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Low Molecular Weight Heparin: A Critical Analysis of Clinical Trials

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I. Comparison of the Biochemical and Pharmacological Properties of Standard Heparin and Low Molecular Weight Heparin

Interest in LMWHs† as potential antithrombotic agents came from the observations in the mid-1970s that LMWH fractions prepared from standard commercial grade heparin progressively lose their ability to prolong the activated partial thromboplastin time but retain their ability to inhibit factor Xa (Johnson et al., 1976; Andersson et al., 1976). Since then considerable progress has been made. The mechanism for the difference between the anticoagulant profiles of LMWHs and UFH has been elucidated (Oosta et al., 1981; Jordan et al., 1980; Lane et al., 1984; Holmer et al., 1981), and other potentially clinically important differences between LMWHs and UFH have been discovered.

A number of LMWHs have been developed commercially and have been shown to be safe and effective for the prevention and treatment of venous thromboembolism. At least five different LMWHs are licensed for clinical use in about 20 countries, including the United States and Canada.

In this section we will review the anticoagulant effects, the experimental antithrombotic and hemorrhagic effects, and the pharmacokinetic and clinical effects of LMWHs. Where appropriate, these properties of LMWHs will be compared and contrasted with heparin and other antithrombotic agents.

A. Biophysical Properties and Anticoagulant Effects of Heparins

Heparin and LMWHs are glycosaminoglycans consisting of chains of alternating residues of D-glucosamine and an uronic acid, either gluconic acid or iduronic acid (Choay and Petitou, 1986). Heparin is a heterogeneous polydispersed mixture of sulfated polysaccharides ranging in molecular weight from 5,000 to 30,000, with an average molecular weight of 15,000 (Johnson and Mulloy, 1979). The anticoagulant activity of heparin is accounted for by a unique pentasaccharide with a high-affinity-binding sequence to ATIII (Rosenberg and Lam, 1979; Rosenberg, 1987; Lindahl et al., 1979, 1984; Choay et al., 1983; Petitou, 1984). The third residue of the pentasaccharide is 3–0-sulfated glucosamine, which is critical for binding to ATIII and is only found in the ATIII-binding sequence (Lindahl et al., 1984; Atha et al., 1987). Only about one-third of the heparin molecules contain the unique pentasaccharide sequence, and its distribution along the heparin chain appears to be random (Oosta et al., 1981; Rosenberg, 1987; Lindahl et al., 1979).

The major anticoagulant effect of heparin is accomplished through its interaction with ATIII (Rosenberg et al., 1979; Bjork and Lindahl, 1982). This interaction produces a conformational change in ATIII (Nordenman and Bjork, 1978; Villanueva and Danishefsky, 1977) and markedly accelerates the ability of ATIII to inactivate the coagulation enzymes thrombin (factor IIa), factor Xa, and factor IXa (Rosenberg et al., 1987). Of these enzymes, thrombin is most sensitive to inhibition by heparin, both because ATIII inhibits thrombin more rapidly than factor Xa (Rosenberg, 1987; Ofosu et al., 1989) and because factor Xa is protected from inhibition by the ATIII/heparin when it is bound to phospholipid in the prothrombinase complex (Beguin et al., 1989a,b; Teitel and Rosenberg, 1983).

Heparin potentiates the inactivation of thrombin by serving as a template to which both ATIII and thrombin bind to form a ternary complex (Atha et al., 1987; Rosenberg, 1987; Lindahl et al., 1979; Rosenberg et al., 1979; Bjork and Lindahl, 1982; Danielsson et al., 1986). In contrast, the accelerated inactivation of factor Xa by heparin/ATIII does not require ternary complex formation but is achieved solely through heparin binding to ATIII (Atha et al., 1987; Bjork and Lindahl, 1982; Rosenberg and Lam, 1979; Rosenberg, 1987; Choay et al., 1983; Ellis et al., 1986). Heparin molecules with fewer than 18 saccharides (molecular weight < 5400) are unable to bind thrombin and ATIII simultaneously and, therefore, are unable to accelerate the inactivation of thrombin by ATIII but retain their ability to catalyze the inhibition of factor Xa by ATIII (Jordan et al., 1980; Lane et al., 1984; Danielsson et al., 1986) (fig. 1, table 1). The anticoagulant activity of heparin is also mediated by a second plasma cofactor, heparin cofactor II (Tollefsen et al., 1982). This anticoagulant effect is specific for thrombin, does not require the unique ATIII-binding pentasaccharide, and requires a minimum chain length of 24 monosaccharide units (molecular weight approximately 7200) (Maimone and Tollefsen, 1988; Sie et al., 1988).

LMWHs are fragments of commercial grade heparin

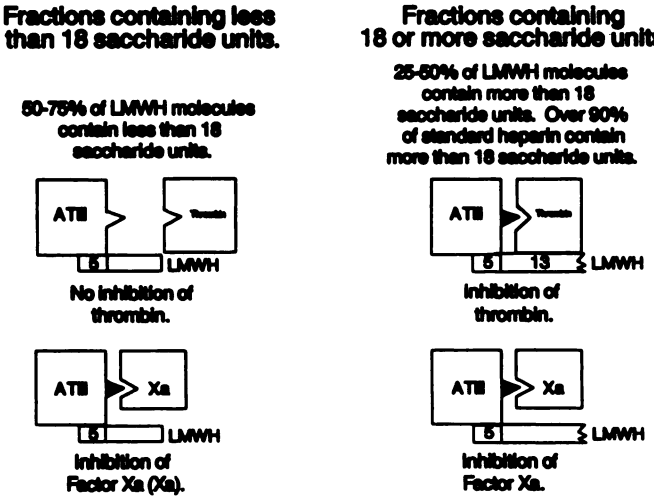

FIG. 1. Mechanism of action of heparin and LMWHs.

† Abbreviations: LMWH, low molecular weight heparin; factor Xa, activated factor X; UFH, unfractionated heparin; ATIII, antithrombin III; DVT, deep-vein thrombosis; THR, total hip replacement; PE, pulmonary embolism; TKR, total knee replacement; BID, twice daily; QD, once daily.

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TABLE 1
Molecular weight and anticoagulant activity of saccharide fractions [Adapted from Lane et al (1986)]

Heparin oligosaccharides	Molecular weight	Anticoagulant activity anti-Xa	Anticoagulant activity anti-IIa
8	2400	1.30	Nil
12	3600	1.58	Nil
16	4800	1.60	Nil
18	5400	0.95	0.51
24	7200	1.30	1.21

produced by either chemical or enzymatic depolymerization (Ofosu and Barrowcliffe, 1990). Depolymerization of heparin leads to partial loss of the original catalytic activity (Rosenberg et al., 1979; Danielsson et al., 1986; Jordan et al., 1982), with the ability to catalyze thrombin inhibition decreasing to a much greater extent than the ability of the fragments to catalyze the inhibition of factor Xa (Ofosu and Barrowcliffe, 1990; Thunberg et al., 1979). Depolymerization is achieved by one of the following methods (table 2): treatment with nitrous acid, cleavage with the enzyme heparinase, hydrolytic cleavage with hydrogen peroxide, or benzylation followed by alkaline depolymerization. The resulting LMWHs contain the unique pentasaccharide required for specific binding to ATIII but in a lower proportion than is contained in their parent standard heparin (Jordan et al., 1982).

Two other glycosaminoglycans (commonly referred to as heparinoids) also have been developed for clinical use. These are dermatan sulfate and the Organon heparinoid, which consists of a mixture of 80% heparan sulfate and 20% dermatan sulfate and chondroitin sulfates. Unlike heparin and LMWH, the anticoagulant effect of dermatan sulfate is solely through its ability to catalyze the inactivation of thrombin by heparin cofactor II (Tollefsen et al., 1982; Maimone and Tollefsen, 1988).

LMWHs developed commercially have different mean molecular weights that vary from 4000 to 6500 (Fareed et al., 1988). LMWHs have reduced ability to catalyze the inactivation of thrombin relative to their ability to inhibit factor Xa because the inactivation of thrombin is mediated only by the larger oligosaccharide chains which contain at least 18 monosaccharides (equivalent to a molecular weight of approximately 5400). Because only 25 to 50% of the LMWH molecules contain at least 18 saccharide units, compared to heparin which by definition has an anti-factor Xa to anti-IIa ratio of 1:1, the various commercial LMWHs have anti-factor Xa to anti-IIa ratios of between 4:1 and 2:1. Because the molecular weight distribution of LMWHs varies widely between preparations (Fareed et al., 1988), the anti-factor IIa activity of the different LMWHs with similar mean molecular weights will also vary between the different commercial preparations (Fareed et al., 1988).

B. Protein Binding and Pharmacokinetics

In 1979, Andersson and associates made the observation that normal plasma contains components that neutralize the anti-factor Xa activity of heparin but not that of smaller molecular weight fractions of heparin. The molecular size of heparins influences the ability of plasma to interfere with their anticoagulant activity because LMWHs differ from heparin in their binding characteristics to plasma proteins (Lane, 1989; Lane et al., 1986) Heparin binds to a number of plasma proteins, platelet proteins, and vascular wall matrix proteins, including histidine-rich glycoprotein (Lane et al., 1986; Lijnen et al., 1983; Peterson et al., 1987), platelet factor 4 (Lane et al., 1986; Holt and Niewiarowski, 1985), vitronectin (Preissner and Muller-Berghaus, 1987), fibronectin (Dawes and Pavuk, 1991), lipoproteins, and von Willebrand factor (Sobel et al., 1991). These interactions have the potential to neutralize the anticoagulant effect of heparin in vivo. Binding to plasma proteins could be responsible for the reduced bioavailability of heparin at low concentrations, for the variability of its anticoagulant response to fixed doses in patients with thromboembolic disorders (Hirsh et al., 1976), for the marked variability in dose-response effects seen between patients treated with heparin (Young et al., 1992), and for the laboratory phenomenon of heparin resistance (Young et al., 1992).

