Nadroparin Calcium

A Review of its Pharmacology and Clinical Use in the Prevention and Treatment of Thromboembolic Disorders

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Contents

Summary

Synopsis

Nadroparin (nadroparin calcium) is a low molecular weight heparin with a mean molecular weight of 4.5kD. Compared with unfractionated heparin (UFH), nadroparin has a greater ratio of anti-factor Xa to anti-factor IIa activity, greater bioavailability and a longer duration of action, allowing it to be administered by subcutaneous injection for prophylaxis or treatment of thromboembolic disorders.

In clinical trials conducted in older patients (mean age usually >60 years), nadroparin was at least as effective as UFH in preventing deep vein thrombosis (DVT) and pulmonary embolism after major general or orthopaedic surgery, and in bedridden medical patients. Nadroparin was also at least as effective as dalteparin or oral acenocoumarol in preventing thromboembolic events following general and orthopaedic surgery, respectively. When used for treatment of established DVT, nadroparin was at least as effective as intravenous UFH. Subcutaneous nadroparin, at dosages similar to those used for the treatment of DVT, produced promising results in older patients with pulmonary embolism, acute ischaemic stroke or unstable angina.

In 1 study, 75% of nadroparin-treated patients were able to complete their treatment at home and 36% did not require admission to hospital; the potential pharmacoeconomic implications of these results deserve further evaluation. Overall treatment costs (drug acquisition and monitoring costs) were similar for nadroparin and UFH in a French study, but nadroparin was associated with significantly less nursing time spent on treatment delivery.

Nadroparin is well tolerated by older patients. The most frequently reported adverse events in a large (n ≈ 4500) placebo-controlled study in general surgical patients were wound and injection site haematoma (11.8 and 10.2%, respectively, vs ≈6.5% for placebo). When used as prophylaxis, no significant differences in bleeding complications were noted between nadroparin and UFH or acenocoumarol recipients. Prophylactic nadroparin was associated with significantly fewer withdrawals because of adverse events than UFH in elderly bedridden medical patients. When used as treatment for DVT, nadroparin was generally associated with lower occurrences of major bleeding than intravenous UFH (0.5 to 2.3% vs 2 to 5%); however, trials were not large enough to demonstrate any significant differences between the 2 agents. Similarly, the incidence of thrombocytopenia was slightly, but generally not significantly, lower in nadroparin (<1%) than in UFH (≤3.5%) recipients.

Thus, nadroparin should be considered an effective and well tolerated alternative to UFH for prophylaxis and treatment of DVT in older patients, with the advantage of more convenient administration and decreased monitoring requirements.

Overview of Pharmacodynamic Properties

Nadroparin (nadroparin calcium) is a low molecular weight heparin (LMWH) with an average molecular weight of 4.5kD; it is produced from porcine heparin by nitrous acid depolymerisation. According to the World Health Organization (WHO) standard, the mean amidolytic anti-Xa activity of nadroparin is about 90 IU/mg in the presence of plasma and about 85 IU/mg in absence of plasma; its anti-factor IIa activity is 27 IU/mg. Nadroparin activity was originally quantified in anti-factor Xa Institute Choay units (ICU), where 1 ICU is equivalent to 0.4 IU.

The principal pharmacological properties of nadroparin include binding affinity for antithrombin III and consequently anti-factor IIa (antithrombin) and anti-

factor Xa activity. Anti-factor Xa to anti-factor IIa ratios for standard un-fractionated heparin (UFH) and nadroparin are reported to be 1 : 1 (by definition) and ≈3.5 : 1, respectively, reflecting the higher proportion of nadroparin molecules which bind to factor Xa compared with those which bind to factor IIa. Nadroparin exhibits dose-proportional inhibition of factor Xa. The relative importance of non–antithrombin III-mediated properties of nadroparin, including neutralisation by platelet factor 4, stimulation of tissue factor pathway inhibitor release, activation of fibrinolysis, and modification of haemorrheological parameters, remains to be fully determined.

In an *ex vivo* model of human venous thrombosis, both nadroparin and UFH at doses commonly prescribed for the treatment of venous embolism (6150 and 12 500IU, respectively) produced similar antithrombotic effects as assessed by fibrin deposition on activated endothelial cells and generation of markers of thrombin and fibrin formation.

Overview of Pharmacokinetic Properties

As with other LMWHs, the pharmacokinetic properties of nadroparin have most often been determined indirectly by measurement of plasma anti-factor Xa activity. The bioavailability of nadroparin has been reported to be ≥89% compared with 24% for UFH. Following single- or multiple-dose subcutaneous injection of nadroparin at doses of up to 185 IU/kg, peak plasma anti-factor Xa and anti-factor IIa activity (A_{max}) increased in a dose-proportional manner. Durations of anti-factor Xa and anti-factor IIa activity >0.1 IU/ml were also dependent on dose, and were 19.3 and 17.2 hours, respectively, after single subcutaneous doses of nadroparin 185 IU/kg. Some accumulation of antithrombotic activity appears to occur with nadroparin dosages above 6150 IU/day. A_{max} has generally been achieved within 3 to 5 hours after subcutaneous or intravenous administration of nadroparin.

The plasma elimination half-life of nadroparin, as measured by disappearance of anti-factor Xa activity, is 2.2 to 3.6 hours after intravenous and 2.3 to 5 hours after subcutaneous injection. Plasma clearance of nadroparin is thought to involve nonsaturable renal mechanisms, although recent data suggest that nadroparin undergoes metabolism in the liver before undergoing renal elimination. Plasma clearance was significantly reduced in older patients (median age 52 to 61 years) with varying degrees of renal impairment compared with healthy volunteers (0.59 to 0.78 *vs* 1.17 L/h). Thus, accumulation of antithrombotic activity is possible in nadroparin recipients with renal impairment, particularly in those receiving a relatively high dosage [e.g. patients with established deep vein thrombosis (DVT)].

Clinical Efficacy

Subcutaneous nadroparin demonstrated thromboprophylactic efficacy in studies in older patients (mean age ≥ 60 years) undergoing general or orthopaedic surgery and in bedridden medical patients. The incidence of venography-confirmed DVT was significantly lower in general surgical patients receiving subcutaneous nadroparin 3075IU once daily than after subcutaneous UFH 5000IU twice (2.5 *vs* 7.5%) or 3 times daily (2.8 *vs* 4.5%) or dalteparin 2500IU once daily (16.3 *vs* 32.3%). The unexpectedly high rate of DVT in the latter study was thought to be due to the high number of patients with multiple risk factors for DVT as well as more intensive evaluation of DVT.

In patients undergoing elective orthopaedic surgery (mostly hip replacement), similar incidences of DVT were observed with nadroparin compared with subcutaneous UFH or oral acenocoumarol. The incidence of proximal DVT was

significantly lower in nadroparin- than in UFH-treated patients in 2 studies. In bedridden hospitalised medical patients, subcutaneous nadroparin 3075 IU/day was as effective as UFH 10 000 to 15 000 IU/day in the prevention of thrombo-embolic events.

A bodyweight-adjusted dosage of nadroparin 8200 to 18 400 IU/day in 2 divided doses was at least as effective as adjusted-dose intravenous UFH for the treatment of venography-confirmed DVT. The percentage of nadroparin-treated patients showing venographic improvement was significantly higher in 1 study (60 *vs* 43%), and similar in another study (56 *vs* 62%). In the latter study, nadroparin recipients showed significantly greater improvement in Arnesen (30.6 *vs* 16.4%) and Marder (28.9 *vs* 15.8%) venographic scores than UFH recipients. Data from a recent abstract suggest that once daily nadroparin is equivalent to twice daily nadroparin for the treatment of DVT. Preliminary results indicated that 8 days' treatment with subcutaneous nadroparin 82 or 123 IU/kg twice daily and activated partial thromboplastin time (aPTT) adjusted-dose intravenous UFH produced similar reductions in pulmonary vascular obstruction in patients with non-massive acute pulmonary embolism.

Significantly fewer Chinese patients with acute ischaemic stroke had a poor 6-month outcome (death or dependency regarding daily living activities) after treatment with subcutaneous nadroparin 4100IU once (52%) or twice (45%) daily for 10 days than with placebo (65%). In patients with unstable angina, subcutaneous nadroparin 88 IU/kg twice daily plus aspirin (acetylsalicylic acid) was significantly more effective than adjusted-dose intravenous UFH plus aspirin 200 mg/day or aspirin alone in reducing adverse clinical events (recurrent angina, nonfatal myocardial infarction and urgent revascularisation procedure).

Although pharmacoeconomic studies involving LMWHs, including nadroparin, are scarce, recent data indicate that despite lower acquisition costs of UFH, LMWHs are more cost effective than UFH for prophylaxis or treatment of DVT, especially when the costs associated with antithrombotic failure and treating bleeding complications are considered. In a French study, overall treatment costs (drug acquisition and monitoring costs) were similar for nadroparin and UFH (FF345 *vs* FF337; 1992 values); use of nadroparin was, however, associated with significantly less nursing time spent on treatment delivery (42 *vs* 104 min/wk for UFH).

Outpatient treatment of DVT with subcutaneous nadroparin was also associated with considerably less hospital resource use than UFH (mean 2.7 *vs* 8.1 days in hospital) but required 2 outpatient nursing visits and 2.2 follow-up telephone calls per patient. Unfortunately, no cost data were applied to either inpatient or outpatient resource use.

