis, carried out from a hospital perspective, was based on clinical data from case report forms and financial data from the participating institutions. The primary method for determining treatment costs was based on standard costs of treatment 'activities' assigned to predefined outcome categories; a secondary method involved the calculation of the average cost per patient from the average length of hospital stay in each treatment group and a standard daily cost for total hip arthroplasty. Calculation of weighted average costs per patient for the inpatient stay and follow-up periods and average lengths of hospital stay resulted in average cost effectiveness ratios for dalteparin and warfarin, respectively, of $US10 925 and $US12 631 per event-free patient under the primary scenario. Corresponding ratios under the secondary scenario were $US13 517 and $US14 575. These results reflected the significantly lower rate of DVT in the dalteparin than in the warfarin group during hospitalisation in the clinical study (14.6 *vs* 25.8%; p = 0.006) [table I]. Incremental cost effectiveness of dalteparin (i.e. the additional cost of dalteparin for each additional event-free patient, a key parameter in policy decision making) was $US375 and $US6509 under the primary and

secondary scenarios, respectively. Sensitivity analysis indicated the findings to be robust.

Preliminary results of a double-blind, placebo-controlled multicentre study carried out in the US and Canada have shown cost effectiveness from a hospital perspective of dalteparin relative to warfarin in patients receiving long term surgical thromboprophylaxis.[126] Of 1130 patients randomised to dalteparin treatment starting before or after surgery or to warfarin therapy, 625 proceeded after a mean 6 days to prophylaxis for a mean 35 days. Cost calculations (year of costing not stated) were based primarily on medical interventions associated with thromboembolic complications and the length of hospital stay. Overall costs per patient were similar under all 6 treatment scenarios [short or long term prophylaxis with dalteparin (started before or after surgery) or warfarin], but a statistically higher incidence of suspected DVT in patients receiving warfarin than in dalteparin recipients resulted in incremental cost effectiveness of dalteparin of between $US1799 and $US4661 per patient.

3.3 Management of Coronary Artery Disease

As reviewed in section 2.4, there has been intense interest in recent years in the management with heparin of patients with CAD. Of particular interest in the light of these continuing research efforts is an analysis carried out in Canada that showed similarity of costs from a hospital perspective of UFH and dalteparin therapy.[130] In this 9-week prospective time and motion study, direct medical costs (in 1998 $Can) were calculated for 116 consecutive patients receiving continuous aPTT-adjusted UFH infusions, of whom 77% had unstable CAD and 23% acute MI. Costs analysed included those associated with nursing-related activities (at a predetermined rate of $Can25/hour), and laboratory, supply, drug and equipment costs. The mean total daily cost of UFH therapy ($Can25.68/patient) included a variety of contributing elements, including establishment of intravenous access, preparation of doses and maintenance of drip lines, adjustment of infusion rates, and costs associated with aPTT monitoring. A projected cost of dalteparin therapy was calculated on the basis of an acquisition cost of $Can0.0015 per unit and a dosage of 120 U/kg twice daily. The mean total daily cost based on an average patient bodyweight of 74kg was $Can28.82, which included a nursing and syringe cost of $Can2.26. There were no other costs associated with dalteparin therapy.

4. Tolerability

Haemorrhage is the adverse effect of greatest concern with anticoagulant therapy. Accordingly, many clinical trials carried out with dalteparin include information on bleeding complications reported during treatment and follow-up, although data from large scale postmarketing studies remain unavailable.

The extensive range of clinical studies reviewed in *Drugs* in 1996[3] showed no significant difference overall in rates of bleeding complications (perioperative blood loss and transfusion requirements and major and minor haemorrhage) between dalteparin and UFH in surgical patients requiring thromboprophylaxis and in individuals receiving treatment for established thromboembolic disease. More recent studies have continued to show no conclusive trends. Collated data from studies in patients receiving dalteparin 2500 or 5000U or UFH 10 000IU daily for thromboprophylaxis in abdominal surgery show rates of haemorrhagic complications to be similar for either heparin, with a tendency towards higher frequencies with increased dosages of dalteparin (fig. 6).[131]

Increased frequencies of bleeding complications relative to placebo were reported with long term (up to 3 months) dalteparin in studies in patients with unstable CAD and with acute treatment for MI (sections 2.4.1 and 2.4.2). After 3 months' treatment in the FRISC II study, major haemorrhage was reported in 3.3% of 1049 dalteparin recipients and 1.5% of 1056 patients who received placebo.[103] Corresponding incidences of minor bleeding were 23 and 8.4%. In 1 study in patients with acute MI, major haemorrhage was reported in 2.9% of 388

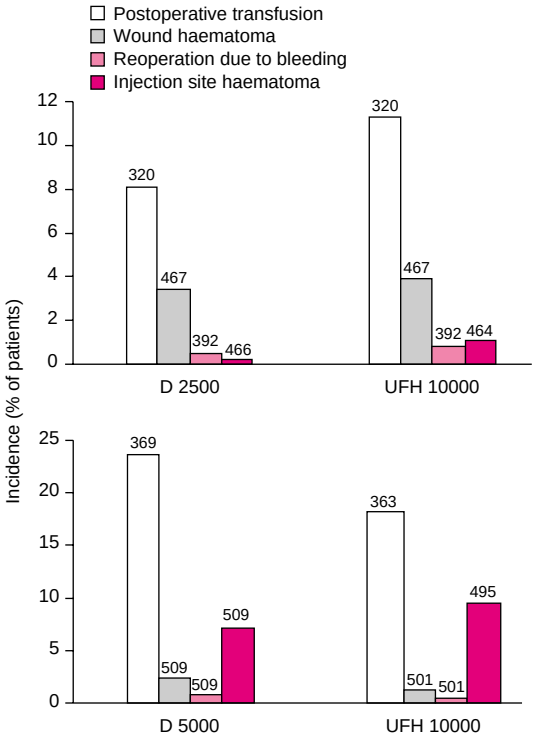

Fig. 6. Incidence of haemorrhagic adverse events in surgical patients receiving thromboprophylactic dalteparin (D) or unfractionated heparin (UFH). Collated results are presented from studies in which D 2500 or 5000U once daily was compared with UFH 5000 IU twice daily.[131] The numbers of patients evaluated for each event are shown above the bars.

evaluable patients who received dalteparin 150 U/kg twice daily and in 0.3% of 388 placebo recipients ($p = 0.006$).[110]

Dalteparin has been well tolerated, with no excess incidence of bleeding complications relative to placebo, in patients undergoing orthopaedic surgery with extended (35-day) thromboprophylaxis,[53-55] and there have been no reports of clinically significant haemorrhagic complications attributed to the drug in pregnant women.[62-65] Anti-factor Xa activity data obtained 3 to 4 hours after subcutaneous injection of dalteparin 2500 or 5000U in nursing women have indicated that the drug is not transferred into breast milk to any clinically significant extent.[132]

Drug-induced osteopenia is of particular relevance in pregnant women because of the physiological changes in calcium and bone homeostasis induced by pregnancy. Previously reviewed data[133] indicated that dalteparin may affect bone density to a smaller extent than UFH, and subsequent studies of bone metabolism and mineral content in rats have shown weaker suppression of bone formation with dalteparin than with UFH.[134] In one of the studies in pregnant women reported in section 2.2,[62] 1 osteoporotic fracture was reported after delivery in a patient who had received a high dosage of dalteparin (15 000U daily) for most of a 36-week treatment period.[62] This patient had no other risk factors for osteoporosis.