LMWHs have a much lower affinity for plasma and matrix proteins (Lane et al., 1986; Dawes and Pavuk, 1991) and for platelet factor 4 (Lane et al., 1986) than

TABLE 2
Commercial LMWHs and their methods of preparation

Agent	Manufacturer	Method of preparation
CY 216 (Fraxiparin)	Sanofi	Nitrous acid depolymerization
PK 10169 (Enoxaparin, Lovenox)	Rhone-Poulenc Rorer	Benzylation followed by alkaline depolymerization
Kabi 2165 (Fragmin)	Kabi	Nitrous acid depolymerization
RD 11885	Wyeth	Peroxidative depolymerization
Novo LMWH (Logiparin)	Novo	Enzymatic (heparinase) depolymerization
ORG 10172 (Lomoparan)	Organon Inc.	Prepared from porcine gut mucosa (contains dermatan sulfate (80%), heparan sulfate, chondroitin sulfate

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does heparin, an observation that probably explains the superior bioavailability of LMWHs at low doses and their more predictable anticoagulant response.

The molecular sizes of heparin and its fragments also influence their binding to endothelial cells. Heparin binds to endothelial cells and macrophages (Barzu et al., 1985), whereas LMWHs do not bind to endothelial cells in culture (Barzu et al., 1984, 1987). These differences in binding properties between LMWHs and heparin could be responsible for the differences in the pharmacokinetics between heparin and LMWHs (Bara and Samama, 1988; Boneu et al., 1988; Stiekema et al., 1989). Thus, the clearance of heparin is dose dependent and occurs through a combination of a rapid saturable phase, due to binding to cells, and a much slower first-order mechanism of clearance (de Swart et al., 1982; Bjornsson et al., 1982). In contrast, the clearance of LMWHs is dose independent, because the molecules do not bind to endothelial cells, and is 2- to 4-fold slower than heparin (table 3). LMWHs are cleared principally by the renal route, and their biological half-life is increased in patients with renal failure (Boneu et al., 1988; Palm and Mattsson, 1987).

C. Antithrombotic and Hemorrhagic Effects of Low Molecular Weight Heparins, Heparinoids, and Heparin in Experimental Models in Animals

The antithrombotic effects of heparin have been compared with LMWHs and the heparinoids, ORG heparinoid, and dermatan sulfate in animal models (Carter et al., 1982; Esquivel et al., 1982; Cade et al., 1984; Holmer et al., 1982; Andriuoli et al., 1985; Bergqvist et al., 1985; Van Ryn-McKenna et al., 1989a,b; Boneu et al., 1985; Henny et al., 1985; Hobbelen et al., 1987). When compared on the basis of anti-Xa activity, heparin is approximately twice as effective as LMWHs (Carter et al., 1982; Esquivel et al., 1982; Van Ryn-McKenna et al., 1989a). Effective inhibition of experimental venous thrombosis with LMWHs is achieved at anti-factor Xa levels ex vivo of 0.2 to 0.3 units/ml, whereas concentrations of LMWHs up to 0.7 anti-factor Xa units/ml are required to produce effective inhibition of thrombus growth (Boneu et al., 1985).

The hemorrhagic effects of heparin, LMWHs, and the two heparinoids have been compared in a variety of animal models by measuring blood loss from a standardized injury to the microvasculature. In most comparative studies, heparin produced more bleeding for an equivalent antithrombotic effect than did the LMWHs and the heparinoids (Carter et al., 1982; Esquivel et al., 1982; Cade et al., 1984; Andriuoli et al., 1985; Bergqvist et al., 1985; Henny et al., 1985; Hobbelen et al., 1987). These differences in the relative antithrombotic to hemorrhagic effects of heparin and LMWHs could be due to the greater effects of heparin on platelet function and vascular permeability (Fabris et al., 1983; Holmer et al., 1980; Fernandez et al., 1986; Blajchman et al., 1989).

D. Clinical Potential of Low Molecular Weight Heparins

LMWHs have been evaluated in a number of randomized clinical trials and have been shown to be safe and effective anticoagulants. By far the greatest experience has been obtained in the prevention of venous thrombosis in high-risk patients; experience is growing with the use of LMWHs for the treatment of venous thrombosis, but their use for other indications is limited to case reports and pilot studies.

Although LMWHs and heparin share a number of common properties, they also differ from one another in the following ways: they have different molecular weight distribution profiles, different specific activities (anti-Xa to anti-IIa activities), different rates of plasma clearance, and different recommended dosage regimens. Therefore, until more information is available concerning their rel-

TABLE 3

Anticoagulant profiles, molecular weights, and plasma half-lives of commercial LMWHs

Drug	Anti-Xa to anti-IIa ratio	Molecular weight (range) [saccharide units]	Plasma half-life (min)
Enoxaparin (Rhone-Poulenc Rorer)	2.7:1	4500 (3,000–8,000) [10–27]	129–180
Fragmin (Kabi)	2.0:1	5000 (2,000–9,000) [7–30]	119–139
Fraxiparin (Sanofi)	3.2:1	4500 (2,000–8,000) [7–27]	132–162
Logiparin (Novo)	1.9:1	4500 (3,000–6,000) [10–20]	111
RD Heparin (Wyeth)	2.0:1	6000 (2,000–15,000) [7–50]	200
Lomoparan (Organon)	20:1	6500	1,100

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ative safety and efficacy, LMWHs should be considered to be distinct and separate compounds.

LMWHs have a number of potential and demonstrated clinical advantages over heparin (table 4). The potential advantage is the reduced hemorrhagic to antithrombotic ratio of LMWH in experimental animals. The demonstrated advantages of LMWHs are their greater bioavailability at low doses, longer half-life, and more predictable anticoagulant response when administered in fixed doses. These properties allow LMWHs to be administered QD and without laboratory monitoring. There is also recent evidence that the incidence of heparin-induced thrombocytopenia is lower with a LMWH than with heparin (Warkentin et al., 1993). The clinical importance of the observation in experimental animal models that LMWHs produce less microvascular bleeding than does heparin for an equivalent antithrombotic effect is uncertain. Both low-dose heparin and LMWHs in prophylactic doses produce only minimal and equivalent bleeding, but there is suggestive evidence that, when given in high doses for the treatment of venous thrombosis, LMWHs produce less bleeding than heparin (Hull et al., 1992; Prandoni et al., 1992).

II. Prophylaxis of Venous Thromboembolism after Major Orthopedic Surgery of the Lower Limb

Venous thromboembolism prophylaxis for patients undergoing major orthopedic surgery of the lower limb is of paramount importance. Without prophylaxis, the prevalence of DVT documented by venography following THR surgery is 50%. Furthermore, up to 20% of patients have thrombosis of the proximal leg veins (popliteal vein or more proximal), which are the ones most frequently associated with symptomatic acute PE (Clagett et al., 1992). Asymptomatic PE may occur in 30% of patients despite standard UFH prophylaxis (Erikkson et al., 1991), and without prophylaxis, PE mortality may reach 3.4 to 6% (Coventry et al., 1973; Collins et al., 1988; Haake and Berkman, 1989). Similarly, the prevalence of DVT following elective unilateral TKR surgery is between 40 and 84% (Cohen et al., 1973; Stulberg et al., 1984; Lynch et al., 1988; Stringer et al., 1989). Most of these DVTs produce no symptoms and are confined to the calf veins, which appear to have a lower rate of associated PE. Asymptomatic PE based on a high-probability lung scan occur in 1.8 to 7% of patients with TKR (Stulberg et al., 1984; Stringer et al., 1989). The incidence of fatal PE in the absence of prophylaxis is unknown, although in a review of 152 patients with TKR receiving only elastic compression stocking prophylaxis, three (2.0%) patients suffered definite or probable symptomatic PE with one (0.7%) death (Mohr et al., 1992). Without prophylaxis, the prevalence of DVT following hip fracture is 43% (Clagett et al., 1992), and mortality may approach 12% (Haake and Berkman, 1989).

Results of animal model studies have suggested that LMWH produces less bleeding for the same antithrombotic effect when compared to standard UFH (Salzman et al., 1980; Carter et al., 1982; Bergqvist et al., 1985). We determined the efficacy and safety of LMWH and heparinoids as venous thromboembolism prophylaxis following major orthopedic surgery of the lower limb based on a critical review of all relevant clinical trials reported to date. A literature search for all English language studies of LMWH DVT prophylaxis following major orthopedic surgery of the lower limb was performed including a review of all study bibliographies for additional trials. Studies of THR, TKR, and hip fracture were analyzed separately because of operation-specific differences in total DVT (proximal plus calf vein DVT), proximal DVT, and PE prevalence. Seven LMWH drugs have been studied for this indication [Enoxaparin (Lovenox), Fragmin, Fraxiparin, Logiparin, RD Heparin (Normiflo), dermatan sulfate (MF 701), and Lomoparan (ORG 10172)]. Each was analyzed separately because of differences in LMWH-specific pharmacokinetics. As of this writing, Enoxaparin (Lovenox) has received United States Food and Drug Administration approval as prophylaxis following THR. In addition, new drug applica-

TABLE 4

Potential and demonstrated advantages of LMWHs over heparin

Potential advantage of LMWHs	Advantage demonstrated clinically	Proposed mechanisms for observed effect
LMWHs have more stable dose response and, therefore, do not require laboratory monitoring.	Yes, in randomized trials.	LMWHs do not bind to heparin-binding proteins.
LMWHs have better bioavailability when injected subcutaneously in low doses.	Yes, in pharmacokinetic studies.	LMWHs bind less to heparin-binding proteins.
LMWHs have longer plasma half-life and can be administered QD.	Yes, in formal pharmacokinetic studies and randomized trials.	LMWHs bind less to endothelial cells and matrix proteins.
LMWHs associated with a lower incidence of heparin-induced thrombocytopenia.	Yes, in a randomized trial.	LMWHs bind less to platelets.
LMWHs produce less bleeding for equivalent antithrombotic effect.	Suggestive evidence when high doses are used but not proven definitively.	LMWHs bind less to platelets.