Tolerability

Nadroparin was well tolerated in studies in older patients. In a large study of prophylaxis in general surgical patients (n = 4498), subcutaneous nadroparin 3075 IU/day was associated with a significantly higher incidence of excessive postoperative bleeding (7.7 *vs* 3.1%) and wound (11.8 *vs* 6.3%) and injection site (10.2 *vs* 6.6%) haematoma than placebo. No significant difference in the incidence of bleeding complications was noted between subcutaneous nadroparin and subcutaneous UFH or oral acenocoumarol in patients undergoing general or orthopaedic surgery. In elderly bedridden hospitalised patients, 10 or 28 days' prophylaxis with subcutaneous nadroparin 3075 IU/day appeared to be better tolerated than subcutaneous UFH 5000IU 2 to 3 times daily; incidences of local

reactions, >3-fold elevations in liver transaminase levels, thrombocytopenia and withdrawals because of drug-related adverse events were significantly lower in nadroparin than in UFH recipients.

Nadroparin ≈185 IU/kg/day in 2 divided doses was associated with lower incidences of major bleeding than aPTT adjusted-dose intravenous UFH (0.5 to 2.3% *vs* 2 to 5%) in patients receiving treatment for DVT; however, the trials were not large enough to demonstrate any significant differences between nadroparin and UFH. Enrolment in patient groups receiving nadroparin 123 or 185 IU/kg twice daily for the treatment of submassive pulmonary embolism was discontinued because of a high incidence of clinically significant major bleeding.

In patients undergoing treatment for unstable angina, the incidence of spontaneous haematomas at injection sites was significantly lower in patients receiving nadroparin plus aspirin than in those receiving UFH plus aspirin (1.5 *vs* 14%). Local tolerability of nadroparin was significantly superior to that of enoxaparin in healthy volunteers and elderly bedridden hospitalised patients, with nadroparin recipients reporting significantly less injection site pain, haematoma, swelling, burning and itching than enoxaparin recipients.

Postmarketing assessment of spontaneous adverse event reports data based on >15 million nadroparin patient treatments in France indicated a low incidence of thrombocytopenia (<0.001%). In comparative clinical trials, the incidence of heparin-induced thrombocytopenia was <1% in nadroparin recipients and ≤3.5% in UFH recipients.

Dosage and Administration

Drug dosages of nadroparin are usually expressed in injection volume in clinical practice; the currently available drug formulation contains 9500IU of nadroparin per 1ml of solution for injection. For prevention of venous thromboembolic disease following general surgery, subcutaneous nadroparin 0.3ml once daily is recommended; the same dosage was used in clinical studies in bedridden medical patients at risk for developing DVT. For prevention of DVT following orthopaedic surgery, the recommended dosages of nadroparin are 0.2, 0.3 and 0.4ml once daily subcutaneously for 3 days in patients weighing, respectively, <50, 50 to 69 and ≥70kg; this is followed by 0.3, 0.4 and 0.6ml once daily from day 4 onwards. Drug administration should continue for at least 10 days or at least until the patient is ambulant.

In patients with DVT, nadroparin 0.4, 0.5, 0.6, 0.7, 0.8 and 0.9ml should be administered twice daily in patients weighing <50, 50 to 59, 60 to 69, 70 to 79, 80 to 89 and ≥90kg, respectively, for a usual duration of 10 days. Preliminary results support a similar dosage regimen for the treatment of pulmonary embolism, acute ischaemic stroke and unstable angina.

Although nadroparin is associated with a low incidence of thrombocytopenia, it is recommended that platelet counts be monitored twice weekly during treatment. Concomitant administration of nadroparin and drugs known to cause bleeding (e.g. nonsteroidal anti-inflammatory drugs, aspirin, ticlopidine) should be avoided or carefully monitored when such combinations cannot be avoided. The dosage of nadroparin may need to be reduced in patients with renal impairment although no specific dosage guidelines are available.

Nadroparin (nadroparin calcium) was one of the first low molecular weight heparins (LMWHs) to become available for clinical use. It is prepared by nitrous acid depolymerisation of porcine heparin and is a mixture of linear polysaccharide chains (fig. 1). Nadroparin has a mean molecular weight of 4.5kD (range 1 to 10kD) and 80% of the polysaccharide chains of nadroparin have a molecular weight of 2.4 to 7.2kD (corresponding to 4 to 12 basic disaccharide units). This evaluation overviews the pharmacology of nadroparin and considers the clinical efficacy and tolerability of the drug in studies conducted in older patient populations.

1. Overview of Pharmacodynamic Properties

The pharmacology of nadroparin has been previously reviewed.[1] This section provides an overview of the most important pharmacological data, particularly relevant new data.

1.1 Mechanism of Action of Unfractionated Heparin

Unfractionated heparin (UFH) is a mixture of heterogeneous polysaccharide chains with a molecular weight range of 1.2 to 40kD (mean ≈15kD).[2] The anticoagulant activity of UFH predominantly reflects its ability to form a ternary complex with antithrombin III (AT III) and factor IIa (thrombin), resulting in inactivation of thrombin.[3-7] About one-third of the molecules of commercial UFH preparations contain a pentasaccharide sequence specific for AT III binding sites. A number of other clotting factors are also inhibited by this ternary complex, including factors IXa, Xa, XIa and XIIa as well as plasmin and kallikrein; however, the inhibition of thrombin and factor Xa is particularly important and clinically relevant.[8]

A heparin chain length of at least 18 to 22 monosaccharide units that includes the pentasaccharide sequence specific for the AT III binding site is required to facilitate the binding of the heparin-AT III complex to thrombin.[8-12] Most molecules of UFH are at least 18 monosaccharide units in length, whereas only a small proportion of chains

of LMWHs are long enough to bind to both thrombin and AT III. In contrast, inhibition of factor Xa activity requires binding only to AT III. The shorter chain length of LMWH components is, therefore, insufficient for formation of a ternary complex involving heparin, AT III and thrombin, but still permits heparin-mediated AT III binding of factor Xa. In addition, platelet factor 4 (PF4), released from activated platelets, preferentially binds to heparin chains with molecular weight >5.4kD (i.e. preferentially neutralises heparin chains with anti-factor IIa activity).[6,13,14] Thus, as the molecular weight of heparin decreases, its anti-factor Xa activity diminishes less rapidly than its anti-factor IIa activity.

1.2 Antithrombotic Profile of Nadroparin

The *in vitro* potency of nadroparin was originally expressed in Institute Choay Units (ICU), where 1 ICU is equivalent to 0.41IU. In this review, nadroparin dosages previously reported in ICU have been converted into IU.

The anti-factor Xa and anti-factor IIa activities of nadroparin and other LMWHs have been extensively studied to define their antithrombotic and anticoagulant effects. However, despite the introduction of the First International Standard for LMWHs by the World Health Organization (WHO) in 1988, there is no overall scientific consensus as to how the *in vitro* potency of UFH and LMWHs may be optimally compared.[15] Based on the WHO standard, the mean amidolytic anti-factor Xa activity of nadroparin is equivalent to about 90 IU/mg (range 85 to 110 IU/mg) and its mean anti-factor IIa activity is 27 IU/mg (data on file, Sanofi
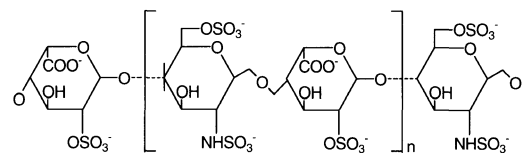

Fig. 1. Chemical structure of nadroparin; n = 2 to 20.

Pharma).[15-17] According to recent European Pharmacopoeia directives, the potency of anti-factor Xa activity of LMWHs must now be evaluated in an isolated system, i.e. without plasma; the amidolytic anti-factor Xa activity of nadroparin is about 85 IU/mg (range 80 to 100 IU/mg) under these conditions (data on file, Sanofi Pharma). Since the *in vivo* antithrombotic activity of a LMWH may not be related to its *in vitro* anti-factor Xa activity, the WHO standard has been criticised.[18,19] Moreover, despite having similar molecular weights (4 to 8kD), LMWHs exhibit considerable differences in molecular structure due to variations in manufacturing processes and thus possess distinct pharmacological and biochemical profiles.[20]

Nadroparin has a higher ratio of anti-factor Xa to anti-factor IIa activity than UFH. *In vitro* this ratio is approximately 3.5 : 1 for nadroparin compared with a ratio of 1 : 1 (by definition) for UFH.[15,21,22] The anti-factor Xa activity of UFH, but not LMWHs, is reduced in the absence of calcium.[23] Since anti-factor Xa assays are commonly performed in the absence of calcium, a spuriously high *in vitro* anti-factor Xa to anti-factor IIa ratio for LMWHs compared with UFH is obtained.[23]

In vitro studies in thromboplastin-activated plasma from healthy volunteers showed that nadroparin exhibits dose-proportional anti-factor Xa activity.[1] In platelet-poor plasma, 55% inhibition of thrombin generation was achieved at nadroparin and UFH concentrations of 1.0 and 0.2 mg/L, respectively.[24] At the same drug concentrations in platelet-rich plasma, nadroparin retained some inhibitory effect on thrombin generation but UFH did not (27 *vs* 0% inhibition). The ultra-low molecular weight fractions (<3.4kD) of nadroparin and UFH were also evaluated in this study and showed similar activity in platelet-poor and platelet-rich plasma. These results and those obtained with the synthetic pentasaccharide that represents the AT III binding site of heparin (which acts on free factor Xa and is not, or is minimally, affected by PF4[25,26]) suggest that:

- in platelet-poor plasma, the most active part of LMWHs is found in the AT III binding fraction with a molecular weight >5.4kD
- in platelet-rich plasma, heparin fractions with no affinity for AT III but high affinity for PF4 protect fractions with high affinity for AT III from neutralisation by PF4.[24,27]

Therefore, it appears that a portion of the inhibitory effect of nadroparin on thrombin generation is due to its anti-factor Xa activity, which is less readily neutralised by PF4, an observation also made by other investigators.[14,16]

Plasma anti-factor Xa activity increased by 2, 7 and 10%, respectively, in surgical patients after 1, 3 and 7 days' treatment with nadroparin 3075 IU/day and increased dose-proportionally in patients with submassive pulmonary embolism (anti-factor Xa activity 1.0 and 1.5 IU/ml at nadroparin dosages of 164 and 246 IU/kg/day).[1]

Non–AT III-dependent properties are thought to contribute to the antithrombotic activity of nadroparin but the relative contribution of these actions remains to be fully determined. These include:

- stimulation of tissue factor pathway inhibitor (TFPI; also known as extrinsic pathway inhibitor) release[20,28,29]
- activation of fibrinolysis via direct release of tissue plasminogen activator from endothelial cells[30-35]
- modification of haemorrheological parameters (decreased blood viscosity and increased platelet and granulocyte membrane fluidity).[36]

A number of *in vivo* studies in rats and rabbits have provided evidence of the antithrombotic and/or thrombolytic activity of nadroparin (reviewed by Barradell & Buckley[1]). These studies generally have shown that low doses of nadroparin inhibited thrombus growth more effectively than equigravimetric doses of UFH; at higher doses both nadroparin and UFH decreased thrombus size. In a recent crossover study using an *ex vivo* model of human venous thrombosis, the anticoagulant and antithrombotic effects of subcutaneous nadroparin and UFH were assessed in 10 healthy men.[37] At doses typically used to treat deep vein thrombosis

(DVT) [6150 and 12 500IU, respectively), fibrin deposition on stimulated endothelial cells was significantly (p ≤ 0.05) reduced by nadroparin and UFH at 3 hours but not at 8 hours. The generation of markers of thrombin and fibrin formation (thrombin-AT III complexes and fibrinopeptide A, respectively) was significantly reduced by nadroparin and UFH at 3 hours (by 50 to 83%), whereas only nadroparin significantly inhibited these markers at 8 hours. The antithrombotic effects of both heparins correlated with their plasma anti-factor Xa and anti-factor IIa activities; these results suggest that nadroparin and UFH possess similar antithrombotic activity at clinically relevant doses. The longer lasting antithrombotic activity of nadroparin relative to UFH is also in good agreement with its pharmacokinetic properties (section 2).

2. Overview of Pharmacokinetic Properties

2.1 Absorption, Distribution and Elimination

The composite molecular structure of nadroparin and other heparins makes absolute determination of their plasma concentrations impossible. Thus, the pharmacokinetic properties of nadroparin have been assessed mainly on the basis of biological activities (i.e. measurement of *ex vivo* amidolytic anti-factor Xa activity). Most studies to date have been conducted in healthy volunteers and no data are available on the effect of age on the pharmacokinetic profile of nadroparin. Pharmacokinetic data for single-dose nadroparin 3075IU in 20 healthy men are presented in table I.

Mean maximum anti-factor Xa activity (A_{max}) of nadroparin 41 IU/kg was higher after intravenous than after subcutaneous administration in healthy volunteers (0.79 *vs* 0.25 IU/ml); wide interindividual variations in anti-factor Xa activity were observed with both administration routes.[39] The bioavailability of subcutaneous nadroparin was reported to be 89% in this study,[39] and 98% compared with 24% for UFH in another study.[40]

After subcutaneous administration of nadroparin 3750 to 9225IU once daily for 5 days in healthy vol-

Table I. Mean pharmacokinetic parameters of nadroparin (based on plasma anti-factor Xa activity) after a single subcutaneous injection of 3075IU in young healthy volunteers[38]

Parameter	Result
A_{max}	0.32 IU/ml
t_{max}	3.62h
AUC_{∞}	2.35 IU/ml • h
Vd	6.77L
CL	1.29 L/h
CL_R	0.05 L/h
$t_{1/2\alpha}$	1.07h
$t_{1/2\beta}$	3.74h

Abbreviations: A_{max} = maximum plasma anti-factor Xa activity; AUC_{∞} = area under the plasma anti-factor Xa activity-time curve extrapolated to infinity; CL = total clearance; CL_R = renal clearance; $t_{1/2\alpha}$ = absorption half-life; $t_{1/2\beta}$ = terminal phase elimination half-life; t_{max} = time to reach A_{max}; Vd = volume of distribution.

unteers, mean A_{max} and area under the anti-factor Xa activity-time curve (AUC) increased dose-dependently.[41] A strong correlation (p < 0.001) between A_{max} and activated partial thromboplastin time (aPTT) was observed in the nadroparin 9225 IU/day group, indicating some drug accumulation at nadroparin dosages above 6150 IU/day.

A_{max} has generally been detected approximately 3 to 5 hours after subcutaneous or intravenous administration of nadroparin.[1,38,42] The mean elimination half-life ($t_{1/2\beta}$) of nadroparin, determined by disappearance of anti-factor Xa activity, was between 2.2 and 3.6 hours after intravenous administration and between 2.3 and 5 hours after subcutaneous administration.[1] Changes in conventional measures of plasma antithrombotic activity (e.g. aPTT, Heptest, anti-factor IIa or anti-factor Xa activity tests) are usually not seen with LMWHs 4 to 6 hours after administration.[43] Indeed, no special coagulation tests are currently recommended for monitoring the efficacy of LMWHs.[44] Nonetheless, most of these agents produce thromboprophylactic actions for up to 24 hours, suggesting the influence of other nonmeasurable actions of LMWHs that modulate antithrombotic activity.[43]

Early pharmacokinetic studies with low doses of LMWHs (including nadroparin) showed that these agents have a very short $t_{1/2\beta}$ of anti-factor IIa activity relative to anti-factor Xa activity.[8,40,45,46] A

recent single-dose crossover study evaluated the antithrombotic activity of subcutaneous nadroparin by standard chromogenic assay in healthy volunteers.[42] At daily doses used for prophylaxis (3075 and 4100IU) and treatment (92 and 185 IU/kg) of DVT:

- A_{max} increased dose-dependently for anti-factor Xa (0.31 to 1.55 IU/ml) and anti-factor IIa (0.22 to 0.87 IU/ml) activity over the study dose range used
- A_{max} for anti-factor Xa and anti-factor IIa activity was achieved approximately 3 to 5 hours after drug administration
- duration of anti-factor Xa and anti-factor IIa activity >0.1 IU/ml was dose-dependent and lasted for up to 19.3 and 17.2 hours, respectively, in the nadroparin 185 IU/kg group (fig. 2).
- mean $t_{1/2\beta}$ of both anti-factor Xa and IIa activity was approximately 4 hours.[42]

The anti-factor IIa activity results in this study were verified with a more sensitive assay (plasma thrombin neutralisation assay; PTNA) that measures the ability of heparins to catalyse the inhibition of thrombin by AT III.[42] The mean $t_{1/2\beta}$ of anti-factor IIa activity of nadroparin assessed with the PTNA was longer than when assessed by chromogenic assay (≈6 vs ≈4 hours). Similar results were obtained with enoxaparin at prophylactic (20 and 40mg) and therapeutic (1 and 2 mg/kg) doses in this study.[42] These data represent the first pharmacokinetic analysis of anti-factor IIa activity of LMWHs at therapeutic doses and provide a rationale for the clinical efficacy of these agents in the treatment of venous thrombosis.[42]

The apparent volume of distribution (Vd) of single-dose nadroparin 3075IU in healthy volunteers was 6.77L (table I).[38] Studies conducted in rats indicate preferential distribution of nadroparin to the liver and kidney, with approximately 90% of radioactivity measurable in the urine 24 hours after a single subcutaneous dose of 3 mg/kg (246 IU/kg);[21] confirmatory data in humans are not available.

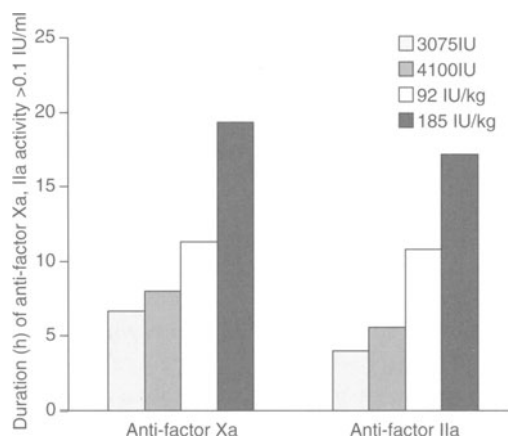Plasma clearance of nadroparin is estimated to be between 1.2 and 1.3 L/h.[1] Similar to that of

Fig. 2. Duration of anti-factor Xa and anti-factor IIa activity >0.1 IU/ml of subcutaneous nadroparin at clinically relevant doses in 6 healthy volunteers. Antithrombotic activity was assessed by standard chromogenic assay in a single-dose crossover study.[42]

other LMWHs, the primary route of elimination of nadroparin is thought to involve a nonsaturable renal mechanism,[47,48] although data to support this are limited. In a recent study in healthy volunteers, renal clearance accounted for only 3.9% of the total clearance of nadroparin (table I).[38] These results indicate that nadroparin is metabolised in the liver before elimination via the kidneys.