The precise incidence of thrombocytopenia (a rare but potentially fatal complication of heparin therapy) associated with dalteparin is not known,[5] but has been reported to be less than 1% in patients receiving the drug for thromboprophylaxis.[131] Dalteparin has been shown to react with plasma from patients susceptible to heparin-induced thrombocytopenia (HIT) who possess UFH-associated antiplatelet antibodies, although the drug did not cause platelet aggregation in all cases.[135-139] LMWHs are not generally recommended in patients with established HIT because of high levels of cross-reactivity with antibodies generated during exposure to UFH,[140] although it has been suggested that *in vitro* cross-reactivity testing might be used to select patients with UFH-associated HIT in whom LMWH therapy might be possible.[141]

5. Dosage and Administration

Dalteparin is presented in single-dose syringes for subcutaneous use in thromboprophylaxis and in vials and ampoules for intravenous or subcutaneous use in a variety of indications.

Since the publication of the last review,[3] there has been an increase in the number of indications for dalteparin, and dosage regimens (most of which are from the UK) are summarised in detail in table V. Briefly, patients at moderate risk of venous

Table V. Dosages of dalteparin as recommended by UK and US authorities[5,6,142,143]

Indication	Dosage (subcutaneous administration unless stated otherwise)
Surgical thromboprophylaxis in patients at moderate risk (e.g. in general surgery)	2500U 1–2h before surgery and od thereafter × 5–10 days[5,143]
Surgical thromboprophylaxis in patients at high risk (e.g. in orthopaedic surgery)	2500U 1–2h before surgery and 8–12h later, then 5000U od × 5–7 days.[143] Alternatively 5000U on evening before, then 5000U od × 5–10 days[5]
Prolonged thromboprophylaxis after hip replacement surgery	5000U on evening before surgery, then 5000U od × 5wks[143]
Treatment of established thromboembolism	200 U/kg (≤18 000U) od or 100 U/kg bid × ≥5 days, with simultaneous commencement of long term oral anticoagulation[6,142]
Prevention of clotting during haemodialysis or haemofiltration	Duration ≥4h: 30–40 U/kg IV bolus, then 10–15 U/kg/h CI. Duration <4h: as above, or single 5000U IV bolus[6]
Unstable coronary artery disease	120 U/kg (≤10 000U) every 12h × 5–8 days with concomitant aspirin therapy[6]

bid = twice daily; **CI** = continuous infusion; **IV** = intravenous; **od** = once daily.

thromboembolism after surgery should receive dalteparin subcutaneously at a dosage of 2500U once daily; patients at high risk should receive 5000U once daily. A dosage of 200 U/kg once daily or 100 U/kg twice daily is recommended for the initial treatment of established thromboembolic disease, and 120 U/kg every 12 hours in addition to aspirin is indicated for patients with unstable CAD. An intravenous weight-adjusted bolus followed by continuous infusion is indicated for haemodialysis or haemofiltration procedures lasting 4 hours or more. Single intravenous boluses of 5000U may be suitable for procedures of less than 4 hours' duration.

The abdomen or the lateral portion of the thigh are the preferred sites for subcutaneous administration. Patients should be supine, and the needle should be introduced vertically into a skin fold held between the thumb and forefinger until after the needle is withdrawn.[5,142]

Laboratory monitoring of therapy is not necessary in most indications. However, in patients undergoing long or short term haemodialysis or haemofiltration, plasma anti-factor Xa activities should be between 500 and 1000 U/L. In acute renal failure, or in chronic renal failure with high risk of bleeding, an initial intravenous bolus of 5 to 10 U/kg should be followed by infusion of 4 to 5 U/kg/hour. Plasma anti-factor Xa activities should be held at 200 to 400 U/L.[6]

Twice-daily subcutaneous administration of 100 U/kg can be used in patients at high risk of bleeding complications who require treatment for established thromboembolic disease (table V). Monitoring of treatment is generally not necessary, but can be carried out with an anti-factor Xa assay if required to maintain an activity in plasma of between 500 and 1000 U/L.[6]

When using dalteparin for surgical thromboprophylaxis or for the treatment of established thromboembolic disease, caution is recommended in patients with severe hepatic or renal insufficiency.[5,6,131] Patients with severely disturbed hepatic function may require dosage reductions and should be monitored accordingly.

6. Place of Dalteparin in Thromboprophylaxis and the Management of Thromboembolic Disease

Data available at the time of the last review indicated dalteparin given subcutaneously once daily to be at least as effective as UFH given 2 to 3 times daily as thromboprophylaxis in surgical patients at moderate to high risk of DVT. More recent studies have continued to show this trend, with an emphasis on 5000U doses of dalteparin. Once-daily dalteparin has also been shown in recent trials to be more effective in the prevention of DVT than laboratory-monitored adjusted-dosage warfarin in patients undergoing orthopaedic surgery (section 2.1.1). These studies covered both long and short term prophylaxis periods, and full details from those available currently in preliminary form only are awaited with interest.

It should be noted here that superiority of dalteparin in patients requiring thromboprophylaxis has generally been expressed in terms of reductions in incidence of venographically detected DVT. However, the acceptability and consistency of interpretation of surrogate end-points have been called into question,[144,145] and it may be argued that such results are not as relevant as clinical endpoints such as symptomatic DVT, PE and death.[146] In addition, it is important to ensure in comparisons with warfarin that target INRs are appropriate, and that they are reached and maintained in patients receiving oral anticoagulation.

Published studies that compare dalteparin with other LMWHs in patients requiring thromboprophylaxis remain few and inconclusive (section 2.1.2). Further studies involving larger numbers of patients than have been assessed to date are required to shed more light on this issue.

The global trend towards early transfer after surgery of patients from hospital to the community has given urgency to the need for definitive and universally accepted recommendations on the optimum duration of thromboprophylaxis.[147] The once-daily administration regimens of LMWHs, with their lack of need for laboratory monitoring, makes these agents potentially suitable for outpatient use, and the feasibility of this approach has been demonstrated in a number of recent studies in patients receiving either surgical prophylaxis or treatment for established thromboembolic disease.[148-151] Results reviewed in section 2.1.1 indicate that long term thromboprophylaxis with dalteparin (extended for around 1 month on an outpatient basis) is more effective than conventional 5- to 7-day prophylaxis.