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tions before the Food and Drug Administration are pending for Logiparin, RD Heparin (Normiflo), Fraxiparin (Dalteparin), and Lomoparan (ORG 10172).

Randomized prospective clinical trials in which at least one LMWH arm was not confounded by other prophylaxis measures (excluding elastic compression stockings) were included in the analysis. A subcutaneous route of administration was used for heparin prophylaxis arms (both LMWH and UFH) in all studies. The efficacy outcome measures analyzed were the total DVT prevalence (proximal plus calf) and proximal DVT prevalence as documented by postoperative venography. Only trials requiring mandatory postoperative venography were reviewed for efficacy. The use of mandatory bilateral venography vs. unilateral leg venography of the only operated leg is noted, because the DVT prevalence in the nonoperated leg may be significant. There was considerable variation among studies in the time interval between surgery and the postoperative venogram, which may invalidate direct comparison of DVT prevalence rates. The PE incidence rate and total mortality rate are also reported, although, in general, these rates were too low to draw meaningful conclusions.

All trials were reviewed for safety outcome regardless of the efficacy outcome measure used. The major safety concern is bleeding. Multiple measures of bleeding were used among studies, making direct comparison difficult. Reported bleeding rates in this analysis reflect each author's definition of total clinically significant bleeding events (major plus minor) and exclude minor wound hematomas. Double-blind, placebo-controlled trials were analyzed separately because the LMWH arm bleeding rate in these trials likely reflects the true rate over and above what would be expected for the operative procedure alone. Double-blind, non-placebo-controlled trials were also analyzed separately for similar reasons. Significant differences in other indices of bleeding (intraoperative blood loss, postoperative drain blood loss, number of blood products transfused, wound hematomas, hemoglobin level) are reported in the text. Other safety issues are noted including the incidence of thrombocytopenia and liver transaminase elevation.

Study design issues that might affect both safety and efficacy are noted. These include the timing of the initial LMWH dose (preoperative vs. postoperative), the interval between LMWH doses (QD vs. BID), and the circulating LMWH anticoagulant activity measured as the anti-Xa level (IU/ml), and when it was measured in relation to the last dose of LMWH. There are no studies in which one LMWH drug was compared directly with another. A comparison of the efficacy and safety of different LMWH drugs as reported among different studies is invalid.

A. *Efficacy*

1. Total hip replacement. Six trials used Enoxaparin as a DVT prophylaxis following THR (table 5). In a double-blind, placebo-controlled trial, Turpie et al. (1986) found a significant reduction in both total DVT (LMWH 10.8% vs. placebo 51.8%) and proximal DVT prevalence (LMWH 5.4% vs. placebo 23.1%) for Enoxaparin 2400 IU BID commenced postoperatively. In a dose-ranging study, Spiro et al. (1991) found an inverse correlation between Enoxaparin dose (800 to 4800 IU/day) and total DVT prevalence (31 to 11%). Spiro et al. (1992) and Planes et al. (1989) subsequently compared Enoxaparin to UH, 5000 units every 8 hours. Spiro et al. (1992) studied two Enoxaparin doses, 2400 IU BID and 3200 IU QD, both commenced postoperatively. They found a significant reduction in total DVT prevalence for only the BID regimen (LMWH BID 5%, LMWH QD 15%, UFH 12%). However, Planes et al. (1989) found that Enoxaparin 3200 IU given QD and initiated preoperatively significantly reduced both total DVT (LMWH 12.5% vs. UFH 25%) and proximal DVT prevalence (LMWH 7.5% vs. UFH 18.5%). Levine et al. (1991) was unable to confirm this reduction using a similar daily Enoxaparin dose (4800 IU/day) vs. UFH (7500 units BID) when both drugs were initiated 12 to 24 hours postoperatively (total DVT: LMWH 19.4% vs. UFH 13.2%; proximal DVT: LMWH 5.4% vs. UFH 6.5%). The Danish Enoxaparin Study Group (1991) found Enoxaparin (3893 IU/day) to be superior to dextran 70. No differences in PE incidence or mortality were found in any of these studies.

Fragmin has been compared to UFH in two trials. In a double-blind study, Eriksson et al. (1991) found a significant reduction in proximal DVT prevalence among patients receiving Fragmin 5000 IU daily started preoperatively compared to UFH 5000 units every 8 hours. Ventilation/perfusion lung scans were performed immediately prior to venography. There were significantly more high-probability lung scans in the UFH arm compared to the Fragmin arm (LMWH 12.3% vs. UFH 30.6%, $P = 0.016$). Three patients had clinical signs of PE (LMWH one patient vs. UFH two patients). There were no deaths due to PE. However, when Dechavanne et al. (1989) compared Fraxiparine to adjusted-dose UFH, there was no difference in total or proximal DVT prevalence among the two prophylaxis arms, although the sample size was relatively small.

Fraxiparin has also been compared to UFH in two trials. In a double-blind study, the German Hip Arthroplasty Trial Group (1992) compared preoperative Fraxiparin 4400 IU given QD to UFH 5000 units administered every 8 hours. Although the total DVT prevalence was similar (LMWH 33.1% vs. UFH 34.3%), there were significantly fewer proximal DVT in the Fraxiparin group (LMWH 10.3% vs. UFH 19.7%). There were two clinical PEs in the Fraxiparin arm compared to six in the UFH arm ($P > 0.05$). Leyvraz et al. (1991) compared adjusted-dose UFH to the following regimen of Fraxiparin: 41 IU/kg given QD initiated preoperatively and

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TABLE 5
*Venous thromboembolism prophylaxis for THR: efficacy**

Author	Drug	Dose (anti-Xa)	First dose commenced	Anti-Xa [(IU/ml)/h post dose]	Bilateral venogram (*n*)	Total DVT [*n* (%)]	Proximal DVT [*n* (%)]
Turpie et al.† (1986)	Enoxaparin	2400 IU every 12 h	12–24 h postop	0.1–0.2/6 h	37	4 (10.8)‡	2 (5.4)‡
	Placebo				39	20 (51.3)	9 (23.1)
Spiro et al.† (1991)	Enoxaparin	800 IU QD	postop	NR	116	36 (31)	NR
		3200 IU QD		NR	149	21 (14)	NR
		2400 IU BID		NR	143	16 (11)	NR
Spiro et al. (1992)	Enoxaparin	2400 IU BID	postop	NR	194	10 (5)‡	NR
		3200 IU QD		NR	203	31 (15)	NR
	UFH	5000 units every 8 h	postop	NR	201	25 (12)	NR
Planes et al. (1989)†	Enoxaparin	3200 IU QD	12 h preop	0.15/12 h	120	15 (12.5)‡	9 (7.5)‡
	UFH	5000 units every 8 h	2 h preop		108	27 (25)	20 (18.5)
Levine et al. (1991)†	Enoxaparin	2400 IU BID	12–24 h postop	NR	258	50 (19.4)	14 (5.4)
	UFH	7500 U BID			263	61 (23.2)	17 (6.5)
Danish Enoxaparin Study Group (1991)	Enoxaparin	3898 IU QD	12 h preop	0.15–0.18/12 h	108	7 (6.5)‡	2 (1.8)
	Dextran 70				111	24 (21.6)	6 (5.4)
Dechavanne et al. (1989)	Fragmin	2500 IU BID	2 h preop	0.16/2 h	38	2 (5.3)	1 (1.60)
	Fragmin	5000 IU QD	2500 IU 2 h preop	0.13/2 h	39	3 (7.7)	1 (2.6)
	UFH (adjusted)	5000 U BID	2 h preop	0.01/2 h	38	4 (10.5)	3 (7.9)
Eriksson et al. (1991)†	Fragmin	5000 IU QD	12 h preop	0.05–0.07/10 h	63	19 (30.2)	7 (11.1)‡
	UFH	5000 units every 8 h	2 h preop		59	25 (42.4)	21 (35.6)
German Hip Arthroplasty Trial Group (1992)†	Fraxiparin	4400 IU QD	12 h preop	NR	136	45 (33.1)	14 (10.3)‡
	UFH	5000 units every 8 h	2 h preop		137	47 (34.3)	27 (19.7)
Leyvraz et al. (1991)	Fraxiparin	41–62 IU/kg	12 h preop	0.29–0.37/4 h	174	22 (12.6)	5 (2.9)‡
	UFH (adjusted)	4000 units every 8 h	16 and 2 h preop		175	28 (16)	23 (13.1)
Lassen et al. (1991)†	Logiparin	50 IU/kg QD	2 h preop	NR	93	29 (31)‡	24 (26)
	Placebo				97	44 (45)	35 (36)
Hull et al.† (1993)	Logiparin	75 IU/kg QD	18–24 h postop	NR	330	69 (20.8)	16 (4.8)
	Warfarin	INR 2.0–3.0	postop		335	79 (23.2)	13 (3.8)
RD Heparin Arthroplasty Group (submitted)	RD heparin	50 IU/kg BID	6–12 h postop	0.14/6 h	178	12 (7)	5 (3)
	RD heparin	90 IU/kg QD	24 h preop	0.24/6 h	171	22 (13)	12 (7)
	Warfarin	Prothrombin time ratio 1.2–1.5			174	20 (12)	11 (6)
Leyvraz et al.† (1992)	Lomoparan	750 IU BID	2 h preop	NR	145	25 (17)‡	7 (4.8)
	UFH/dihydro-ergotamine	5000 units/0.5 mg BID	2 h preop		139	44 (32)	9 (6.5)
Hoek et al. (1989)†	Lomoparan	750 IU BID	preop	NR	97	15 (15)‡	8 (8)‡
	Placebo				99	56 (57)	25 (25)

* postop, postoperative; pre, preoperative; NR, not reported.
† Double-blind study.
‡ $P < 0.05$.

continued for the first 3 days, followed by 62 IU/kg QD for the remaining 7 days. The total DVT prevalence was similar among the two groups (LMWH 12.6% vs. adjusted-dose UFH 16%), but the proximal DVT prevalence was significantly lower in the Fraxiparin arm (LMWH 2.9% vs. adjusted-dose UFH 13.1%). There were four symptomatic PEs in the adjusted-dose UFH arm compared to one in the Fraxiparin arm ($P > 0.05$).