2.2 Effect of Renal Impairment

The pharmacokinetics of nadroparin have been investigated in older patients (median age 52 to 61 years) with varying degrees of renal impairment (table II).[49] Compared with healthy volunteers, there was little difference in values for A_{max} or Vd in patients with renal impairment, but AUC and $t_{1/2\beta}$ were significantly increased and clearance was significantly decreased (table II). The pharmacokinetics of nadroparin appeared to be independent of the severity of renal impairment; this result may reflect the wide interindividual variability in the study and/or other unexplained factors that influence the elimination of nadroparin.[49] Nonetheless, these results indicate that accumulation of nadroparin is possible in patients with impaired re-

nal function, which suggests that the drug should be used with caution in such individuals; a dosage reduction should also be considered, particularly in those receiving relatively high dosages (e.g. patients with established DVT) [section 5].[49,50]

3. Clinical Efficacy

Pulmonary embolism arising from DVT of the lower limbs is a major cause of preventable death in developed countries.[51,52] Patients who have undergone surgery with prolonged general anaesthesia experience a period of postoperative immobility which predisposes them to venous thromboembolism. Prophylaxis is more effective for preventing death than is treatment of established disease. When prophylactic measures are not used, the risk of fatal pulmonary embolism ranges from 0.1 to 0.8% in patients undergoing elective general surgery, 2 to 3% in patients undergoing elective hip surgery, and 4 to 7% in patients undergoing surgery for a fractured hip.[51]

The risk of venous thromboembolism depends on a number of factors relating to the patient and the procedure involved; age is an important independent risk factor, as a result of physiological alterations

of the haemostatic system and the vessel wall with advancing age (reviewed by Nurmohamed et al.[53]). Moreover, in older individuals there is an increased incidence of comorbid conditions (e.g. immobility, malignancy and surgery), which may be independently associated with an increased risk of development of thrombosis. Indeed, without prophylactic measures, DVT is reported to occur in 20 to 30% of patients aged >40 years after major general surgery (moderate risk), increasing to approximately 50% after major orthopaedic procedures (high risk).[54,55]

The efficacy of nadroparin has been evaluated for the prevention of DVT in orthopaedic and general surgical patients and in bedridden hospitalised medical patients. It has also been evaluated in the treatment of established DVT, pulmonary embolism, stroke and unstable angina. Many of these studies recruited an older patient population (mean age ≥60 years) and form the basis of this section.

3.1 Prophylaxis of Thromboembolic Events

3.1.1 General Surgery

The majority of general surgical patients in studies evaluating nadroparin underwent elective abdominal surgery and about one-third of patients were operated on for malignant disease. DVT was confirmed by venography and pulmonary embolism was confirmed by perfusion ventilation scanning or angiography; initial screening with ^{125}I-fibrinogen uptake leg scanning was used in 2 trials in general surgical patients.[56,57] Elastic compression stockings were used in all surgical patients until full mobility was established. All study drugs were administered subcutaneously unless otherwise specified; nadroparin was administered once daily, starting 2 hours before surgery, for 7 to 10 days or until discharge. General surgical and bedridden medical patients received nadroparin 3075IU daily and orthopaedic surgical patients received nadroparin dosages adjusted by bodyweight and/or time relative to procedure (range 2050 to 6150 IU/day). In all studies, the incidence of pulmonary embolism was similar or slightly lower for nadroparin than UFH but because of the low overall incidence of

Table II. Mean pharmacokinetic parameters (based on anti-factor Xa activity) of nadroparin 41 IU/kg following single-dose intravenous administration to patients with renal impairment and to healthy volunteers (HV)[49]

Parameter	Patients with renal impairment (CL_{CR}, L/h)			HV (CL_{CR}, L/h)
	<0.6^a (n = 7)	0.6-1.2 (n = 7)	1.8-3.0 (n = 5)	>4.5 (n = 12)
Median age in years (range)	52 (29-75)	58 (37-63)	61 (34-78)	(19-24)
A_{max} (IU/ml)	0.82	0.94	0.82	0.78
AUC_∞ (IU/ml • h)	3.8*	4.6*	3.6*	2.3
Vd (L/kg)	0.058	0.060	0.052	0.055
CL (L/h)	0.78*	0.59*	0.74*	1.17
$t_{1/2\beta}$ (h)	3.6*	4.6*	3.0*	2.2

a   Haemodialysed patients.

Abbreviations and symbol: A_{max} = maximum plasma anti-factor Xa activity; AUC_∞ = area under the plasma anti-factor Xa activity-time curve extrapolated to infinity; CL = total clearance; CL_{CR} = creatinine clearance; $t_{1/2\beta}$ = terminal phase elimination half-life; Vd = volume of distribution; *p < 0.01 *vs* HV.

Table III. Summary of randomised multicentre comparative trials of nadroparin (N) for prophylaxis against deep vein thrombosis (DVT) in patients undergoing general or orthopaedic surgery, and in bedridden medical patients. In surgical patients, nadroparin was administered subcutaneously once daily, starting 2 hours before surgery, for 7 to 10 days or until discharge unless specified otherwise

Reference	Trial design	Patient parameters		Regimen[a]	Results (% of patients)		Overall efficacy
		no. evaluated	mean age (y)		DVT[b]	PE[b]	
General surgery							
Bounameaux et al.[58]c	sb, pl	92	63	N 3075 od	16.3*		N > D
		93		D 2500 od	32.3		
Eurin[59]	nb, pl	240	62.4	N 3075 od	0.4	0	N ≡ UFH
		239	62.2	UFH 5000 q8h[d]	0	0	
European Fraxiparin Study Group[56]	nb, pl	960	61	N 3075 od	2.8*	0.2	N > UFH
		936	61	UFH 5000 q8h	4.5	0.5	
Kakkar & Murray[57]	db, pl	199	59.6	N 3075 od	2.5*	0.5	N > UFH
		196	58.9	UFH 5000 q12h	7.5	0.5	
Pezzuoli et al.[60]	db, pl	2247	59.2	N 3075 od		0.09[e]	N > Placebo
		2251	59.5	Placebo		0.18[e]	
Orthopaedic surgery							
German Hip Arthroplasty Trial (GHAT) Group[61]	db, pl	136	64.2	N 4100 (mean 57/kg) od	27.5	1.2	N ≡ UFH
		137	63.9	UFH 5000 q8h	29.7	3.6	
Haentjens and The Belgian Fraxiparine Study Group[62]	nb, pl	76	61.7	Nfixed 3075 od × 6wk	1.3	1.3	Nfixed ≡ Nadj
		74	60.5	Nadj 2050, 3075 or 4100 od × 3days then 3075, 4100 or 6150 od × 6wk in patients weighing <50, 50 to 70 or >70kg, respectively	5.4	2.7	
Hamulyák et al.[63]	sb, pl	260	67.3	N 25/kg od	16.5	0	N ≡ A
		257	66.7	A[f]	19.5	0	
Leyvraz et al.[64]	nb, pl	174	64.3	N 41/kg od × 3 days, then 62/kg od × 7 days	12.6	0.6	N ≡ UFH
		175	64.6	UFH[g] q8h × 10 days	16	2.3	
Palareti et al.[65]	db, pl	65	62.3	Npreop 3075 od × 3 days, then 6150 od × 11 days	41.5	0	Npreop ≡ Npostop
		66	61.3	Npostop 3075 od × 3 days, then 6150 od × 11 days	36.4	0	
Bedridden medical patients							
Forette & Wolmark[66]	nb, pl	146	82.8	N 3075 od	2	0	N ≡ UFH
		149	83.8	UFH 5000 or 7500 bid in patients weighing <70kg or ≥70kg	2	0.7	
Harenberg et al.[67]	db, pl	810	69.7	N 3075 od	0.74	0.37	N ≡ UFH
		780	69.9	UFH 5000 q8h	0.51	0.38	

a   All drug dosages in IU and administered subcutaneously unless otherwise specified.
b   DVT was confirmed by venography, with or without Doppler or ^{125}I-fibrinogen scanning. PE was confirmed by perfusion scanning or angiography, with the exception of 1 study,[60] in which PE was assessed at autopsy.
c   Single-centre study.
d   Drug administration initiated 2 hours after completion of operation.
e   Fatal PE.
f   Patients received an initial dose of oral A 4mg on the day before surgery and 2mg on the evening after surgery; subsequent daily dosages were adjusted to maintain an International Normalised Ratio between 2 and 3.
g   UFH dosage adjusted to maintain the activated partial thromboplastin time at 2 to 5 seconds above control values.
h   Npreop and Npostop groups received their first doses 12 hours before and 8 to 12 hours after surgery, respectively.

Abbreviations and symbols: A = acenocoumarol; adj = dosage adjusted by bodyweight; bid = twice daily; D = dalteparin; db = double-blind; fixed = fixed dosage; nb = nonblind; od = once daily; PE = pulmonary embolism; pl = parallel; postop = postoperatively; preop = preoperatively; q8h = every 8 hours; q12h = every 12 hours; sb = single-blind; UFH = unfractionated heparin; *p ≤ 0.05 vs comparator; ≡ indicates equivalent efficacy; > indicates that the first agent was significantly better than the second (p ≤ 0.05).

events the differences did not reach statistical significance (table III).

In the large, multicentre double-blind placebo-controlled Studio Embolia Polmonare (STEP) study, nadroparin 3075 IU/day was significantly more effective than placebo in reducing DVT, total mortality and total thromboembolic mortality (fig. 3).[60] Patients in this study underwent elective general surgery with general anaesthesia lasting ≥45 minutes and a hospital stay of ≥8 days. The incidence of fatal pulmonary embolism was also lower in the nadroparin group (0.09% *vs* 0.18% for placebo) [fig. 3].