At the time of the last review,[3] dalteparin given subcutaneously once or twice daily or by intravenous infusion had been shown to be of similar efficacy to intravenously infused aPTT-adjusted UFH in the acute management of established DVT. More recent data (section 2.3) also show equivalence of the 2 therapies, with up to 14 years' follow-up showing no difference in eventual clinical outcomes. In addition, home treatment with dalteparin for 3 months appears on the basis of current data to be of similar efficacy to adjusted-dosage warfarin therapy (section 2.3.1). These results indicate that dalteparin is likely to be an effective and practical alternative to warfarin, particularly in the management of patients who cannot tolerate coumarin anticoagulants. It has also been suggested that combined therapy with LMWH and warfarin is warranted in patients in whom warfarin therapy alone is likely to fail, although this requires further study.[152]

A lack of data from controlled trials to show conclusive evidence of benefit with acceptable tolerability in pregnancy precludes any firm recommendations on the use of LMWHs in this setting. However, reports to date (section 2.2) suggest that dalteparin is effective, with no adverse effects on pregnancy outcomes or excess haemorrhagic complications, in pregnant women at high risk of thromboembolic disease. The authors of a comprehensive review of data from a large number of clinical studies have recently concluded that frequencies of maternal complications and adverse fetal outcomes in women receiving LMWHs are similar to those seen in general populations of pregnant women.[153] Further studies are needed to provide more information on the use of dalteparin in these patients, particularly with reference to the use of anti-factor Xa activity-adjusted versus standard dosages and the identification of any advantage over UFH in terms of antithrombotic efficacy and rates of HIT and osteoporosis.[154]

Subcutaneous dalteparin has been shown consistently in major clinical studies to be effective when used in addition to aspirin therapy in the acute management of patients with unstable CAD (section 2.4.1). The first FRISC study indicated benefit after 40 days' continued treatment in non-smoking and nonobese patients, although it should be noted that subgroup analyses (which are subject to limitation in terms of statistical power) were used to obtain these results.[102] Evidence is available from the more recent FRISC II study to suggest benefit of dalteparin when continued for 3 months in patients with unstable CAD.[103] Subsequent findings have suggested a link between

long term benefit of dalteparin and the presence of high plasma levels of the cardiac marker troponin-T.[104] Overall, further research is needed to quantify the benefit of dalteparin treatment (in addition to aspirin) when continued beyond 1 month in patients with unstable CAD.

The management of CAD is a rapidly evolving field, and efforts are ongoing to refine acute and long term treatment strategies and to tailor therapy to patients on the basis of risk stratification.[155] Although further studies are required to determine whether subcutaneous dalteparin has advantages over intravenously infused UFH in terms of efficacy, this LMWH nevertheless appears to be an easily administered alternative that is likely to be of particular value where therapy is continued beyond the initial period of hospitalisation in patients with unstable angina or non–Q-wave MI.

Recent treatment guidelines strongly recommend the use of anticoagulant therapy (in addition to aspirin) in patients with acute MI, whether or not they are eligible for thrombolytic treatment.[156] Such anticoagulation has traditionally taken the form of intravenous UFH (bolus followed by aPTT-adjusted infusion), with low-dosage subcutaneous therapy being suitable for some patients. Early studies (section 2.4.2) indicate that dalteparin is a viable alternative in the management of acute MI, but comparative studies are currently not available. Further data are required to clarify the place of the drug in the management of this condition.

Studies continue to show that dalteparin is of equivalent efficacy to UFH in the maintenance of patency of haemodialysis circuits, although recent data show that it is possible to manage some patients with a single dose of dalteparin, administered intravenously at the start of each session (section 2.5). Further studies are needed to evaluate fully the potential of this approach. The use of dalteparin in patients undergoing haemodialysis has also been associated with improvements relative to UFH in blood lipid profiles over periods of up to 5 years (section 1.2); whether these improvements translate into better long term clinical outcomes (e.g. in terms of cardiovascular events) remains to be clarified.

A role for dalteparin in the management of acute ischaemic stroke has not been demonstrated. The most reliable data available[124] (section 2.6), which show no advantage of the drug over aspirin, have been obtained in patients with atrial fibrillation, which is thought to account for some 20% of ischaemic strokes.[157]

The ease of administration of dalteparin and the lack of need for laboratory monitoring that is required for therapeutic regimens of UFH or warfarin have led not only to increasing experimentation with long term treatment and therapy in the home setting, but have also generated much interest in economic benefits that might accrue from the use of the drug. Cost analyses carried out from a hospital perspective have indicated that cost savings are indeed achieved when acute episodes of thromboembolism are managed on an outpatient basis rather than in hospital. In addition, costs are reduced when dalteparin is used in place of UFH in acute management or warfarin in long term (3-month) treatment (section 3.1). Cost effectiveness of dalteparin has been shown in patients requiring surgical thromboprophylaxis after total hip arthroplasty (section 3.2). Dalteparin also appears on the basis of 1 Canadian study to be no more expensive overall than UFH when used in patients with CAD (section 3.3).

These findings support the use of dalteparin in place of UFH or warfarin from a pharmacoeconomic viewpoint, but it should be noted that some current data are based on retrospective comparisons or on the assignment of monetary values to previously obtained clinical trial data, and well designed prospective pharmacoeconomic studies are now required to confirm these findings. In addition, the indirect and societal cost implications of dalteparin treatment or prophylaxis are not yet known, and effects on quality of life of the different treatment options have not been compared. Future analyses need also to account for the effects of the shifting of costs from hospitals to the community when outpatient management is adopted.

As discussed in section 4, haemorrhagic complications with dalteparin are infrequent and are no more prevalent than with UFH in patients receiving treatment for established thromboembolic disease or thromboprophylaxis, or in patients undergoing haemodialysis or haemofiltration. Data from patients receiving dalteparin for up to 3 months for the management of unstable CAD have shown some trends towards increased haemorrhage relative to placebo, and increased major bleeding has been reported with dalteparin in a comparison with placebo in patients with acute MI.

In conclusion, dalteparin is effective and well tolerated when given subcutaneously once daily in the prophylaxis and treatment of thromboembolic disease. The simplicity of the administration regimens used and the lack of necessity for laboratory monitoring of therapy facilitate home or outpatient treatment and appear to translate into cost advantages from a hospital perspective over UFH or warfarin. Dalteparin also maintains the patency of haemodialysis and haemofiltration circuits, with beneficial effects on blood lipid profiles and the potential for prophylaxis with a single bolus injection in some patients. Data are also accumulating to show dalteparin to be an effective and easily administered alternative to UFH in patients with CAD.