In two double-blind studies, Logiparin was compared to either placebo or low-intensity warfarin anticoagulation (international normalized ratio 2.0 to 3.0), respectively. Compared to placebo, Logiparin 50 IU/kg given QD significantly reduced the total DVT prevalence (LMWH 31% vs. placebo 45%), although the proximal DVT prevalence was not significantly different (LMWH 26% vs. placebo 36%), possibly because of an inadequate sample size (Lassen et al., 1991). There was one symptomatic PE in each prophylaxis arm. When Logiparin 75 IU/kg given QD (initiated postoperatively) was compared to low-intensity warfarin, the total DVT (LMWH 20.8% vs. warfarin 23.2%) and proximal DVT prevalences (LMWH 4.8% vs. warfarin 3.8%) were not significantly different (Hull et al., 1993).

The RD Heparin Arthroplasty Group (1993) compared two postoperative doses of RD heparin (Normiflo) to low-intensity warfarin (prothrombin time ratio 1.2 to 1.5). In both LMWH arms, RD heparin 50 IU/kg was given postoperatively on the evening of the day of surgery

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followed by either RD heparin 50 IU/kg BID or RD heparin 90 IU/kg QD. Unilateral venography of the operated leg and a noninvasive test for DVT (impedance plethysmography or compression ultrasonography) of the nonoperated leg were performed. Although there was a trend favoring the BID RD heparin dose for reduction of both total DVT (LMWH BID 7%, LMWH QD 13%, warfarin 12%) and proximal DVT prevalence (LMWH BID 3%, LMWH QD 7%, warfarin 6%), this did not reach statistical significance. The DVT prevalence rates in this study may have been substantially higher had bilateral venography been performed, because subsequent studies have shown noninvasive testing to be insensitive for the detection of these predominantly asymptomatic postoperative DVTs. There were no symptomatic PEs in any of the prophylaxis arms.

The heparinoid Lomoparan (ORG 10172) 750 IU given BID was studied in two double-blind trials. In a placebo-controlled trial, Hoek et al. (1989) found a significant reduction in both total DVT (LMWH 15% vs. placebo 57%) and proximal DVT prevalence (LMWH 8% vs. placebo 25%). Leyvraz et al. (1992) compared Lomoparan to UH/dihydroergotamine given BID and found a significant reduction in the total DVT prevalence (LMWH 7% vs. UH/dihydroergotamine 32%), although the prevalence of proximal DVT was similar (LMWH 4.8% vs. UH/dihydroergotamine 6.5%). There were no symptomatic PEs in either study.

2. Total knee replacement. Only three studies of LMWH DVT prophylaxis following TKR have been reported (table 6). Leclerc et al. (1992) performed a double-blind, placebo-controlled trial of Enoxaparin 2400 IU administered BID beginning postoperatively in patients undergoing major knee surgery (TKR, $n = 106$; upper tibial osteotomy, $n = 25$). There was a significant reduction in both total DVT (LMWH 19% vs. placebo 65%) and proximal DVT prevalence (LMWH 0% vs. placebo 20%) with Enoxaparin prophylaxis.

In an open-label study, the RD Heparin Arthroplasty Group (1993) randomized patients with TKR to the same two RD heparin (Normflo) dosage arms vs. low intensity warfarin as described above for THR. Similarly, unilateral venography of the operated leg and a noninvasive test for DVT of the nonoperated leg were performed. Compared to warfarin, there was a significant reduction in the total DVT prevalence for the BID RD heparin arm (LMWH BID 25% vs. warfarin 41%) and a trend favoring QD RD heparin (LMWH QD 28%). The prevalence of proximal DVT was similar among the three arms (LMWH BID 6%, LMWH QD 5%, warfarin 10%). There were two symptomatic PEs; one each in the QD RD heparin and warfarin arms. Again, it should be noted that the DVT prevalence rates may have been higher had bilateral venography been performed, although following TKR fewer DVTs occur in the nonoperated leg compared to THR.

In a double-blind study, Hull et al. (1993) randomized patients with TKR to either Logiparin 75 IU/kg administered QD or low-intensity warfarin (INR 2.0 to 3.0). Both drugs were commenced postoperatively. There was a significant reduction in the total DVT prevalence (LMWH 45.0% vs. warfarin 54.9%), although the proximal DVT prevalence was similar (LMWH 7.8% vs. warfarin 12.3%).

3. Hip fracture. LMWH DVT prophylaxis for patients requiring surgery for acute hip fracture was addressed in four studies (table 7). In a double-blind trial, Barsotti et al. (1990) compared two regimens of Enoxaparin in which 3200 IU was given 8 hours preoperatively in both prophylaxis arms followed by either 3200 IU QD vs. 1600 IU BID. Although the total DVT prevalence was similar (LMWH QD 10.4% vs. LMWH BID 18.3%), the proximal DVT prevalence was significantly lower in the QD group (LMWH QD 4.2% vs. LMWH BID 12.2%). Symptomatic PE did not occur in either group.

Monreal et al. (1989) performed a double-blind trial of Fragmin 2500 IU administered 2 hours prior to surgery followed by 5000 IU QD compared to UFH 5000 units

TABLE 6
*Venous thromboembolism prophylaxis for TKR: efficacy**

Author	Drug	Dose (anti-Xa)	First dose commenced	Anti-Xa [(IU/ml)/h post dose]	Bilateral venogram (*n*)	Total DVT [*n* (%)]	Proximal DVT [*n* (%)]
Leclerc et al. (1992)†	Enoxaparin	2400 IU BID	24 h postop	NR	41	8 (19)‡	0‡
	Placebo				54	35 (65)	11 (20)
RD Heparin Arthroplasty Group (submitted)	RD heparin	50 IU/kg BID	6–12 h postop	0.14/6 h	150	37 (25)‡	9 (6)
	RD heparin	90 IU/kg QD	24 h preop	0.24/6 h	149	41 (28)	7 (5)
	Warfarin	Prothrombin time ratio 1.2–1.5			147	60 (41)	15 (10)
Hull et al.† (1993)	Logiparin	75 IU/kg QD	18–24 h postop	NR	249	116 (45.0)‡	20 (7.8)
	Warfarin	INR 2.0–3.0	postop		268	154 (54.9)	34 (12.3)

* NR, not reported.
† Double-blind study.
‡ $P < 0.02$.

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TABLE 7
*Venous thromboembolism prophylaxis for hip fracture: efficacy**

Author	Drug	Dose (anti-Xa)	First dose commenced	Anti-Xa [(IU/ml)/h post dose]	Bilateral venogram (*n*)	Total DVT [*n* (%)]	Proximal DVT [*n* (%)]
Barsotti et al. (1990)	Enoxaparin	3200 IU QD	8 h preop	0.1–0.12/12 h	48	5 (10.4)	2 (4.2)‡
	Enoxaparin	1600 IU BID	8 h preop	0.07–0.09/12 h	49	9 (18.3)	6 (12.2)
Monreal et al. (1989)†	Fragmin	5000 IU QD	2500 IU 2 h preop	NR	32	14 (43.7)	12 (37.5)
	UFH	5000 units every 8 h	2 h preop		30	6 (20)‡	5 (16.7)
Bergqvist et al. (1991)	Lomoparan	750 IU BID	At diagnosis	NR	107	14 (13)‡	5 (4.7)
	Dextran 70				115	40 (35)	10 (8.7)
Agnelli et al. (1992)†	Dermatan sulfate	100 mg BID	Within 48 h of fracture	NR	37	24 (65)	15 (40.5)
	Placebo				37	19 (51.4)	11 (29.7)
	Dermatan sulfate	300 mg BID		NR	74	28 (37.8)‡	15 (20.3)‡
	Placebo				36	23 (63.9)	15 (41.7)

* NR, not reported.
† Double-blind study.
‡ $P < 0.05$.

every 8 hours. In the first 57 patients enrolled, venography was performed only for a clinical suspicion of DVT. In the last 33 patients enrolled, mandatory bilateral venography was performed on postoperative day 9. Consequently, a total of 62 patients underwent bilateral venography. All patients had ventilation/perfusion lung scanning on postoperative day 8. The total DVT prevalence was significantly less in the UFH arm (LMWH 43.7% vs. UFH 14%). The proximal DVT prevalence was not significantly different, although there was a trend favoring UFH (LMWH 37.5% vs. UFH 16.7%, $P = 0.059$). Furthermore, there were significantly more high-probability lung scans in the Fragmin arm (LMWH 6 vs. UFH 0, $P = 0.016$).

Bergqvist et al. (1991) compared Lomoparan 750 IU administered BID to dextran 70. Both were started immediately following the diagnosis of hip fracture. The total DVT prevalence was significantly lower in the Lomoparan arm (LMWH 13% vs. dextran 70 35%), whereas the proximal DVT prevalence was not significantly different (LMWH 4.6% vs. dextran 70, 8.7%). Symptomatic PE occurred in five patients of the dextran 70 group (three patients died). One asymptomatic PE was discovered at autopsy in the Lomoparan group in a patient dying of acute myocardial infarction on postoperative day 18.

Agnelli et al. (1992) performed a double-blind placebo-controlled trial using the heparinoid dermatan sulfate (MF 701). In phase 1 of this study, dermatan sulfate, 100 mg given BID and initiated within 48 hours of the acute fracture, failed to significantly reduce either the total DVT (LMWH 65% vs. placebo 51.4%) or proximal DVT prevalence (LMWH 40.5% vs. placebo 29.7%). One patient in the placebo group died with a clinically suspected PE. In a second phase, the dermatan sulfate dose was increased to 300 mg BID. In this phase, both the total DVT (LMWH 37.8% vs. placebo 63.9%) and proximal DVT prevalences (LMWH 20.3% vs. placebo 41.7%) were significantly reduced in the dermatan sulfate arm. No patients in this phase suffered symptomatic PE.