Nadroparin 3075 IU/day showed thromboprophylactic efficacy similar to UFH 15 000 IU/day in patients undergoing general surgery with epidural anaesthesia; only 1 case of DVT was reported in this study (table III).[59] 65% of patients in this study were aged >65 years and prostate or hernia surgery accounted for approximately 60% of procedures.

In 2 randomised multicentre trials,[56,57] the thromboprophylactic efficacy of nadroparin 3075 IU/day was superior to that of UFH 10 000 and 15 000
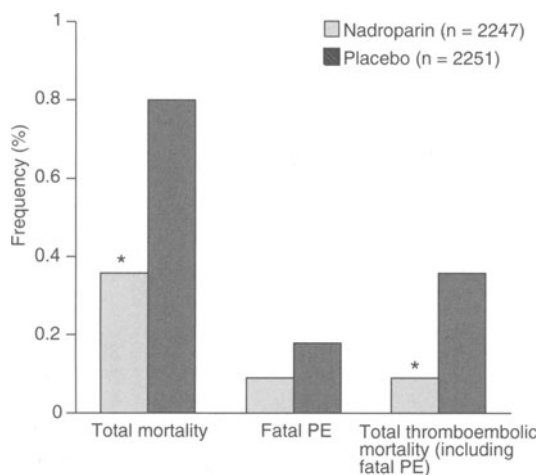
IU/day as evidenced by significantly lower rates of DVT (table III). The incidence of proximal vein thrombosis was also significantly lower in nadroparin than in UFH recipients (0.4 *vs* 1.4%; p < 0.05) in 1 study that differentiated between distal and proximal vein thromboses.[56]

In a more recent study comparing 2 LMWHs in 185 patients undergoing general abdominal surgery, DVT was observed in significantly fewer nadroparin 3075 IU/day than dalteparin 2500 IU/day recipients (table III).[58] The lower dosage used in the dalteparin compared with the nadroparin group may have partly accounted for the difference in DVT rates; increasing the dosage of dalteparin to 5000 IU/day reduced the rate of DVT to 14.1% in a noncomparative study in 116 patients with a similar risk pattern.[68] The unexpectedly high rate of DVT in both groups in this study probably reflects the high number of patients with risk factors for thromboembolism. Indeed, nearly 100% of patients were >40 years old, nearly 50% had a malignant neoplasm, and nearly 50% underwent a procedure lasting >4 hours. Furthermore, in contrast to the other general surgery studies in table III,[56,57,59] which performed venography only after a positive Doppler or ^{125}I-fibrinogen screening test, venography was performed on all patients by the ninth postoperative day in this study.

3.1.2 Orthopaedic Surgery

Nadroparin was as effective as UFH in preventing DVT in 2 studies in older patients (mean age ≈64 years) undergoing elective hip replacement (table III).[61,64] Importantly, nadroparin was associated with a significantly lower incidence of proximal DVT than UFH (fig. 4); these findings are clinically relevant in that patients with proximal DVT have a ≥35% chance of developing pulmonary embolism.[69,70]

In 517 patients undergoing elective hip (75%) or knee (25%) replacement, the incidence of DVT was similar in nadroparin 25 IU/kg/day and oral acenocoumarol recipients (16.5 and 19.5%) [table III][63] as was the incidence of proximal DVT (6.5 and 5.8%). The mean daily nadroparin dosage was lower in this study than in the other orthopaedic

Fig. 3. Efficacy of nadroparin in preventing thromboembolic mortality in patients undergoing general surgery. Patients received nadroparin 3075IU subcutaneously once daily for ≥7 days or placebo.[60] *Abbreviation and symbol:* PE = pulmonary embolism; *p < 0.05 *vs* placebo.
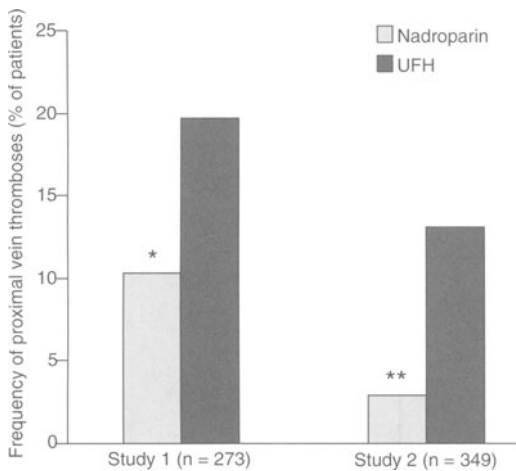
Fig. 4. Incidence of proximal deep vein thrombosis associated with subcutaneous nadroparin and unfractionated heparin (UFH) prophylaxis in older patients undergoing orthopaedic surgery. Dosages of nadroparin 4100IU once daily and UFH 5000IU every 8 hours were used in study 1.[61] In study 2, patients received nadroparin 41 IU/kg once daily for 3 days then 62 IU/kg once daily for 7 days and dosage-adjusted heparin to maintain the activated partial thromboplastin time at 2 to 5 seconds above control values.[64] *Symbols:* *p ≤ 0.05, **p ≤ 0.01 *vs* UFH.

surgery studies in table III (25 *vs* 41 to 62 IU/kg) but the rates of DVT were similar. Assessment of study designs and patient demographics provided no clear explanation for this observation.

A recent randomised double-blind multicentre study in 131 patients undergoing elective hip replacement (mean age 62 years) found no significant differences in rates of DVT associated with nadroparin initiated 12 hours preoperatively versus 8 to 12 hours postoperatively (table III).[65] Similarly, there were no significant difference in the frequency of proximal (10.8 *vs* 6.1%) or distal (30.8 *vs* 30.3%) DVT.

The incidences of DVT for nadroparin and UFH were approximately twice as high in the German Hip Arthroplasty Trial (GHAT)[61] and in the Palareti et al.[65] study as those reported by Leyvraz et al.[64] (table III). Most patients in the GHAT[61] and Palareti et al.[65] studies underwent preoperative blood collection and/or intraoperative blood sal-

vage and reinfusion of washed erythrocytes; these transfusional procedures may have affected postoperative coagulation.[65] Although the dosage of nadroparin in the Palareti study was similar to the bodyweight- and time-adjusted dosage used in the Leyvraz et al.[64] study, the incidence of DVT was slightly higher (table III). This may be partly accounted for by the fact that a number of the venographies originally classified as normal (by local radiologists from the 7 study centres) were subsequently rated as inadequate (by the 2 independent trial radiologists) and were excluded from the efficacy analysis.[65] Furthermore, a fixed dosage regimen was used for both drugs in the GHAT study,[61] whereas the Leyvraz et al.[64] study adjusted nadroparin dosages for bodyweight and time relative to procedure (table III) and adjusted UFH dosages to maintain an aPTT of 2 to 5 seconds above control values. A subgroup analysis in the GHAT study indicated that the majority (≈75%) of thromboses in the nadroparin group occurred in patients receiving nadroparin dosages ≤62 IU/kg and in those weighing ≥70kg.[61] Thus, prophylactic nadroparin dosages based on bodyweight and the time relative to the operation are preferable to a fixed dosage regimen in patients undergoing hip or knee replacement.

Prophylaxis with fixed dosage nadroparin 3075 IU/day was as effective as bodyweight-adjusted nadroparin (≈40 to 60 IU/kg/day) in preventing DVT and pulmonary embolism in patients after orthopaedic trauma (spinal fracture, pelvic fracture or a lower limb injury) [table III].[62] Patients received prophylaxis for up to 6 weeks and approximately 85% of patients had surgery (mostly osteosynthesis).

3.1.3 Bedridden Medical Patients

Nadroparin 3075 IU/day showed efficacy equivalent to that of UFH 5000IU 2 or 3 times daily in preventing DVT in elderly bedridden hospitalised medical patients (table III).[66,67] In a large multicentre double-blind 10-day study (n = 1590),[67] the overall mortality rate was significantly higher in the nadroparin group than in the heparin group (2.8 vs 1.2%; p = 0.02); however, this difference

might be explained by patient factors such as poor prognosis, a longer duration of pre-study bed rest and a greater number of patients with clinical risk factors for thromboembolism (e.g. varicosis, previous DVT or pulmonary embolism) in the nadroparin group.

3.2 Treatment of Established Thromboembolism

3.2.1 Deep Vein Thrombosis

UFH, the standard antithrombotic agent for the initial treatment of DVT, is generally administered by continuous or intermittent intravenous or subcutaneous injection for 5 days or longer.[71,72] Oral anticoagulation is usually started within 24 hours after initiation of UFH therapy and continued for 2 to 6 months.

The efficacy of nadroparin has been compared with that of UFH in the treatment of patients with venography-confirmed DVT (table IV). In these studies, bodyweight-adjusted nadroparin 8200 to 18 860 IU/day was administered in 2 divided doses without laboratory monitoring and UFH was administered by intravenous infusion or subcutaneously with dosage adjustments made to maintain aPTT at 1.5 to 2 times the pretreatment value. Oral anticoagulant treatment was initiated either on the first[73] or seventh[74,75] day of heparin therapy. Drug administration was nonblind because of the different methods of administration and the need for dosage adjustment in the UFH groups. Efficacy was assessed by change in venographic score at 10 days and/or confirmed symptomatic recurrent DVT or pulmonary embolism during the 6-month follow-up period.