References

1. Pineo GF, Hull RD. Unfractionated and low-molecular-weight heparin: comparisons and current recommendations. Med Clin North Am 1998; 82 (3): 587-99
2. Hirsh J, Warkentin TE, Raschke R, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety. Chest 1998; 114 (5) Suppl.: 489S-510S
3. Dunn CJ, Sorkin EM. Dalteparin sodium. A review of its pharmacology and clinical use in the prevention and treatment of thromboembolic disorders. Drugs 1996 Aug; 52: 276-305
4. Wolf H. Low-molecular-weight heparin. Med Clin North Am 1994; 78 (3): 733-43
5. Dalteparin sodium. In: McEvoy GK, editor. AHFS drug information. Bethesda, MD: American Society of Health-System Pharmacists, 1999: 1253-5
6. Fragmin ampoules. In: Walker G, editor. ABPI compendium of data sheets and summaries of product characteristics 1998-99. London: Datapharm Publications Ltd, 1998: 1000-1
7. Holmer E, Söderberg K, Bergqvist D, et al. Heparin and its low molecular weight derivatives: anticoagulant and antithrombotic properties. Haemostasis 1986; 16 Suppl. 2: 1-7
8. Barrowcliffe TW, Curtis AD, Johnson EA, et al. An international standard for low molecular weight heparin. Thromb Haemost 1988; 60: 1-7
9. Agnelli G, Borm J, Cosmi B, et al. Effects of standard heparin and a low molecular weight heparin (Kabi 2165) on fibrinolysis. Thromb Haemost 1988 Oct 31; 60: 311-3
10. Andrassy K, Mörike K, Koderisch J, et al. Human pharmacological studies of a defined low molecular weight heparin fraction (Fragmin®) evidence for a simultaneous inhibition of factor Xa and IIa (thrombin). Thromb Res 1988 Mar 15; 49: 601-11
11. Mätzsch T, Bergqvist D, Burmark US, et al. The influence of surgical trauma on factor XaI and IIaI activity and heparin concentration after a single dose of low-molecular-weight heparin. Blood Coagul Fibrinolysis 1991 Oct; 2: 651-7
12. Bara L, Combe-Tamzali S, Conard J, et al. Comparative biological modifications induced by 3 low molecular weight heparins, PK 10169, Kabi 2165 and CY 216 and a non-fractionated heparin, injected subcutaneously in healthy volunteers, general surgery patients and elderly patients with medical disorders [in French]. J Mal Vasc 1987; 12 Suppl. B: 78-84
13. Eriksson BI, Söderberg K, Widlund L, et al. A comparative study of three low-molecular weight heparins (LMWH) and unfractionated heparin (UH) in healthy volunteers. Thromb Haemost 1995 Mar; 73: 398-401
14. Eriksson E, Wollter IM, Christenson B, et al. Heparin and fibrinolysis – comparison of subcutaneous administration of unfractionated and low molecular weight heparin. Thromb Haemost 1988 Apr 8; 59: 284-8
15. Eriksson BI, Zachrisson BE, Teger-Nilsson A-C, et al. Thrombosis prophylaxis with low molecular weight heparin in total hip replacement. Br J Surg 1988 Nov; 75: 1053-7
16. Ockelford PA, Patterson J, Johns AS. A double-blind randomized placebo controlled trial of thromboprophylaxis in major elective general surgery using once daily injections of a low molecular weight heparin fragment (Fragmin). Thromb Haemost 1989 Dec 29; 62: 1046-9
17. Prins MH, Gelsema R, Sing AK, et al. Prophylaxis of deep venous thrombosis with a low-molecular-weight heparin (Kabi 2165/Fragmin®) in stroke patients. Haemostasis 1989; 19 (5): 245-50
18. Onarheim H, Lund T, Heimdal A, et al. A low molecular weight heparin (KABI 2165) for prophylaxis of postoperative deep venous thrombosis. Acta Chir Scand 1986 Oct; 152: 593-6
19. Caen JP. A randomized double-blind study between a low molecular weight heparin Kabi 2165 and standard heparin in the prevention of deep vein thrombosis in general surgery. A French multicenter trial. Thromb Haemost 1988 Apr 8; 59: 216-20
20. Koller M, Schoch U, Buchmann P, et al. Low molecular weight heparin (KABI 2165) as thromboprophylaxis in elective visceral surgery. A randomized, double-blind study versus unfractionated heparin. Thromb Haemost 1986 Dec 15; 56 (3): 243-6
21. Bergqvist D, Burmark US, Frisell J, et al. Prospective double-blind comparison between Fragmin and conventional low-dose heparin: thromboprophylactic effect and bleeding complications. Haemostasis 1986; 16 Suppl. 2: 11-8
22. Schrader J, Stibbe W, Armstrong VW, et al. Comparison of low molecular weight heparin to standard heparin in hemodialysis/hemofiltration. Kidney Int 1988; 33: 890-6
23. Padilla A, Gray E, Pepper DS, et al. Inhibition of thrombin generation by heparin and low molecular weight (LMW) heparins in the absence and presence of platelet factor 4 (PF4). Br J Haematol 1992 Oct; 82: 406-13