B. Safety Results

With the exception of one study (Levine et al., 1991), none of the reported trials were specifically designed to test the null hypothesis in clinical bleeding event rates between LMWH and the comparator prophylaxis arm. Therefore, all studies in which no significant difference is found for the bleeding rate suffer the potential of a type II error. For these studies, a significant difference in bleeding may have been missed because of an inadequate sample size.

1. Double-blind placebo-controlled trials. Clinical bleeding event rates (major plus minor) have been reported in four double-blind placebo-controlled trials of LMWH prophylaxis (table 8), two involving THR and one each for TKR and hip fracture. The clinical bleeding rate was not significantly different compared to placebo for: (*a*) Enoxaparin (Turpie et al., 1986), and Logiparin (Lassen et al., 1991) for THR, (*b*) Enoxaparin (Leclerc et al., 1992) for major knee surgery, and (*c*) dermatan sulfate (Agnelli et al., 1992) for hip fracture. In the Logiparin study of patients requiring THR, Lassen et al. (1991) found a trend suggesting more clinical bleeding in patients randomized to the Logiparin arm (LMWH 12.3% vs. placebo 6.7%). As mentioned above, a significant difference in bleeding may have been missed because of an inadequate sample size. Patients assigned to the Logiparin arm also had a significantly greater postoperative transfusion requirement and lower average hemoglobin level.

Analysis of the other double-blind, placebo-controlled studies was difficult because bleeding data were not reported in the form of total clinical bleeding event rates. Torholm et al. (1989) randomized 112 patients undergoing THR to either placebo or a regimen of Fragmin 2500 IU administered 2 hours preoperatively and 12 hours

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TABLE 8
*Venous thromboembolism prophylaxis safety: double-blind placebo-controlled trials**

Condition/author	Drug	Dose (anti-Xa IU)	First dose commenced	Anti-Xa [(IU/ml)/h post dose]	Patients treated (*n*)	Bleeding [*n* (%)]
THR						
Turpie et al. (1986)	Enoxaparin	2400 IU every 12 h	12 h preop	0.1–0.2/6 h	50	2 (4.0)
	Placebo				50	2 (4.0)
Lassen et al. (1991)	Logiparin	50 IU/kg QD	2 h preop	NR	105	13 (12.3)
	Placebo				104	7 (6.7)
TKR						
Leclerc et al. (1992)	Enoxaparin	2400 IU BID	24 h postop	NR	66	4 (6.1)
	Placebo				65	5 (7.6)
Hip fracture						
Agnelli et al. (1992)	Dermatan sulfate	100 mg BID	Within 48 h of fracture	NR	37	2 (5.4)
	Placebo				37	2 (5.4)
	Dermatan sulfate	300 mg BID		NR	79	2 (2.5)
	Placebo				36	1 (2.7)

* NR, not reported.

postoperatively, followed by 5000 IU given QD. There were no differences between the two groups for operative bleeding, wound drain bleeding, transfusion requirement, or hemoglobin level. In the study by Hoek et al. (1989), in which patients undergoing THR were randomized to either Lomoparan or placebo, there were no major hemorrhages and no differences in wound drain blood loss or transfusion requirements. Minor wound hematomas developed in six patients in the Lomoparan group. Jorgensen et al. (1992) randomized 68 patients with hip fractures to either placebo or a Fragmin regimen similar to that of Torholm et al. (1989) (2500 IU administered 2 hours preoperatively and 12 hours postoperatively, followed by 5000 IU QD). There were no significant differences between the two arms for operative blood loss, wound drain blood loss, or hemoglobin level, although the LMWH patient group had a significantly greater transfusion requirement.

2. Double-blind, non-placebo-controlled trials. Investigators of most double-blind, non-placebo-controlled studies have reported no significant difference in the clinical bleeding event rate for LMWH compared to (*a*) UFH (Planes et al., 1989; Eriksson et al., 1991; German Hip Arthroplasty Trial Group, 1992), warfarin (Hull et al., 1993), or UFH/dihydroergotamine (Leyvraz et al., 1992) among THR patients; (*b*) warfarin (Hull et al., 1993) among patients with TKR; or (*c*) UFH (Monreal et al., 1989) among patients with hip fractures (table 9). However, only the study by Levine et al. (1991) was specifically designed to test the hypothesis of no difference in the total clinical bleeding event rate between LMWH and the comparator arm. In this study, patients undergoing THR were randomized to either Enoxaparin 2400 IU or UFH 7500 units, both given BID and administered 12 to 24 hours postoperatively. The total clinical bleeding event rate (major plus minor) was significantly less in the LMWH arm (LMWH 5.1% vs. UFH 9.3%). When Levine et al. compared the major and minor bleeding event rates separately, there were no significant differences. In addition, there was no significant difference in the amount of transfused blood products or nadir hemoglobin level. In a similar study of patients with THRs in which Enoxaparin was commenced preoperatively, Planes et al. (1989) could find no difference in the operative transfusion requirement, but the amount of postoperative blood products transfused was significantly greater and the nadir hemoglobin level was significantly lower for Enoxaparin compared to UFH. Hull et al. (1992a,b,c) found significantly more wound hematomas in patients with THR receiving Logiparin compared to warfarin (LMWH 5.8% vs. warfarin 2.5%). In a similar study of patients with TKR, Hull et al. (1993) found a trend suggesting a lower incidence of wound hematomas in patients randomized to warfarin as compared to those receiving Logiparin, although this did not reach statistical significance (LMWH 8.8% vs. warfarin 5.9%). In the hip fracture trial by Monreal et al. (1989), patients randomized to Fragmin required a total of 40 units of transfused blood products compared to 20 units for the patients with UFH.

3. Open-label, non-placebo-controlled trials. No significant differences for clinical bleeding event rates were found when LMWH was compared in an open-label design to (*a*) UFH (Spiro et al. (1992), dextran 70 (The Danish Enoxaparin Study Group, 1991), adjusted-dose UFH (Leyvraz et al., 1991), and warfarin (RD Heparin Arthroplasty Group, 1993) among patients with THR; (*b*) warfarin (RD Heparin Arthroplasty Group, 1993) among patients with TKR; and (*c*) dextran 70 (Bergqvist et al., 1991) and warfarin (Gerhart et al., 1991) among patients with hip fractures (table 10). For patients with THR, the Danish Enoxaparin Study Group (1991) compared Enoxaparin to dextran 70 and found that the postoperative wound drain blood loss and number of blood products transfused was significantly greater in the dextran 70 group. The RD Heparin Arthroplasty Group (1993) assessed the difference between preoperative baseline and postoperative hospital dismissal he-

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TABLE 9
*Venous thromboembolism prophylaxis safety: double-blind, non-placebo-controlled trials**

Condition/author	Drug	Dose (anti-Xa)	First dose commenced	Anti-Xa [(IU/ml)/h post dose]	No. of patients treated	Bleeding events *n* (%)
THR						
Levine et al. (1991)	Enoxaparin	2400 IU BID	12–24 h postop	NR	333	17 (5.1)†
	UFH	7500 U BID			332	31 (9.3)
Planes et al. (1989)	Enoxaparin	3200 IU QD	12 h preop	0.15/12 h	124	3 (2.4)
	UFH	5000 units every 8 h	2 h preop		112	2 (1.8)
Spiro et al. (1991)	Enoxaparin	800 IU QD	NR	NR	161	8 (5.0)
	Enoxaparin	3200 IU QD	NR	NR	199	21 (10.6)
	Enoxaparin	2400 IU BID	NR	NR	208	27 (13.0)
Eriksson et al. (1991)	Fragmin	5000 IU QD	12 h preop	0.05–0.07/10 h	67	1 (1.5)
	UFH	5000 units every 8 h	2 h preop		68	5 (7.4)
German Hip Arthroplasty Trial Group (1992)	Fraxiparin	41 IU/kg QD	12 h preop	NR	167	11 (6.6)
	UFH	5000 units every 8 h	2 h preop		168	8 (4.8)
Hull et al. (1993)	Logiparin	75 IU/kg QD	18–24 h postop	NR	398	16 (4.0)
	Warfarin	INR 2.0–3.0	postop		397	15 (3.8)
Leyvraz et al. (1992)	Lomoparan	750 IU BID	2 h preop	NR	153	2 (1.3)
	UFH/dihydro-ergotamine	5000 IU/0.5 mg BID	2 h preop		150	3 (2.0)
TKR						
Hull et al. (1993)	Logiparin	75 IU/kg QD	18–14 h postop	NR	317	14 (4.4)
	Warfarin	INR 2.0–3.0	postop		324	8 (2.5)
Hip fracture						
Monreal et al. (1989)	Fragmin	5000 IU QD	2500 IU 2 h preop	NR	46	2 (4.4)
	UFH	5000 units every 8 h	8 h preop		44	1 (2.0)
Barsotti et al. (1990)	Enoxaparin	3200 IU QD	8 h preop	0.1–0.12/12 h	49	0
	Enoxaparin	1600 IU BID	8 h preop	0.07–0.09/12 h	54	0

* postop, postoperative; preop, preoperative; NR, not reported.
† $P < 0.05$.

moglobin levels after controlling for the number of units of blood products transfused. For patients with THR there was no significant difference between the two RD heparin arms and low-intensity warfarin. However, for patients with TKR, there was a significantly greater reduction in hemoglobin in both RD heparin arms compared to warfarin, amounting to approximately 0.5 g/dl of hemoglobin. For patients with hip fractures, Bergqvist et al.(1991) found the dextran 70 group required significantly more postoperative blood products transfused compared to Lomoparan.

There were no reported cases of heparin-associated thrombocytopenia in patients receiving LMWH prophylaxis. Transient liver transaminase elevations were occasionally noted in patients receiving both LMWH and UFH and were not considered of clinical significance.