Nadroparin was at least as effective as UFH in the treatment of DVT in comparative studies (table IV). Both nadroparin and UFH recipients showed venographic improvement as well as significant improvements in Arnesen venographic scores from day 0 to day 10 (table IV);[74,75] a significantly higher percentage of nadroparin-treated patients showed venographic improvement in 1 study (60 *vs* 43%; $p \leq 0.05$).[75] In another study, a similar percentage of patients showed venographic improvement (56

Table IV. Efficacy of nadroparin (N) versus unfractionated heparin (UFH) in the treatment of deep vein thrombosis (DVT): summary of randomised multicentre nonblind parallel group trials in patients with venography-confirmed DVT

Reference	Patient parameters		Regimen[a]	Follow-up period	Improvement in Arnesen venographic score relative to baseline (%)	Venographic improvement (% of patients)	Symptomatic extension or recurrent DVT during 6-month follow-up (% of patients)	Overall efficacy
	no. evaluated	mean age (y)						
Koopman et al.[73]	202	59	N 8200, 12 300 or 18 400 daily in 2 divided doses × 6.1 days (mean) in patients weighing <50, 50 to 70 or >70kg, respectively	6mo			8.6	N ≡ UFH
	198	62	UFH 5000 IVB, then 1250/h IVI × 6.1 days (mean) → aPTT 1.5-2 × control				6.9	
Ninet et al.[74]	85	62.9	N 10 250, 12 300 or 14 350 daily in 2 divided doses × 10 days in patients weighing <55, 55 to 80 or >80kg, respectively	10 days	30.6*†	56		N ≥ UFH
	81	60.9	UFH 20/kg/h IVI × 10 days → aPTT or CCT 1.5-2 × control		16.4*	62		
Prandoni et al.[75]b	83	NA^c	N 10 250, 12 300 or 14 350 daily in 2 divided doses × 10 days in patients weighing <55, 55 to 80 or >80kg, respectively	6mo	NA	60†	7	N ≥ UFH
	85	NA^c	UFH 100/kg IVB, then 35 000/day IVI × 10 days → aPTT 1.5-2 × control		NA	43	14	

a All drug dosages in IU and all nadroparin dosages administered subcutaneously.
b Single-centre study.
c 48 and 53% of nadroparin and UFH recipients were aged >65 years.

Abbreviations and symbols: aPTT = activated partial thromboplastin time; CCT = calcium clotting time; IVB = intravenous bolus; IVI = intravenous infusion; NA = data not available; *p < 0.001 vs baseline; †p < 0.05 vs UFH; → indicates dosage adjustments to obtain the desired anticoagulant activity; ≡ indicates equivalent efficacy; ≥ indicates greater efficacy towards greater efficacy, with some clinical assessments showing statistically significant (p < 0.05) differences in favour of the first agent.

vs 62%),[74] but improvement in Arnesen (30.6 *vs* 16.4%) and Marder (28.9 *vs* 15.8%) venographic scores was significantly (p < 0.05) greater for nadroparin than UFH recipients. During 6-month follow-up, no statistically significant differences in the development of recurrent DVT (table IV) or mortality rate (overall and due to pulmonary embolism) were observed between nadroparin and UFH recipients.[73,75]

Preliminary evidence from a recent abstract suggests that once daily nadroparin is as effective as twice daily nadroparin in the treatment of established DVT.[76] Patients received a bodyweight-adjusted regimen of nadroparin ≈193 IU/kg/day for a mean duration of 7 days and were followed for 3 months. The incidence of fatal (0.6 *vs* 1.8%) or nonfatal pulmonary embolism (0.9 *vs* 1.2%) or DVT recurrence (2.5 *vs* 3.9%) was not significantly different between once daily (n = 316) and twice daily (n = 335) nadroparin recipients.

In the Koopman et al.[73] study, patients in the nadroparin group were treated at home as soon as appropriate, either by self-injection or, if this was not possible, injection by a relative or nurse. No significant difference in symptomatic extension or recurrent DVT was observed between nadroparin and UFH recipients (6.9 *vs* 8.6%) during the 6-month follow-up. Importantly, only 25% of patients in the nadroparin group were treated entirely in hospital, 22% were treated in hospital for <48 hours and 36% did not require hospital admission. This had a positive effect on hospital resource use and patient quality of life (section 3.3).

3.2.2 Acute Pulmonary Embolism

In a dosage-ranging study in 101 older patients (mean age approximately 60 years) with acute angiography-confirmed non-massive pulmonary embolism (pulmonary vascular obstruction between 15 and 55%; Miller's index of severity 5 to 18), nadroparin 82 or 123 IU/kg twice daily showed efficacy similar to aPTT adjusted-dose intravenous UFH.[77] Similar decreases in pulmonary vascular obstruction were observed over the 8-day treatment period in the nadroparin and UFH groups. In this study, enrolment in the nadroparin 123 and 185

IU/kg twice daily patient groups was discontinued prematurely because of a high incidence of major haemorrhagic complications requiring treatment discontinuation, transfusion or surgery (19.2% of 26 patients and 57.1% of 7 patients, respectively).

3.2.3 Acute Ischaemic Stroke

UFH has not been conclusively shown to improve functional status or reduce mortality in patients with acute ischaemic stroke.[78-80] However, recent evidence suggests that nadroparin may improve outcomes in these patients. Nadroparin was well tolerated in a noncomparative pilot study in 55 patients with acute ischaemic stroke[81] and, thus, was evaluated in a randomised double-blind placebo-controlled study in 306 older Chinese patients (mean age 67 years).[82] Within 48 hours of onset of symptoms of acute ischaemic stroke, patients received high-dosage nadroparin (4100IU twice daily), low-dosage nadroparin (4100IU once daily) or placebo for 10 days. 45, 52 and 65% of patients in the high-dosage, low-dosage and placebo groups, respectively, had a poor outcome (defined as death or dependency regarding daily living activities) at 6 months; a significant (p = 0.005) dosage-dependent trend in the reduction of poor outcomes was observed over this period. At 3 months, there was a similar trend in favour of treated patients, but it was not statistically significant (53, 60 and 64% of patients, respectively, had poor outcomes); however, between 3 and 6 months, more nadroparin-treated patients than placebo recipients showed clinical improvement.

3.2.4 Unstable Angina

In a recent single-blind study, nadroparin 88 IU/kg twice daily plus aspirin (acetylsalicylic acid) 200 mg/day was compared with intravenous UFH 400 IU/kg/day (dosage adjusted to maintain aPTT at twice the control value) plus aspirin and aspirin alone in 211 patients (mean age 63 years) with unstable angina (fig. 5).[83] Nadroparin plus aspirin was significantly more effective than UFH plus aspirin and aspirin alone in reducing the incidence of adverse clinical events (recurrent angina, nonfatal myocardial infarction, urgent revascularisation procedure and total major events). There were
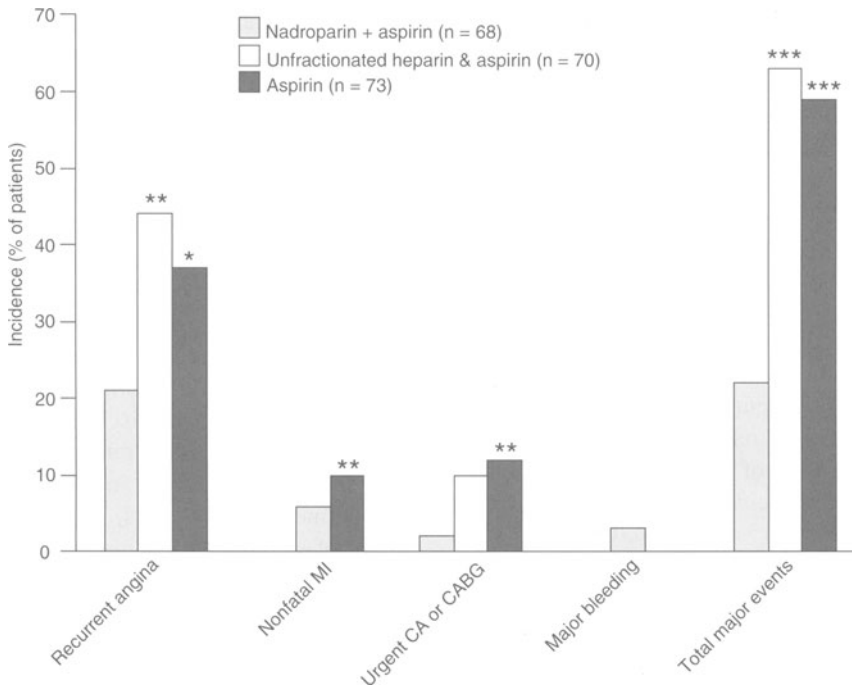
Fig. 5. Comparative efficacy of nadroparin (N) plus aspirin (ASA) [acetylsalicylic acid], unfractionated heparin (UFH) plus ASA, and ASA alone in older patients (mean age 63 years) with unstable angina.[83] Medications were administered for 5 to 7 days and the dosages were as follows: N 88 IU/kg subcutaneously twice daily; UFH 400 IU/kg/day by intravenous infusion with dosage adjusted to maintain the aPTT at twice control values; ASA 200 mg/day. *Abbreviations and symbols:* aPTT = activated partial thromboplastin time; CA = coronary angioplasty; CABG = coronary artery bypass graft; MI = myocardial infarction; *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001 *vs* N + ASA.

no deaths during the study period in any group. In addition, the incidence of silent ischaemia, defined as an episode of ECG changes without pain, was lower in the nadroparin group than in the UFH plus aspirin and aspirin alone groups (25 *vs* 41 and 38%) but reached statistical significance (p ≤ 0.05) only versus the UFH plus aspirin group.[83]

3.3 Pharmacoeconomic Considerations

It is accepted that use of some form of thrombo-embolic prophylaxis is needed to reduce postoperative mortality and morbidity in high risk surgical procedures, and studies have demonstrated the clear economic benefit of such prophylaxis.[84-88] Unfortunately, there are few pharmacoeconomic analyses involving LMWHs. Cost analyses based on

prophylaxis studies in patients undergoing elective hip replacement[88,89] or general abdominal surgery[88] indicate that LMWHs are less costly to the healthcare system than no prophylaxis, UFH, dextran 70 or selective treatment of DVT.