24. O'Brien JR, Etherington MD, Pashley MA. The heparin-mobilisable pool of platelet factor 4: a comparison of intravenous and subcutaneous heparin and Kabi heparin fragment 2165. Thromb Haemost 1985 Dec 17; 54: 735-8
25. Andersen BS. Postoperative activation of the haemostatic system – influence of prolonged thromboprophylaxis in patients undergoing total hip arthroplasty. Haemostasis 1997 Sep-Oct; 27: 219-27
26. Wolzt M, Eder M, Weltermann A, et al. Comparison of the effects of different low molecular weight heparins on the hemostatic system activation in vivo in man. Thromb Haemost 1997 Aug; 78: 876-9
27. Ernofsson M, Strekerud F, Toss H, et al. Low-molecular weight heparin reduces the generation and activity of thrombin in unstable coronary artery disease. Thromb Haemost 1998 Mar; 79: 491-4
28. Myrmel T, Larsen TS, Reikerås O. Lipolytic effect of low-molecular-weight-heparin (Fragmin®) and heparin/dihydroergotamine in thromboprophylactic doses during total hip replacement. Scand J Clin Lab Invest 1992 Nov; 52: 741-5
29. Schmitt Y, Schneider H. Low-molecular-weight heparin (LMWH): influence on blood lipids in patients on chronic haemodialysis. Nephrol Dial Transplant 1993; 8 (5): 438-42
30. Persson E. Lipoprotein lipase, hepatic lipase and plasma lipolytic activity. Effects of heparin and a low molecular weight heparin fragment (Fragmin). Acta Med Scand Suppl 1988; 724: 1-56
31. Persson E, Nordenström J, Hagenfeldt L, et al. Plasma lipolytic activity after subcutaneous administration of heparin and a low molecular weight heparin fragment. Thromb Res 1987; 46: 697-704
32. Deuber HJ, Schulz W. Reduced lipid concentrations during four years of dialysis with low molecular weight heparin. Kidney Int 1991; 40: 496-500
33. Schmitt Y, Schneider H. The influence of low molecular weight heparin on blood lipoproteins in patients on chronic hemodialysis [abstract]. Atherosclerosis 1997 1-2, Oct No; 134: 49
34. Lüders S, Kandt M, Schrader J. Low molecular weight heparin versus standard heparin in patients with hypertriglyceridemia on hemodialysis - 5 years follow-up [abstract]. Nephrol Dial Transplant 1996 Jun; 11: A221
35. Bratt G, Törnebohm E, Lockner D, et al. A human pharmacological study comparing conventional heparin and a low molecular weight heparin fragment. Thromb Haemost 1985; 53: 208-11
36. Bratt G, Törnebohm E, Widlund L, et al. Low molecular weight heparin (Kabi 2165, Fragmin): pharmacokinetics after intravenous and subcutaneous administration in human volunteers. Thromb Res 1986 Jun 1; 42: 613-20
37. Dryjski M, Schneider DE, Mojaverian P, et al. Investigations on plasma activity of low molecular weight heparin after intravenous and oral administrations. Br J Clin Pharmacol 1989 Aug; 28: 188-92
38. Collignon F, Frydman A, Caplain H, et al. Comparison of the pharmacokinetic profiles of three low molecular mass heparins - dalteparin, enoxaparin and nadroparin - administered subcutaneously in healthy volunteers (doses for prevention of thromboembolism). Thromb Haemost 1995 Apr; 73: 630-40
39. Simoneau G, Bergmann JF, Kher A, et al. Pharmacokinetics of a low molecular weight heparin [Fragmin] in young and elderly subjects. Thromb Res 1992 Jun 1; 66: 603-7
40. Palm M, Mattsson C. Pharmacokinetics of heparin and low molecular weight heparin fragment (Fragmin) in rabbits with impaired renal or metabolic clearance. Thromb Haemost 1987 Oct 28; 58: 932-5
41. Jørgensen B, Nielsen C, Rasmussen LH. Erythrocyte adhesion affects the bioavailability of low-molecular-weight heparin [abstract]. Haemostasis 1998 Nov; 28 Suppl. 3: 134
42. Stiekema JCJ, van Griensven JM, van Dinther TG, et al. A crossover comparison of the anti-clotting effects of three low molecular weight heparins and glycosaminoglycuronan. Br J Clin Pharmacol 1993 Jul; 36: 51-6
43. Greer IA, Gibson JL, Young A, et al. Effect of ketorolac and low molecular weight heparin individually and in combination on haemostasis. Blood Coagul Fibrinolysis 1998 Nov; 10: 367-73
44. Bergqvist D. Modern aspects of prophylaxis and therapy for venous thrombo-embolic disease. Aust N Z J Surg 1998; 68 (7): 463-8
45. Thromboembolic Risk Factors (THRIFT) Consensus Group. Risk of and prophylaxis for venous thromboembolism in hospital patients. BMJ 1992 Sep 5; 305: 567-74
46. Flordal PA, Bergqvist D, Burmark US, et al. Risk factors for major thromboembolism and bleeding tendency after elective general surgical operations. Eur J Surg 1996 Oct; 162: 783-9
47. Nurmohamed MT, Rosendaal FR, Büller HR, et al. Low-molecular-weight heparin versus standard heparin in general and orthopaedic surgery: a meta-analysis. Lancet 1992 Jul 18; 340: 152-6
48. Nurmohamed MT, Büller HR, ten Cate JW. Physiological changes due to age: implications for the prevention and treatment of thrombosis in older patients. Drugs Aging 1994 Jul; 5 (1): 20-33
49. Bergqvist D, Mätzsch T, Burmark US, et al. Low molecular weight heparin given the evening before surgery compared with conventional low-dose heparin in prevention of thrombosis. Br J Surg 1988 Sep; 75 (9): 888-91
50. Eriksson BI, Kälebo P, Anthmyr BA, et al. Prevention of deep-vein thrombosis and pulmonary embolism after total hip replacement. J Bone Joint Surg Am 1991 Apr; 73A (4): 484-93
51. Francis CW, Pellegrini Jr VD, Totterman S, et al. Prevention of deep-vein thrombosis after total hip arthroplasty. Comparison of warfarin and dalteparin. J Bone Joint Surg Am 1997 Sep; 79: 1365-72
52. Pineo GF, Hull RD. A double-blind randomized comparison of low-molecular-weight heparin prophylaxis using dalteparin in close proximity to surgery [abstract]. Blood 1999; 94 Suppl. 1 (Pt 1): 30a
53. Hull RD, Pineo GF. A double-blind, randomized comparison of low-molecular-weight heparin prophylaxis using dalteparin extended out-of-hospital versus warfarin-placebo in hip-arthroplasty patients [abstract]. Blood 1999; 94 Suppl. 1 (Pt 1): 29a
54. Dahl OE, Andreassen G, Aspelin T, et al. Prolonged thromboprophylaxis following hip replacement surgery – results of a double-blind, prospective, randomised, placebo-controlled study with dalteparin (Fragmin). Thromb Haemost 1997 Jan; 77: 26-31
55. Lassen MR, Borris LC, Anderson BS, et al. Efficacy and safety of prolonged thromboprophylaxis with a low molecular weight heparin (dalteparin) after total hip arthroplasty - the Danish Prolonged Prophylaxis (DaPP) Study. Thromb Res 1998 Mar 15; 89: 281-7
56. Hartl P, Brücke P, Dienstl E, et al. Prophylaxis of thromboembolism in general surgery: comparison between standard heparin and Fragmin. Thromb Res 1990 Feb 15; 57: 577-84
57. Kakkar VV, Cohen AT, Edmondson RA. Low molecular weight versus standard heparin for prevention of venous thromboembolism after major abdominal surgery. Lancet 1993 Jan 30; 341: 259-65