C. Conclusions

1. Efficacy. For patients undergoing THR, LMWH provides a 31 to 79% reduction in the total DVT prevalence compared to placebo. LMHW is either as effective or more effective than UFH 15,000 units/day or adjusted-dose UFH and more effective than dextran 70. The efficacies of LMWH and low-intensity warfarin appear to be similar. For patients undergoing TKR, there is a 71% reduction in the total DVT prevalence for LMWH compared to placebo. LMWH is more effective than low-intensity warfarin anticoagulation. For patients with hip fractures, LMWH is more effective than dextran 70 and less effective than UFH 15,000 units per day.

2. Safety. In double-blind, placebo-controlled trials of patients undergoing THR, TKR, or surgery for acute hip fracture, the total clinical bleeding event rate was not significantly different for LMWH compared to placebo. This suggests that LMWH prophylaxis does not contribute to bleeding over and above what would be expected for the operative procedure alone. However, none of these trials provide data regarding the power of the study sample size to detect a significant difference in bleeding. For double-blind, non-placebo-controlled trials, only the study by Levine et al. (1991) was designed to test the null hypothesis of no difference in bleeding for LMWH compared to UFH 15,000 units/day (both commenced postoperatively) for patients undergoing THR. In this study, only the total bleeding (major plus minor) rate was significantly lower for the LMWH arm. The safety of LMWH compared to low-intensity warfarin and UFH/dihydroergotamine for THR appears to be similar. For TKR, the safety of LMWH compared to warfarin was similar, although in both reported trials there was a trend suggesting more bleeding in the LMWH arm. For hip fracture, the safety of LMWH compared to either UFH, dextran 70, or warfarin appears to be similar.

D. Summary of Orthopedic Trials

LMWH DVT prophylaxis is effective and safe for patients undergoing major orthopedic surgery of the

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TABLE 10

*Venous thromboembolism prophylaxis safety: open-label, non-placebo-controlled trials**

Condition/author	Drug	Dose (anti-Xa)	First dose commenced	Anti-Xa [(IU/ml)/h post dose]	No. of patients treated	Bleeding events *n* (%)
THR						
Spiro et al. (1992)	Enoxaparin	2400 IU BID	postop	NR	194	8 (4.1)
	Enoxaparin	3200 IU QD	postop	NR	203	3 (1.5)
	UFH	5000 units every 8 h	postop		201	13 (6.5)
Danish Enoxaparin Study Group (1991)	Enoxaparin	3898 IU QD	12 h preop	0.15–0.18/12 h	108	1 (0.9)
	Dextran 70				111	1 (0.9)
Leyvraz et al. (1991)	Fraxiparin	41 IU/kg QD	12 h preop	0.29–0.37/4 h	198	1 (0.5)
	UFH (adjusted)	4000 units every 8 h	16 and 2 h preop		199	3 (1.5)
RD Heparin Arthroplasty Group (submitted)	RD heparin	50 IU/kg BID	6–12 h postop	0.14/6 h	211	15 (7)
	RD heparin	90 IU/kg QD		0.24/6 h	214	9 (4)
	Warfarin	Prothrombin time ratio 1.2–1.5	24 h preop		218	11 (5)
TKR						
RD Heparin Arthroplasty Group (submitted)	RD heparin	50 IU/kg BID	6–12 h postop	0.14/6 h	169	10 (6)
	RD heparin	90 IU/kg QD		0.24/6 h	175	11 (6)
	Warfarin	Prothrombin time ratio 1.2–1.5	24 h preop		180	10 (6)
Hip fracture						
Bergqvist et al. (1991)	Lomoparan	750 IU BID	At diagnosis	NR	117	5 (4.3)
	Dextran 70				130	2 (1.5)
Gerhart et al. (1991)	Lomoparan	750 IU BID	At diagnosis	NR	132	5 (3.8)
	Warfarin	Prothrombin time ratio 1.5			131	3 (2.3)

* postop, postoperative; preop, preoperative; NR, not reported.

lower limb. The efficacy and safety profile of LMWH for patients with THR appears to be similar to low-intensity warfarin. Therefore, the utility of LMWH for this procedure will depend on convenience and cost. For patients with TKR, LMWH is significantly more effective than all other anticoagulant-based prophylaxis methods. However, the DVT prevalence for this procedure as well as acute hip fracture remains unacceptably high, and additional studies of LMWH in combination with other prophylaxis methods, such as external pneumatic compression, are needed. Finally, only one adequately designed trial found that less bleeding resulted from LMWH prophylaxis administered at an equivalent antithrombotic dose to UFH. Additional clinical trials are needed in which the sample size is designed to test the hypothesis of no difference in bleeding with LMWH compared to other venous thromboembolism prophylaxis methods.

III. Thromboprophylaxis for Nonorthopedic Conditions

LMWH has been used for thrombus prevention in a variety of nonorthopedic conditions. However, it has been difficult to establish benefit because the disorders are heterogeneous and the risks of thromboembolism are not as well defined as in orthopedic conditions. Nevertheless, randomized, controlled trials have been reported involving general medical patients, general surgical patients, stroke and spinal cord-injured subjects, and those undergoing hemodialysis. A listing of the various nonorthopedic disorders considered appropriate for thromboprophylaxis with LMWH is given in table 11.

A. Conditions Evaluated

1. General medicine. The risk of thromboembolism in general medical patients is quite variable, depending on which disease entities are most represented in the population being studied. For example, having a large percentage of patients with congestive heart failure and malignancy will result in higher rates of thrombosis. The method for detection of thrombosis will also impact the rates; the fibrinogen uptake test is more sensitive than

TABLE 11

Nonorthopedic disorders in which the safety and efficacy of LMWH is under evaluation

Nonorthopedic disorders
General medicine
General surgery
Pelvic surgery
Acute stroke
Spinal cord injury
Extracorporeal perfusion
Hemodialysis
Cardiopulmonary bypass
Graft patency
Coronary artery
Peripheral artery

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is impedance plethysmography for detecting calf thrombi. Thus, Belch et al. (1981) studied patients with heart failure using the uptake test and recorded thrombosis in 26%, whereas Dahan et al. (1986), using the same detection method but examining a heterogeneous population of elderly patients, found thrombosis in only 9%; this declined to 3% in those treated with LMWH. Harenberg et al. (1990) conducted a trial in patients, one-third of whom had malignancy or heart failure, and used serial impedance plethysmography and Doppler examinations to detect thrombosis. Evidence of thrombosis was found in 4.5% of those receiving UFH and 3.6% receiving LMWH. More recently, Mottier et al. (1993) examined the safety and efficacy of Enoxaparin (20 mg daily) and UFH (5000 units BID) in elderly medical inpatients. The frequency of thrombosis was 4.8% in the LMWH group and 4.6% in the UFH group; bleeding was infrequent in both groups (LMWH 0.9%; UFH 1.8%). These studies are interpreted as indicating that, in high-risk medical patients, heparin prophylaxis provides significant protection against thromboembolism and that LMWH appears to be as effective as UFH. With regard to safety, neither study found an increased incidence of bleeding with LMWH, but Harenberg et al. (1990) noted larger injection site hematomas with UFH than with LMWH. Finally, it should be noted that LMWH was given as a single daily injection, whereas most regimens of UFH require injections every 8 to 12 hours.

It is difficult to predict whether LMWH will replace UFH as the thromboprophylactic agent of choice in medical patients, because the cost effectiveness of LMWH compared to UFH is still unknown, and UFH is generally accepted as a safe and efficacious agent for this indication.

2. General surgery. UFH in doses of 5000 units subcutaneously every 12 hours has been very effective in preventing thromboembolism in general surgery patients (Clagett et al., 1992). A number of randomized studies have been performed to determine whether LMWH is as safe and effective as UFH. These have been reviewed and analyzed by Nurmohamed et al. (1992) and comprise 17 studies encompassing more than 6800 patients. The relative risk of DVT with LMWH compared with UFH was 0.79 (95% confidence limits, 0.65 to 0.95). The relative risk of PE was 0.44 (95% confidence limits, 0.21 to 0.95), and the risk of bleeding, 1.01 (95% confidence limits, 0.70 to 1.48). Eight studies were considered to have "strong" methodology as defined on the basis of an 8-point scale which included full descriptions of the study population, use of fibrinogen uptake test for DVT screening, and blinded end point assessment. The analysis of these "strong" studies, in comparison with "weak" studies, is shown in table 12. The stronger studies show equivalence in terms of DVT prophylaxis, an advantage for LMWH in PE prevention, and a marginally increased frequency of major bleeding. Overall, Nurmohamed et al. (1992) concluded that 71 patients would need to be treated with LMWH to prevent one additional episode of DVT and at no lesser bleeding risk than with UFH.

TABLE 12
Summary of studies of LMWH and UFH in general surgical patients [modified from Nurmohamed et al. (1992)]

	LMWH	UFH	Relative risk
Strong methodology			
DVT	6.7	7.4	0.91
PE	0.4	0.7	0.62
Major bleeding	1.7	1.3	1.32
Weak methodology			
DVT	3.8	5.6	0.67
PE	0.2	0.7	0.37
Major bleeding	3.0	3.5	0.86

Recently, Kakkar et al. (1993) used a double-blind randomized design to study 3809 patients having abdominal surgery; patients received prophylaxis with either UFH 5000 units BID or LMWH 2500 units QD 1 to 4 hours preoperatively. Major bleeding events occurred in 4.8% of the UFH group and 3.6% of the LMWH group ($P = 0.1$), However, severe bleeding was less frequent in the LMWH group than in the UFH group (1 vs. 1.9%), as were wound hematomas (1.4 vs. 2.7%). Efficacy was excellent, with rates of DVT (0.6%) and PE (0.7%) low and identical in the two groups and no differences in overall mortality, wound infections, or integrity of anastomoses. Whether efficacy would have been maintained and bleeding been less frequent if prophylaxis had been begun postoperatively is an important but unanswered question. Thus, LMWH in general surgery appears as effective as UFH and needs to be given only QD. The bleeding risks with this agent remain unsettled, and a cost-benefit analysis will be required if LMWH is proposed to replace UFH in these patients.