Recent data from researchers in New Zealand indicated that despite higher drug acquisition costs for LMWHs relative to UFH:[90]

- LMWHs are more cost effective than UFH for surgical prophylaxis of DVT if the costs of failed prophylaxis are considered
- the overall treatment costs (including those associated with treatment of pulmonary emboli and major haemorrhages) of using subcutaneous LMWH as therapy for established DVT are lower than those for UFH administered as a continuous infusion

- the economic benefit of treatment with LMWH becomes more pronounced when the rates of antithrombotic failure and bleeding complications are incorporated
- the cost differential favouring LMWH for the treatment of DVT becomes less favourable if UFH is administered subcutaneously.

In this study, overall costs of LMWH and UFH were calculated using recently published clinical data and local cost information.

Two studies comparing nadroparin and UFH in patients (mean age 60 years) with established DVT have included economic analysis.[73,91] In a French study, the overall treatment cost of 6 days' treatment with nadroparin 92 IU/kg subcutaneously every 12 hours was similar to that of a continuous intravenous infusion of UFH 30 000 IU/day (dosage adjusted to maintain activated cephalin times between 1.5 and 2.5 times control values) in 40 patients with confirmed DVT of the lower limbs (FF345 vs FF337; 1992 values).[91] Treatment costs were based on drug acquisition and monitoring costs. However, the average nursing time spent on the delivery and monitoring of drug therapy was significantly shorter in the nadroparin group (42 vs 104 min/wk for UFH; p < 0.05).

In a recent study[73] in 400 patients with proximal vein thrombosis (section 3.2.1), 75% of nadroparin recipients received some or all of their therapy on an outpatient basis. Compared with UFH (which was administered as a standard course of therapy in hospital), nadroparin was associated with considerably less hospital resource use (mean length of stay 8.1 vs 2.7 days). This decreased use of inpatient resources was partially offset by the costs associated with an average of 2 outpatient nursing visits and 2.2 telephone calls per patient. Unfortunately, no cost data were applied to either inpatient or outpatient resource use.

Based on Medical Outcome Study Short Form-20 survey results, quality of life significantly (p < 0.001) improved from baseline for all indicators (e.g. physical activity, social functioning, mental health, thrombosis symptoms, effort to cope and overall quality of life) over the 6-month study period.[73]

Changes over time were similar for both nadroparin and UFH groups with the exception of scores for physical activity and social functioning, which were significantly (p ≤ 0.002) better in the nadroparin than the UFH group at the 1- to 2-week evaluation. This result is not surprising because the quality-of-life questionnaires were designed for evaluation of outpatients, with phrasing of questions such that simply being in hospital would tend to produce worse patient scores, regardless of the level of illness.[92] Nonetheless, the results of this study are encouraging and warrant further clinical and pharmacoeconomic evaluation of outpatient administration of nadroparin.

4. Tolerability

The major haemorrhagic complications associated with the clinical use of heparins are peri- and postoperative bleeding and formation of wound haematomas. In a large study that assessed prophylaxis in 4498 general surgical patients (mean age 60 years), nadroparin did not significantly increase most measures of intraoperative bleeding relative to placebo.[60] Nadroparin was associated with significantly (p < 0.01) higher incidences of excessive postoperative bleeding as assessed by the surgeon (7.7 vs 3.1% for placebo), and wound (11.8 vs 6.3%) and injection site (10.2 vs 6.6%) haematoma.

Comparative studies of nadroparin and UFH used for prophylaxis of DVT showed no significant difference in the incidence of bleeding complications in patients who underwent general[56,57] or orthopaedic surgery.[61,64] The incidence of clinically important bleeding was also similar with nadroparin (1.5% of 330 patients) and acenocoumarol (2.3% of 342 patients) in patients who underwent elective hip or knee replacement.[63] Compared with the standard preoperative initiation of nadroparin, beginning therapy postoperatively offered no clinically significant advantages in terms of bleeding complications in patients undergoing elective hip replacement.[65] Similarly, in orthopaedic trauma patients who received prophylaxis with fixed-dosage (3075 IU/day) or bodyweight-adjusted (≈40 to 60 IU/kg/day) nadroparin for up to 6 weeks, the

incidence of major bleeding was 3.5% in both groups.[62]

In a large trial in bedridden hospitalised medical patients (mean age 70 years), the incidence of major and minor bleeding complications was similar (<1%) for prophylactic treatment with subcutaneous nadroparin 3075IU once daily (n = 810) and UFH 5000IU every 8 hours (n = 780) for 10 days.[67] Compared with that in the nadroparin group, the incidence of subcutaneous haematoma with a diameter >2.5cm was significantly (p = 0.0001) higher in the UFH group (actual incidence not reported), as were the incidences of local erythema at injection site (7.2 *vs* 4.1%; p = 0.02), >3-fold elevations in liver transaminase levels (2.7 *vs* 0.8%; p = 0.01) and thrombocytopenia (platelet count values between 40 and 80 × 10^9/L) [0.5 *vs* 0%; p = 0.05].

Data are also available from a randomised multicentre tolerability study in bedridden hospitalised elderly patients (mean age 83 years) who received 28 days' prophylaxis with either subcutaneous nadroparin 3075 IU/day (n = 146) or UFH 5000 or 7500IU twice daily (n = 149).[66] Although the overall rate of treatment withdrawal was similar for the 2 groups, significantly fewer patients in the nadroparin group withdrew because of drug-related adverse events than in the UFH group (fig. 6); 1 nadroparin recipient withdrew because of an allergic reaction and 10 UFH recipients discontinued therapy because of a major bleeding event such as retroperitoneal bleeding or gastrointestinal bleeding with haematemesis or melaena (n = 4), allergic reaction (n = 3), DVT, pulmonary embolism or thrombocytopenia (n = 1 each).[66] The incidence of haemotoma was also significantly lower in the nadroparin group than in the UFH group (fig. 6).

Although the trials were not large enough to demonstrate statistically significant differences between treatments, the incidence of major bleeding (e.g. retroperitoneal bleeding, haemoptysis, gastrointestinal bleeding) was lower with nadroparin ≈185 IU/kg/day in 2 divided doses (0.5 to 2.3%) than with aPTT adjusted-dose UFH (2 to 5%) in patients receiving treatment for DVT (section 3.2.1; table
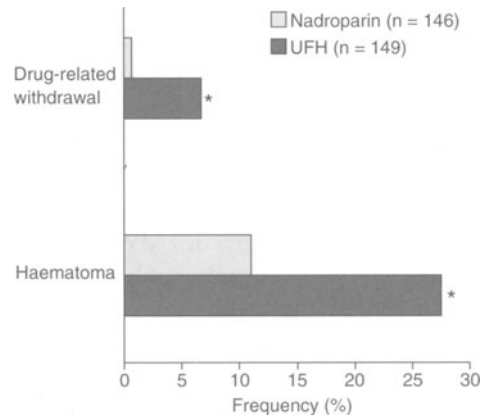

Fig. 6. Comparative tolerability of subcutaneous nadroparin and unfractionated heparin (UFH) as thromboprophylaxis in elderly bedridden medical patients (mean age 83 years).[66] Patients received nadroparin 3075IU once daily or UFH 5000 or 7500IU twice daily for 28 days. *Symbol:* *p ≤ 0.05 *vs* nadroparin.

IV).[73-75] Treatment with nadroparin 123 or 185 IU/kg twice daily was associated with clinically significant major bleeding in patients with submassive pulmonary embolism, leading to discontinuation of enrolment of patients into these groups (section 3.2.2).[77] The frequency of minor bleeding (e.g. epistaxis, skin haematoma) was reported to be higher (7 *vs* 2%),[75] lower (7.6 *vs* 13.4%),[73] or similar (1% in each group)[74] for UFH- versus nadroparin-treated patients in these studies.

The incidence of minor bleeding, defined as spontaneous haematoma at injection sites, in 211 patients undergoing treatment for unstable angina was similar for aspirin alone (0%) and aspirin plus nadroparin (1.5%); these rates were significantly (p ≤ 0.01) lower than those observed in aspirin plus UFH-treated patients (14%).[83]

Tolerability data are also available from an analysis of spontaneous adverse event reports based on 220 698 million units of nadroparin sold in France from 1986 to 1993 (>15 million patient treatments).[21] Rash or local injection site events (n = 168), haemorrhagic events (n = 161), thrombocytopenia (n = 137) and skin necrosis (n = 24) were the most frequently reported events thought to be pos-

sibly or probably associated with nadroparin treatment; these occurred in <0.001% of patients. The severity of haemorrhagic events varied, but was usually minor (haematoma at injection site or minor bleeding of postoperative wound) and rarely severe (gastrointestinal haemorrhage, deep haematoma or intracranial bleeding). Thrombocytopenia, defined as a platelet count $<100 \times 10^9$/L or a >40% decrease during treatment, had a latency period to onset of 5 to 12 days.