58. Ward B, Pradhan S. Comparison of low molecular weight heparin (Fragmin) with sodium heparin for prophylaxis against postoperative thrombosis in women undergoing major gynaecological surgery. Aust NZ J Obstet Gynaecol 1998 Feb; 38: 91-2
59. Kollár L, Scholz ME, Roszos I. Comparison of pentosan polysulfate sodium (Na-PPS) with a low-molecular-weight heparin in the prevention of venous thrombosis after abdominal surgery. Perfusion 1994 Apr; 7 (4): 123-30
60. Bounameaux H, Huber O, Khabiri E, et al. Unexpectedly high rate of phlebographic deep venous thrombosis following elective general abdominal surgery among patients given prophylaxis with low-molecular-weight heparin. Arch Surg 1993 Mar; 128: 326-8
61. Røise O, Nurmohamed M, Reijnders P, et al. A multicentre, randomised, assessor-blind, pilot study comparing the efficacy in the prophylaxis of DVT and the safety of Orgaran (Org 10172), Fragmin, Clexane/Lovenox in patients undergoing surgery for a fractured hip [abstract]. Thromb Haemost 1993 Jun; 69 (6): 620
62. Hunt BJ, Doughty HA, Majumdar G, et al. Thromboprophylaxis with low molecular weight heparin (Fragmin) in high risk pregnancies. Thromb Haemost 1997 Jan; 77: 39-43
63. Pettilä V, Kaaja R, Leinonen P, et al. Thromboprophylaxis with low molecular weight heparin (Dalteparin) in pregnancy. Thromb Res 1999; 96 (4): 275-82
64. Blombäck M, Bremme K, Hellgren M, et al. Thromboprophylaxis with low molecular mass heparin, 'Fragmin' (dalteparin), during pregnancy - a longitudinal safety study. Blood Coagul Fibrinolysis 1998 Jan; 9: 1-9
65. Geisen U, Abou-Mandour N, Grossman R, et al. Long-term thromboprophylaxis with low-molecular-weight-heparin (dalteparin) in high-risk pregnancies [abstract]. Haemostasis 1998 Nov; 28 Suppl. 3: 137
66. Charland SL, Klinter DEJ. Low-molecular-weight heparins in the treatment of pulmonary embolism. Ann Pharmacother 1998; 32 (2): 258-64
67. Marder VJ, Soulen RL, Atichartakarn V, et al. Quantitative venographic assessment of deep vein thrombosis in the evaluation of streptokinase and heparin therapy. J Lab Clin Med 1977; 89 (5): 1018-29
68. Albada J, Nieuwenhuis HK, Sixma JJ. Treatment of acute venous thromboembolism with low molecular weight heparin (Fragmin). Results of a double-blind randomized study. Circulation 1989 Oct; 80: 935-40
69. Lockner D, Bratt G, Törnebohm E, et al. Intravenous and subcutaneous administration of Fragmin in deep venous thrombosis. Haemostasis 1986; 16 Suppl. 2: 25-9
70. Aiach M, Fiessinger JN, Vitoux JF, et al. Deep vein thrombosis treatment. A comparative study: subcutaneous Fragmin versus unfractionated heparin administered by continuous infusion. Multicenter trial [in French]. Rev Med Interne 1989 Jul-Aug; 10: 375-81
71. Bratt G, Åberg W, Johansson M, et al. Two daily subcutaneous injections of Fragmin as compared with intravenous standard heparin in the treatment of deep vein thrombosis (DVT). Thromb Haemost 1990 Dec 28; 64: 506-10
72. Fiessinger J-N, Lopez-Fernandez M, Gatterer E, et al. Once-daily subcutaneous dalteparin, a low molecular weight heparin, for the initial treatment of acute deep vein thrombosis. Pharmacia & Upjohn (Stockholm). Data on file
73. Holm HA, Ly B, Handeland GF, et al. Subcutaneous heparin treatment of deep vein thrombosis: a comparison of unfractionated and low molecular weight heparin. Haemostasis 1986; 16 Suppl. 2: 30-7
74. Lindmarker P, Holmström M, Granqvist S. Comparison of once-daily subcutaneous Fragmin® with continuous intravenous unfractionated heparin in the treatment of deep vein thrombosis. Thromb Haemost 1994 Aug; 72: 186-90
75. Luomanmäki K, Grankvist S, Hallert C, et al. A multicentre comparison of once-daily subcutaneous dalteparin (low molecular weight heparin) and continuous intravenous heparin in the treatment of deep vein thrombosis. Pharmacia & Upjohn (Stockholm). Data on file
76. Luomanmäki K, Grankvist S, Hallert C, et al. A multicentre comparison of once-daily subcutaneous dalteparin (low molecular weight heparin) and continuous intravenous heparin in the treatment of deep vein thrombosis. J Intern Med 1996 Aug; 240: 85-92
77. Fiessinger JN, Lopez-Fernandez M, Gatterer E, et al. Once-daily subcutaneous dalteparin, a low molecular weight heparin, for the initial treatment of acute deep vein thrombosis. Thromb Haemost 1996; 76 (2): 195-9
78. Meyer G, Brenot F, Pacouret G, et al. Subcutaneous low-molecular-weight heparin fragmin versus intravenous unfractionated heparin in the treatment of acute non massive pulmonary embolism: an open randomized pilot study. Thromb Haemost 1995 Dec; 74: 1432-5
79. Holmström M, Lindmarker P, Granqvist S, et al. A 6-month venographic follow-up in 164 patients with acute deep vein thrombosis. Thromb Haemost 1997 Aug; 78: 803-7
80. Holmström M, Åberg W, Lockner D, et al. Long-term clinical follow-up in 265 patients with deep venous thrombosis initially treated with either unfractionated heparin or dalteparin: a retrospective analysis. Thromb Haemost 1999; 82 (4): 1222-6
81. Bick RL. Low molecular weight heparins in the outpatient management of venous thromboembolism. Semin Thromb Hemost 1999; 25 Suppl. 3: 97-9
82. Büller HR. Outpatient therapy with low-molecular-weight heparins: new perspectives for treatment of deep vein thrombosis. Haemostasis 1998; 28 Suppl. 3: 91-4
83. Lindmarker P, Holmström M. Use of low molecular weight heparin (dalteparin), once daily, for the treatment of deep vein thrombosis. A feasibility and health economic study in an outpatient setting. Swedish Venous Thrombosis Dalteparin Trial Group. J Intern Med 1996 Dec; 240: 395-401
84. Savage KJ, Wells PS, Schulz V, et al. Outpatient use of low molecular weight heparin (dalteparin) for the treatment of deep vein thrombosis of the upper extremity. Thromb Haemost 1999; 82 (3): 1008-10
85. Kovacs MJ, Anderson D, Morrow B, et al. Outpatient treatment of pulmonary embolism with dalteparin. Thromb Haemost 2000 Feb; 83: 209-11
86. Ting SB, Ziegenbein RW, Gan TE, et al. Dalteparin for deep venous thrombosis: a hospital-in-the-home program. Med J Aust 1998 Mar 16; 168: 272-6
87. Wilson SJ, Gray L, Anderson DR. Outpatient treatment of deep vein thrombosis and pulmonary embolism: a hospital-based program. Can J Hosp Pharm 1999; 52 (5): 282-8
88. Stockelberg D, Jonsson T, Hansson E. Long term follow up of patients with deep vein thrombosis treated in an outpatient setting [abstract]. Thromb Haemost 1997 Jun Suppl.: 288-9
89. Wells PS, Kovacs MJ, Bormanis J, et al. Expanding eligibility for outpatient treatment of deep venous thrombosis and pulmonary embolism with low-molecular-weight heparin: a comparison of patient self-injection with homecare injection. Arch Intern Med 1998 Sep 14; 158: 1809-12
90. Bick RL, Rice J. Long-term outpatient dalteparin (Fragmin) therapy for arterial and venous thrombosis: efficacy and safety