3. Pelvic surgery. More than 200 patients older than 40 years having major gynecological surgery were randomized to receive either LMWH, 5000 anti-Xa units every 24 hours, or UFH, 5000 units every 12 hours (Borstad et al., 1988). The initial injection of LMWH was given 1 hour preoperatively. Using impedance plethysmography as a screening test, the investigators were unable to detect thrombosis in any patient, but half of the subjects had bleeding. Those receiving the LMWH had significantly more wound hematomas and required more blood transfusions ($P = 0.02$) for both comparisons. Plasma heparin levels were measured and found to be considerably higher in those receiving LMWH (0.34 vs. 0.13 units/ml). The investigators concluded that, although both regimens were effective in preventing thrombosis, the dose of LMWH used contributed to the high rate of bleeding.

More recently, Godwin et al. (1993) completed a double-blind randomized trial of LMWH vs. UFH in patients undergoing abdominal or pelvic surgery because of cancer. Three groups of approximately 300 patients each received either 90 anti-Xa units per kg of LMWH QD,

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50 units per kg BID, or 5000 units of UFH BID. The first dose was administered 2 hours preoperatively. Thrombosis, as detected by noninvasive tests, was infrequent (0.4% in the QD LMWH group, 0 in the BID LMWH group, and 1.5% in the UFH group; P = nonsignificant). Clinically important bleeding occurred in 10.7% of the QD LMWH group, 8.2% of the BID LMWH group, and 6.8% of the UFH group. These differences were not statistically significant.

The low rates of thrombosis in these trials may reflect the fact that venography was not mandatory in all patients; noninvasive tests are relatively insensitive in patients with or without symptoms (Davidson et al., 1992; Anderson et al., 1993). Therefore, the efficacy of the treatments cannot be reliably assessed. The high bleeding rates are likely due to the administration of the anticoagulants preoperatively; it may be that effectiveness will not be compromised by giving prophylaxis postoperatively. A study of the heparinoid, ORG 10172, in patients undergoing transurethral resection of the prostate also demonstrated a dose-dependent increase in urinary blood loss (ten Cate et al., 1987). No efficacy data were provided; therefore, it is unclear whether the lowest dose used, which did not produce significant hemoglobin loss, would be adequate to prevent thromboembolism in this patient population.

4. Acute stroke. The incidence of thromboembolism in patients with acute strokes has been reported to be as high as 60 to 75% (Warlow et al., 1972). Three trials evaluated the safety and efficacy of LMWH for this disorder. In the study of Fragmin LMWH by Prins et al. (1989), 60 patients were randomized. There were six DVTs and one PE in those receiving Fragmin vs. 15 DVTs and two PEs in those receiving placebo ($P = 0.05$). On the other hand, bleeding occurred in five of those receiving Fragmin vs. two receiving placebo, and nine of the LMWH-treated patients died compared to four of those receiving placebo.

Turpie et al. (1987, 1992) performed two studies of ORG 10172 in patients with strokes. In the first, venous thrombosis occurred in only 4% of those receiving the heparinoid as compared to 28% of those receiving placebo ($P = 0.005$). There was one major hemorrhage in the patients receiving ORG 10172 and one minor bleeding incident in the placebo group. In the second study, in which ORG 10172 was compared with UFH 5000 units BID, thrombosis occurred in 9% of the heparinoid group and 31% of the UFH group, a highly significant reduction ($P = 0.014$). The incidence of hemorrhage was 2% in each group. Hemorrhagic transformation of the infarct occurred in 9.3% of patients receiving ORG 10172 and 5.6% of patients receiving UFH compared with 7% of placebo-treated subjects enrolled in an earlier trial.

These trials of ORG 10172 suggest that this agent may replace UFH in the prophylaxis of thromboembolism in the stroke population. Investigations of larger numbers of patients and evaluation of other LMWHs in comparison with UFH are clearly indicated. Currently, a major study (Treatment of Acute Stroke Trial) is underway to evaluate ORG 10172 in the treatment of acute thrombotic stroke.

5. Spinal cord injury. The incidence of clinically evident DVT in spinal cord-injured patients is 16% and of thrombosis detected by objective tests, 79% (Weingarden et al., 1992). Most thrombi form within the first 3 weeks after injury (Green et al., 1982); fatal PE may occur anytime within the first 3 months following injury. Prevention of thromboembolism is very difficult in patients with this condition because of the thrombogenic effects of immobilization, bone and soft tissue injury, surgery, stress, and often infection. Trials of UFH have revealed that low doses are ineffective in preventing thrombosis, and high doses are associated with unacceptable rates of bleeding (Green et al., 1988). In view of this difficult clinical situation, trials of LMWH were initiated in the late 1980s.

The first investigation was a small study comparing LMWH with UFH; the former was given in a dose of 3500 anti-Xa units QD and the latter dose was 5000 units every 8 hours (Green et al., 1990). In 20 patients treated with LMWH, there were no events (bleeding or thromboses), whereas five episodes of thrombosis (three DVTs and two PEs) and two bleeding events occurred in 21 patients treated with UFH. This remarkable difference ($P < 0.04$) prompted discontinuation of the use of UFH and further study of LMWH. Of an additional 48 subjects treated with LMWH, thrombosis developed in seven (six DVTs and one PE) and one subject had bleeding (Green et al., 1993). The overall experience with LMWH, when compared to a similar number of patients treated with various regimens of UFH, showed the superiority of LMWH [event rates (number of patients with events/number receiving agent) for LMWH were eight of 68 (12%) and for UFH were 25/79 (32%), $P = 0.007$]. Therefore, it is anticipated that LMWH will be the thromboprophylactic agent of choice for patients with acute spinal cord injury.

6. Renal dialysis. UFH is used during hemodialysis to prevent clotting in the membrane filter. The main disadvantage of UFH is that it may provoke hemorrhage in azotemic patients, many of whom have abnormal platelet function and lesions likely to bleed. Another less common problem is heparin-associated thrombocytopenia, which may be present in an occasional patient repeatedly exposed to UFH. Schrader et al. (1988) compared UFH with LMWH (Fragmin) in 70 patients starting hemodialysis. The frequency of clotting and bleeding was similar in the two groups, but blood transfusions were required more often by those receiving UFH. Interestingly, the latter also had a greater increase in triglyceride levels, and UFH stimulated more post-heparin lipolytic activity, chiefly hepatic lipase.

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ORG 10172 was selected as the anticoagulant for acute hemodialysis in 12 patients with bleeding or a high risk of bleeding by Henny et al. (1983). No exacerbation of hemorrhage or deposition of labeled fibrinogen in the dialysis membrane was observed. Dermatan sulfate, a related glycosaminoglycan, has also been studied in patients undergoing hemodialysis, and although the studies supporting its use are of a preliminary nature, it appears to be safe and effective (Lane et al., 1992).

7. Cardiopulmonary bypass. UFH is a mainstay for patients undergoing cardiopulmonary bypass, preventing clot formation in the various lines and the pump oxygenator. However, it undoubtedly increases blood loss and is contraindicated for those individuals with heparin-associated thrombocytopenia. Laboratory studies in dogs showed that an LMWH (ORG 10172) was as effective as UFH in preventing clotting in the extracorporeal circuit and caused less postoperative blood loss (Henny et al., 1985).

Experience in humans with LMWH for cardiopulmonary bypass is limited. There is a description of a successful operation in one patient with heparin-associated thrombocytopenia (Gouault-Heilmann et al., 1983) and a second report of another patient with this disorder, observing that in the dose given ORG 10172 failed to prevent clots in the filters (Marshall et al., 1992). It appears unlikely that LMWH will supplant UFH for cardiopulmonary bypass surgery except for those patients who are intolerant of UFH.

8. Arterial patency. Restenosis occurs in as many as 40% of patients who have coronary angioplasty (Blackshear et al., 1987), and thrombosis is common in grafts performed for patients with peripheral arterial occlusions. UFH is known to inhibit smooth muscle cell proliferation (Guyton et al., 1980); LMWH was found to inhibit intimal proliferation and significantly ($P = 0.001$) prevent restenosis in the rabbit iliac artery model (Currier et al., 1991). In an open, randomized study (Samama, 1993), 201 patients scheduled for femorodistal reconstructive surgery were given either Enoxaparin, 75 anti-Xa IU/kg, or UFH, 50 IU/kg, both administered intravenously prior to arterial cross-clamping and then BID subcutaneously for 10 days. Arterial thrombosis occurred in eight patients in the LMWH group and 20 patients in the UFH group ($P = 0.02$). Nine major hemorrhages were recorded in each group. Other multicenter trials in humans (ERA) are presently underway.

B. Conclusions

During the past two decades, many physicians have incorporated the use of heparin prophylaxis into their clinical practices. When used in doses of 5000 units BID, UFH is very safe and provides effective protection against thromboembolism in a broad range of clinical situations, ranging from general surgery to myocardial infarction (Clagett et al., 1992a). To supplant UFH, LMWH must have other advantages, such as ease of administration or lower cost, and be at least, if not more, safe and effective (Barrowcliffe et al., 1992). Tentative recommendations are listed in table 13.

In general medical patients, studies have shown that LMWH is as effective as UFH and has the advantages of less frequent injections and fewer injection site hematomas. In general surgical patients, a lesser risk of thrombosis, particularly PE, was observed with LMWH, but there was a trend toward an increase in bleeding events. Thrombotic complications were significantly less frequent in patients with strokes receiving LMWH, and there was no increase in bleeding when ORG 10172 was administered. In subjects with spinal cord injuries, LMWH was clearly a better thromboprophylactic agent than UFH; the frequencies of both thromboembolism and bleeding were less in patients receiving the LMWH, and the QD administration was a clear advantage.