Heparin-induced thrombocytopenia (HIT) can manifest as a mild transient reaction or as a severe immunologically mediated reaction; the latter occurs in up to 5% of patients treated with UFH and can be complicated by thrombotic events which cause substantial morbidity and mortality.[8,93,94] HIT was reported in <1% of nadroparin recipients and in up to 3.5% in UFH recipients in comparative studies.[59-64,67,74,75] In 2 large comparative studies, the incidence of thrombocytopenia with nadroparin was similar to that with placebo in 4498 surgical patients (0.6 vs 0.4%),[60] and significantly lower than that with UFH in 1590 bedridden medical patients (0 vs 0.5%; p = 0.05).[67] There have been a few reports of HIT with clinical sequelae in nadroparin-treated patients,[95,96] as well as a number of reports of successful treatment of HIT with nadroparin.[97-100] Nonetheless, in vitro cross-reactivity rates of >80% have been reported with nadroparin and other LMWHs (enoxaparin and dalteparin),[101] indicating the need for assessment of in vitro cross-reactivity prior to initiating LMWHs in this clinical situation.

Subcutaneous injections of nadroparin were rated significantly less painful than subcutaneous injections of enoxaparin on visual analogue and verbal category pain scales in single-[102] and double-blind[103] crossover studies. In 60 bedridden elderly patients (mean age 79 years), the incidence and severity of haematoma, swelling, pain, burning and itching associated with injection were all significantly lower with nadroparin 3075IU than with enoxaparin 20 or 40mg (p < 0.05 and < 0.01, respectively) 30 minutes and 3 hours after injection.[102] Both physician and patient judgements of

local tolerability were significantly (p < 0.01) better for nadroparin than for either dose of enoxaparin. Similarly, significantly less injection pain was observed with nadroparin 4100IU than enoxaparin 40mg at 1 and 5 minutes after injection in 12 healthy men.[103]

5. Dosage and Administration

Nadroparin is usually administered by subcutaneous injection into the anterolateral abdominal wall but may also be administered intravenously. In clinical practice, drug dosages are typically expressed in injection volume; the currently available drug formulation contains 9500IU of nadroparin per 1ml of solution for injection based on amidolytic anti-factor Xa activity of about 85 IU/mg (section 1.2).[50]

In general surgical patients, nadroparin should be administered in a single daily injection of 0.3ml beginning 2 to 4 hours before surgery and continued for at least 7 days or at least until the patient is ambulatory.[50] A similar daily dose has been administered to hospitalised bedridden medical patients at risk of developing DVT. In patients undergoing orthopaedic surgery, initial doses should be given 12 hours before surgery and 12 hours after the end of surgery; these and subsequent once daily dosages should be adjusted according to bodyweight as outlined in table V.[50] Drug administration should continue for at least 10 days or at least until the patient is ambulant.

The bodyweight-adjusted dosages recommended by the manufacturer for the treatment of DVT are presented in table V. The usual duration of therapy is 10 days. Preliminary results support a similar administration regimen for the treatment of pulmonary embolism, acute ischaemic stroke and unstable angina.

Although the incidence of thrombocytopenia is low with nadroparin, platelet counts should be monitored before initiation of therapy and then twice weekly thereafter.[1,50] Systemic studies on drug interactions with nadroparin or LMWHs in general are not available.[20] Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs or ticlop-

Table V. Summary of bodyweight-adjusted dosages of subcutaneous nadroparin for thromboprophylaxis in patients undergoing orthopaedic surgery and for treatment of deep vein thrombosis[50]

Bodyweight (kg)	Volume of nadroparin to be injected (ml)[a]	
Orthopaedic surgery [initial dose (first column) is administered 12 hours before surgery and once daily until day 3; subsequent doses (second column) are administered once daily from day 4 onwards]		
<50	0.2	0.3
50-69	0.3	0.4
≥70	0.4	0.6
Treatment of deep vein thrombosis (doses to be administered twice daily)		
<50	0.4	
50-59	0.5	
60-69	0.6	
70-79	0.7	
80-89	0.8	
≥90	0.9	

a   The currently available formulation contains 9500IU of nadroparin per 1ml, where the amidolytic anti-factor Xa activity of nadroparin is equivalent to about 85 IU/mg (range 80 to 100 IU/mg) in an isolated system (without plasma) [data on file, Sanofi Pharma].

idine may increase the risk of bleeding; careful clinical monitoring is required when such combinations cannot be avoided.[21] The dosage of nadroparin may need to be reduced in patients with renal impairment, although no specific guidelines are available. Similarly, nadroparin should be used with caution in patients with hepatic insufficiency, uncontrolled arterial hypertension, history of peptic ulceration or any other organic lesion likely to bleed as well as in patients who have undergone surgery of the brain, spinal cord or eye.[50]

6. Place of Nadroparin in the Management of Thromboembolic Disorders in Older Patients

Antithrombotic prophylaxis to prevent DVT after surgery is well established and is particularly important for high risk orthopaedic procedures and for other types of major surgery when associated risk factors (e.g. advanced age, obesity, varicose veins, previous DVT, malignancy, underlying disease) are present. UFH has been used for the treatment of thrombosis for more than 50 years and has

more recently been used as prophylaxis of thromboembolic events.[55] However, this agent has been associated with undesirable effects such as bleeding and thrombocytopenia and requires aPTT monitoring in many circumstances; UFH also has a relatively short elimination half-life and limited bioavailability when administered subcutaneously, necessitating administration of 2 to 3 injections daily.[43]

The LMWHs were developed in an attempt to overcome the shortcomings of UFH. Nadroparin was the first LMWH to become available for clinical use and as such it is an important agent. Indeed, there are currently at least a dozen LMWHs available for clinical use.[20] Clinical experience has shown LMWHs to have advantages over UFH. These include greater bioavailability (with longer biological half-life and less frequent administration), more predictable anticoagulant activity and lack of need for laboratory monitoring.[8,43,54,89,104-108] Available data seem to show equal or better efficacy for LMWHs compared with UFH in the prophylaxis or treatment of thromboembolic disorders but have failed to support a reduced risk of bleeding complications.[43,53,54,106-109] In addition, the widely held view of a reduced risk of thrombocytopenia with LMWHs relative to UFH has yet to be confirmed in a well-designed study.

Once daily subcutaneous nadroparin is effective for the prevention of DVT and pulmonary embolism following orthopaedic or general surgery, and in elderly bedridden medical patients. In these contexts, nadroparin was at least as effective as UFH and dalteparin in general surgical patients, UFH and oral acenocoumarol in orthopaedic surgical patients, and UFH in bedridden medical patients. No significant differences in bleeding complications were noted between nadroparin and comparators in surgical patients. In elderly bedridden medical patients, nadroparin was associated with a significantly lower incidence of local reactions, elevated transaminase levels, thrombocytopenia and treatment withdrawals because of adverse events than UFH.

A bodyweight-adjusted dosage of subcutaneous nadroparin was at least as effective as dose-adjusted intravenous UFH in the treatment of DVT. Preliminary evidence suggests that treatment with once daily nadroparin is as effective as the same dosage of nadroparin administered twice daily in patients with DVT. 75% of nadroparin recipients in 1 study were able to complete their drug treatment as outpatients, indicating an advantage for nadroparin over intravenous UFH (which requires hospitalisation and frequent monitoring and dosage adjustment). Preliminary results with nadroparin in the treatment of pulmonary embolism, acute ischaemic stroke and unstable angina are encouraging and further investigations in these areas are warranted.

The higher acquisition costs of LMWHs compared with UFH have led to concerns for purchasers that the use of these drugs may have serious implications for healthcare budgets.[110] Pharmacoeconomic studies of LMWHs are limited but recent data indicate that despite their higher acquisition costs, LMWHs are more cost effective than UFH for prophylaxis or treatment of DVT, particularly when the costs associated with treatment failure are considered. Overall treatment costs (drug acquisition and monitoring costs) were similar for subcutaneous nadroparin and intravenous UFH in a French study in patients with DVT. Outpatient treatment of DVT with nadroparin resulted in considerably less hospital resource use than UFH but, as expected, was associated with increased outpatient resource use. Unfortunately, the costs associated with inpatient and outpatient resource use were not quantified and therefore limited conclusions can be drawn from these results.

Anticoagulant therapy represents a compromise between prevention of thrombosis and impairment of haemostasis, and the use of LMWHs is no exception. In studies conducted in most older patient populations, subcutaneous nadroparin has been shown to be an effective and well tolerated drug for the prevention of DVT and pulmonary embolism in general and orthopaedic surgical and in bedridden medical patients, and for the treatment of established DVT. Nadroparin also has poten-

tial for the treatment of pulmonary embolism, acute ischaemic stroke and unstable angina in this patient population. More well-designed trials are needed to clearly define its advantages over UFH in terms of efficacy, tolerability (particularly bleeding complications) and cost effectiveness. In addition, comparisons with other agents (especially other LMWHs) are required to define the relative place of nadroparin in the management of thromboembolic disorders. The ease of administration and reduced need for laboratory monitoring of LMWHs, including nadroparin, are undisputed advantages of these agents compared with UFH, and both may have positive cost implications.

In summary, nadroparin is at least as effective and as well tolerated as standard antithrombotic agents in older patients. Available clinical and tolerability data support its use over UFH, dalteparin and oral acenocoumarol for the prevention of DVT in surgical patients, over UFH for the prevention of DVT in bedridden patients, and over UFH for the treatment of established DVT. Nadroparin is, therefore, an effective, well tolerated, and easily administered and monitored antithrombotic agent for the prophylaxis and treatment of DVT in older patients.

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