– a preliminary report. Clin Appl Thrombosis/Hemostasis 1999; 5 Suppl. 1: S67-71
91. Das SK, Cohen AT, Edmondson RA, et al. Low-molecular-weight heparin versus warfarin for prevention of recurrent venous thromboembolism: a randomized trial. World J Surg 1996; 20 (5): 521-7
92. Campbell RWF, Wallentin L, Verheugt FWA, et al. Management strategies for a better outcome in unstable coronary artery disease. Clin Cardiol 1998; 21 (5): 314-22
93. Brieger DB, Freedman SB. Low molecular weight heparins: promising therapy for unstable angina and non-Q wave myocardial infarction. Asia Pacific Heart J 1997; 6 (3): 173-7
94. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. N Engl J Med 1998; 338: 1498-505
95. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. N Engl J Med 1998; 338: 1488-97
96. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. N Engl J Med 1998; 339: 436-43
97. Goa KL, Noble S. Eptifibatide: a review of its use in patients with acute coronary syndromes and/or undergoing percutaneous coronary intervention. Drugs 1999 Mar; 57 (3): 439-62
98. RISC group. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. Lancet 1990; 336: 827-30
99. Oler A, Whooley MA, Oler J, et al. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. JAMA 1996; 276 (10): 811-5
100. Théroux P, Waters D, Lam J, et al. Reactivation of unstable angina after the discontinuation of heparin. N Engl J Med 1992; 327 (3): 141-5
101. Klein W, Buchwald A, Hillis SE, et al. Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease. Fragmin in unstable coronary artery disease study (FRIC). Circulation 1997 Jul 1; 96: 61-8
102. Fragmin During Instability in Coronary Artery Disease (FRISC) study group. Low-molecular-weight heparin during instability in coronary artery disease. Lancet 1996 Mar 2; 347: 561-8
103. Fragmin and Fast Revascularisation During Instability in Coronary Artery Disease (FRISC II) investigators. Long-term low-molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. Lancet 1999 Aug 28; 354: 701-7
104. Lindahl B, Venge P, Wallentin L. Troponin T identifies patients with unstable coronary artery disease who benefit from long-term antithrombotic protection. J Am Coll Cardiol 1997 Jan; 29: 43-8
105. Lindahl B, Diderholm E, Kontny F, et al. Long term treatment with low molecular weight heparin (dalteparin) reduces cardiac events in unstable coronary artery disease with troponin-T elevation: a FRISCII substudy [abstract]. Circulation 1999 Nov 2; 100 Suppl. 1: 498
106. Beller GA. Diagnosis and management of patients with unstable angina. Curr Probl Cardiol 1999; 24 (11): 687-744
107. Fragmin and Fast Revascularisation During Instability in Coronary Artery Disease (FRISC II) investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. Lancet 1999 Aug 28; 354: 708-15
108. Frostfeldt G, Ahlberg G, Gustafsson G, et al. Low molecular weight heparin (dalteparin) as adjuvant treatment of thrombolysis in acute myocardial infarction – a pilot study: biochemical markers in acute coronary syndromes (BIOMACS II). J Am Coll Cardiol 1999 Mar; 33: 627-33
109. Bleich SD, Nichols TC, Schumacher RR, et al. Effect of heparin on coronary arterial patency after thrombolysis with tissue plasminogen activator in acute myocardial infarction. J Am Coll Cardiol 1990; 66: 1412-7
110. Kontny F, Dale J, Abildgaard U, et al. Randomized trial of low molecular weight heparin (dalteparin) in prevention of left ventricular thrombus formation and arterial embolism after acute anterior myocardial infarction: the Fragmin in Acute Myocardial Infarction (FRAMI) Study. J Am Coll Cardiol 1997 Oct; 30: 962-9
111. Kakkar VV, Iyengar SS, de Lorenzo F. Multicentre randomised prospective trial of LMWH (Dalteparin sodium - Fragmin®) in acute myocardial infarction. Blood 1999; 94 Suppl. 1 (Pt 2): 106b
112. Beijering RJR, Ten Cate H, Nurmohamed MT, et al. Anticoagulants and extracorporeal circuits. Semin Thromb Hemost 1997; 23 (2): 225-33
113. Anastassiades E, Ireland H, Flynn A, et al. A low-molecular-weight heparin (Kabi 2165, 'Fragmin') in repeated use for haemodialysis: prevention of clotting and prolongation of the venous compression time in comparison with commercial unfractionated heparin. Nephrol Dial Transplant 1990 Feb; 5: 135-40
114. Borm JJJ, Krediet R, Sturk A, et al. Heparin versus low molecular weight heparin K 2165 in chronic hemodialysis patients: a randomized cross-over study. Haemostasis 1986; 16 Suppl. 2: 59-68
115. Kerr PG, Mattingly S, Lo A, et al. The adequacy of Fragmin as a single bolus dose with reused dialyzers. Artif Organs 1994 Jun; 18: 416-9
116. Ljungberg B, Blombäck M, Johnsson H, et al. A single dose of a low molecular weight heparin fragment for anticoagulation during hemodialysis. Clin Nephrol 1987 Jan; 27: 31-5
117. Suzuki T, Ota K, Naganuma S, et al. Clinical application of Fragmin (FR-860) in hemodialysis: multicenter cooperative study in Japan. Semin Thromb Hemost 1990 Oct; 16 Suppl.: 46-54
118. Reeves JH, Cumming AR, Gallagher L, et al. A controlled trial of low-molecular-weight heparin (dalteparin) versus unfractionated heparin as anticoagulant during continuous venovenous hemodialysis with filtration. Crit Care Med 1999; 27 (10): 2224-8
119. Kwon TH, Kim YL, Cho DK. A comparison of low molecular weight heparin with unfractionated heparin for anticoagulation during hemodialysis [abstract]. Kidney Int 1997 Mar; 51 (3): 953
120. Beijering RJR, Stevens P, Vanholder R, et al. First randomized longterm comparative clinical trial for efficacy and safety of two LMWH in hemodialysis: tinzaparin versus dalteparin [abstract]. Nephrol Dial Transplant 1998 Jun; 13: A179
121. de Pont AC, Oudemans van Straaten HM, Roozendaal KJ, et al. Nadroparin versus dalteparin anticoagulation in high-volume, continuous venovenous hemofiltration: a double-blind, randomized, crossover study. Crit Care Med 2000; 28 (2): 421-5
122. Bonita R. Epidemiology of stroke. Lancet 1992; 339: 342-4
123. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy - I: prevention of

death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994; 308: 81-106
124. Berge E, Abdelnoor M, Nakstad PH, et al. Low molecular-weight heparin versus aspirin in patients with acute ischaemic stroke and atrial fibrillation: a double-blind randomised study. Lancet 2000; 355: 1205-10
125. Heaton D, Pearce M. Low molecular weight versus unfractionated heparin: a clinical and economic appraisal. PharmacoEconomics 1995 Aug; 8: 91-9
126. Pleil A, Calais M, Vreeland M, et al. An economic assessment of dalteparin versus warfarin in total hip replacement [abstract]. Value Health 1999 Sep-Oct; 2 (5): 350-1
127. Williamson TE. Outpatient DVT treatment with Fragmin® can result in cost and bed savings [abstract]. Am J Managed Care 1997; 3 (3) Suppl.: S60-3
128. Soto Alvarez J, Fernández Cano P. Evaluación económica del uso de dalteparina sódica versus heparina no fraccionada en el tratamiento de la trombosis venosa profunda. Farm Hosp 1997; 21 (2): 111-6
129. Francis CW, Pleil AM, Reinhart SP, et al. A pharmacoeconomic evaluation of low-molecular-weight heparin in patients after total hip-replacement surgery. Pharmacol Ther 1999; 24 (3): 136-45
130. Paradiso-Hardy FL, Oh P. The cost of unfractionated and low-molecular weight heparin in the management of acute coronary syndromes. Can J Hosp Pharm 1999; 52 (2): 72-6
131. Dalteparin sodium. In: Mosby's GenRx: the complete reference for generic and brand drugs. 9th ed. St Louis, MO: Mosby, 1999: II-603-II-604
132. Richter C, Huch A, Huch R. Transfer of low molecular heparin during breast feeding [abstract]. Thromb Haemost 1997 Jun Suppl.: 734
133. Monreal M, Olive A, Lafoz E. Heparins, coumarin, and bone density [letter]. Lancet 1991 Sep 14; 338: 706
134. Nishiyama M, Itoh F, Ujiie A. Low-molecular-weight heparin (dalteparin) demonstrated a weaker effect on rat bone metabolism compared with heparin. Jpn J Pharmacol 1997 May; 74: 59-68
135. Kikta MJ, Keller MP, Humphrey PW, et al. Can low molecular weight heparins and heparinoids be safely given to patients with heparin-induced thrombocytopenia syndrome? Surgery 1993 Oct; 114: 705-10
136. Greinacher A, Michels I, Mueller-Eckhardt C. Heparin-associated thrombocytopenia: the antibody is not heparin specific. Thromb Haemost 1992 May 4; 67: 545-9
137. Makhoul RG, Greenberg CS, McCann RL. Heparin-associated thrombocytopenia and thrombosis: a serious clinical problem and potential solution. J Vasc Surg 1986; 4: 522-8
138. Greinacher A, Michels I, Kiefel V, et al. A rapid and sensitive test for diagnosing heparin-associated thrombocytopenia. Thromb Haemost 1991; 66 (6): 734-6
139. Messmore Jr HL, Griffin B, Fareed J, et al. *In-vitro* studies of the interaction of heparin, low molecular weight heparin and heparinoids with platelets. Ann N Y Acad Sci 1989; 556: 217-31
140. Cohen M. Heparin-induced thrombocytopenia and the clinical use of low molecular weight heparins in acute coronary syndromes. Semin Hematol 1999; 36 Suppl. 1: 33-6
141. Farag SS, Savoia H, O'Malley CJ, et al. Lack of *in vitro* cross-reactivity predicts safety of low-molecular weight heparins in heparin-induced thrombocytopenia. Clin Appl Thrombosis/Hemostasis 1997; 3 (1): 58-62
142. Fragmin multidose vial. In: Walker G, editor. ABPI data sheet compendium and summaries of product characteristics 1998-99. London: Datapharm Publications Ltd, 1998: 1001
143. Fragmin 2500 IU and 5000 IU syringes. In: Walker G, editor. ABPI data sheet compendium and summaries of product characteristics 1998-99. London: Datapharm Publications Ltd, 1998: 1001-2
144. Prentice CR. Are symptomatic endpoints acceptable in thromboprophylactic studies? Haemostasis 1998; 28 Suppl. 3: 109-12
145. Kalodiki E, Nicolaides AN, Al Kutoubi A, et al. How "gold" is the standard? Interobservers' variation on venograms. Int Angiol 1998 Jun; 17 (2): 83-8
146. Collins MF. The optimum duration of low molecular weight heparin for thromboembolism prevention in high risk orthopedic surgery. Can J Hosp Pharm 1998 Dec; 51: 274-9
147. Gallus AS. Applying risk assessment models in orthopaedic surgery: overview of our clinical experience. Blood Coagul Fibrinolysis 1999; 10 (6) Suppl. 2: S53-61
148. Levine M, Gent M, Hirsh J, et al. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. N Engl J Med 1996; 334: 677-81
149. Koopman MMW, Prandoni P, Piovella F, et al. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. N Engl J Med 1996; 334: 682-7
150. The Columbus Investigators. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. N Engl J Med 1997; 337: 657-62
151. Bergqvist D, Benoni G, Björgell O, et al. Low-molecular-weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. N Engl J Med 1996; 335: 696-700
152. Schulman S. Long-term prophylaxis in venous thromboembolism: LMWH or oral anticoagulation? Haemostasis 1998; 28 Suppl. 3: 17-21
153. Sanson B-J, Lensing AWA, Prins MH, et al. Safety of low-molecular-weight heparin in pregnancy: a systematic review. Thromb Haemost 1999; 81 (5): 668-72
154. Ensom MHH, Stephenson MD. Low-molecular-weight heparins in pregnancy. Pharmacotherapy 1999; 19 (9): 1013-25
155. Mishra B, Jackson G. Unstable angina: a review and practical guide to management. Int J Clin Pract 1999; 53 (7): 530-4
156. Cairns JA, Théroux P, Lewis Jr HD, et al. Antithrombotic agents in coronary artery disease. Chest 1998; 114 (5) Suppl.: 611S-33S
157. Sandercock P, Bamford J, Dennis M, et al. Atrial fibrillation and stroke: prevalence in different types of stroke and influence on early and long term prognosis (Oxfordshire community stroke project). BMJ 1992; 305: 1460-5

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