Other potential indications for LMWH, such as in hemodialysis, cardiopulmonary bypass, and preservation of graft patency, are under review. The rationale for replacing UFH with LMWH for these conditions is less bleeding tendency, less risk for heparin-associated thrombocytopenia, and equivalent or better antithrombotic effect. In the few studies reported, these benefits have yet to be realized, and further trials must be conducted before LMWH will have a secure position in the management of any of these entities.

IV. Treatment of Established Deep-Vein Thrombosis with Low Molecular Weight Heparins

Although most experience with LMWHs has been in the prevention of venous thromboembolism, and they have been shown to be useful (Hirsh and Levine, 1992; Nurmohamed et al., 1992), there is accumulating evidence that these new anticoagulants are also safe and effective for the treatment of acute DVT.

We have reviewed randomized clinical trials that compared adjusted-dose UFH with fixed-dose subcutaneous LMWH for the treatment of patients with acute venous

TABLE 13

Recommendations for thromboprophylaxis in nonorthopedic conditions

Condition	Recommendation
General medicine	LMWH 50 units*/kg QD or UFH 5000 units every 12 h
General surgery	UFH 5000 units every 12 h or LMWH 2500 units QD
Pelvic surgery	Mechanical compression devices
Acute stroke	Heparinoid 750 units every 12 h or LMWH 2500 units every 12 h or UFH 5000 units every 12 h
Spinal cord injury	LMWH 50 U/kg daily
Hemodialysis	UFH 2–4000 unit bolus, 1–2000 units/h; LMWH 2500 or 5000 unit bolus, 800 units/h (with 5000-unit bolus, no need for continuous infusion)

* Units = anti-Xa units.

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thrombosis. All truly randomized trials comparing the results of LMWH therapy with those of adjusted-dose UFH for the treatment of DVT were selected if they used objective tests to confirm the diagnosis of DVT (Büller et al., 1991; Sackett et al., 1985).

The following data were extracted: (*a*) the change in venographic score between pre- and posttreatment venograms, (*b*) the incidence of symptomatic recurrent venous thromboembolism, and (*c*) the frequency of major hemorrhagic episodes during initial treatment.

The changes in thrombus size between pre- and posttreatment venograms and the relative efficacy and safety were assessed using the Mantel-Haenszel test (Collins et al., 1987; Mantel and Haenszel 1959).

Four studies were not eligible for this review (Handeland et al., 1990; Lockner et al., 1986; Albada et al., 1989; Lindmarker et al., 1993). Nine studies were considered for this analysis; the LMWH preparations used and their dosages are summarized in table 14. In one of the nine studies, venography was not repeated after initial treatment (Hull et al., 1992).

A. Results

1. Quantitative venographic assessments. The combined results of the eight studies in which the pre- with the post-heparin treatment venograms were compared show a reduction of thrombus size in 64% of LMWH-treated patients and in 50% of patients treated with UFH, whereas an increase in thrombus size was observed in 6% of LMWH-treated patients and in 12% of heparin-treated patients (table 15). The difference between the two treatment groups was statistically significant ($P < 0.001$).

2. Symptomatic thromboembolic complications. Prospective long-term clinical follow-up was conducted in studies in which Fraxiparin, Logiparin, and Enoxaparin were used. The analysis of the pooled results of these studies revealed a statistically significant risk reduction (63%; 95% confidence interval, 30 to 80%; $P < 0.005$) in thromboembolic complications; 12 (2.7%) of the 439 LMWH-treated patients had complications vs. 31 (7.0%) of the 443 UFH-treated patients (table 16).

3. Hemorrhagic complications during heparin treatment. In the pooled results, major bleeding was observed in six (0.9%) of the 652 LMWH treated patients and 21 (3.2%) of the 656 UFH-treated patients, for a risk reduction of 68% (95% confidence interval, 31 to 85%; $P < 0.005$; table 17).

TABLE 14

*Randomized trials of fixed-dose LMWH vs. adjusted-dose UFH for the treatment of patients with DVT**

Author	Trial
Bratt et al. (1985)	Fragmin 120 anti-Xa units/kg/BID IV vs. UFH IV
Holm et al. (1986)	Fragmin 57–107 anti-Xa units/kg/BID† SC vs. UFH† SC
Faivre et al. (1987)	CY 222 155 anti-Xa units/kg/BID SC vs. UFH SC
Bratt et al. (1990)	Fragmin 120 anti-Xa units/kg/BID SC vs. UFH IV
Duroux et al. (1991)	Fraxiparin ± 90 anti-Xa units/kg/BID SC vs. UFH IV
Prandoni et al. (1992)	Fraxiparin ± 90 anti-Xa units/kg/BID SC vs. UFH IV
Lopaciuk et al. (1992)	Fraxiparin 92 anti-Xa units/kg/BID SC vs. UFH IV
Hull et al. (1992)	Logiparin 175 anti-Xa units/kg/QD SC vs. UFH IV
Simonneau et al. (1993)	Enoxaparin ± 100 anti-Xa units/kg/BID SC vs. UFH IV

* Abbreviations: IV, intravenous; SC, subcutaneous.

† Dosage adjusted for age and gender.

B. Discussion

The results of this analysis indicate that LMWH preparations are both more effective and safer than UFH for the treatment of venous thrombosis. The recurrence rate for symptomatic venous thromboembolism during 3 to 6 months of follow-up and the incidence of major bleeding in the UFH group are consistent with results of other contemporary studies (Hirsh, 1991). The observed reductions in recurrence and major bleeding are both statistically significant and clinically important. The development of LMWH preparations constitutes an important advance for the treatment of venous thrombosis. The observation that LMWHs are effective and safe when administered QD or BID by subcutaneous injection, without the need for laboratory monitoring, indicates that these new anticoagulants can be used to replace conventional UFH. It might also be possible to use LMWH preparations to treat selected patients with proximal vein thrombosis in an out-of-hospital setting. Clinical trials are currently underway to test this possibility.

V. Summary

LMWHs are an important new class of antithrombotic agents. They differ from UFH in having relatively more anti-Xa activity, greater bioavailability at low doses, longer half-life, and more predictable anticoagulant response when administered in fixed doses. These properties allow LMWHs to be administered QD or at most BID and without laboratory monitoring. The incidence of heparin-induced thrombocytopenia also appears to be lower with an LMWH than with heparin. Given their favorable pharmacological profile, it was of interest to critically appraise clinical trials of thromboprophylaxis and treatment with these new agents.

In orthopedic trials, it was noted that LMWH provided safe and effective thromboprophylaxis for patients undergoing major orthopedic surgery of the lower limb. In those having hip arthroplasty, LMWH was as effective as low-intensity warfarin therapy, but its use was associated with more wound hematomas. In those having total knee arthroplasty, LMWH was more effective than warfarin and did not increase bleeding. However, the

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TABLE 15

Quantitative assessment of pre- and post-heparin treatment venograms

	No. of patients receiving LMWH/UFH	Quantitative venographic assessment			Quantitative venographic assessment			*P* value
		LMWH improved	Unchanged	Deteriorated	UFH improved	Unchanged	Deteriorated	
Fragmin	83/103	54 (65%)	26 (31%)	3 (4%)	56 (54%)	39 (38%)	8 (8%)	0.13
CY 222	30/29	19 (63%)	11 (37%)	0	19 (66%)	8 (28%)	2 (7%)	0.73
Fraxiparin	228/222	149 (65%)	59 (26%)	20 (9%)	112 (50%)	74 (33%)	36 (16%)	0.001
Enoxaparin	60/57	35 (58%)	24 (40%)	1 (2%)	18 (33%)	34 (62%)	5 (5%)	0.003
All patients	401/411	257 (64%)	120 (30%)	24 (6%)	205 (50%)	155 (38%)	51 (12%)	0.001

TABLE 16

Symptomatic thromboembolic complications during initial treatment with heparin and long-term follow-up

	Symptomatic thromboembolic complications					Risk reduction for all events		
	LMWH		Total	UFH		Total	%	*P* value
	Initial treatment	Follow-up		Initial treatment	Follow-up			
Fragmin	1/95* (1.1%)			0/97				
CY 222	1/33 (3.0%)	Not done		1/35 (2.9%)	Not done			
Fraxiparin	2/244 (0.8%)	5/159 (3.1%)	6/159 (3.8%)	7/238 (2.9%)	10/157 (6.4%)	15/157 (9.6%)	61%	<0.04
Logiparin			6/213 (2.8%)			15/219 (6.8%)	60%	0.08
Enoxiparin	0/67	0/67	0/67	2/67 (3.0%)	1/67 (1.5%)	3/67 (4.5%)	100%	>0.2
All studies	4/439 (0.9%)	5/226 (2.2%)	12/439 (2.7%)	10/437 (2.3%)	11/224 (4.9%)	33/443 (7.4%)	62%	<0.005

* No. of patients with complications/total no. of patients.

TABLE 17

Incidence of major bleeding complications during heparin treatment

	Major bleeding complications		Risk reduction	
	LMWH	UFH	%	*P* value
Fragmin	2/95* (2.1%)	2/97 (2.1%)	−3%	>0.2
CY 222	0/33	0/35		>0.2
Fraxiparin	3/244 (1.2%)	8/238 (3.4%)	62%	0.11
Logiparin	1/213 (0.5%)	11/219 (5.0%)	91%	<0.01
Enoxaparin	0/67	0/67		>0.2
All studies	6/652 (0.9%)	21/656 (3.2%)	68%	<0.005

* No. of patients with complications/total no. of patients.

prevalence of DVTs complicating this procedure as well as acute hip fracture remains unacceptably high, and additional studies of LMWH in combination with other prophylactic methods, such as external pneumatic compression, are needed. Only one adequately designed trial found less bleeding resulted from LMWH prophylaxis administered at an equivalent antithrombotic dose to UFH.

In general medical patients, LMWH appeared to be as effective as UFH and had the advantages of less frequent injections and fewer injection site hematomas. In general surgical patients, there was a lower risk of thromboembolism but a trend toward an increase in bleeding events. Subjects with strokes and spinal cord injuries benefited from fewer thrombotic events, and the latter had fewer bleeding complications. Other potential indications for LMWH, such as cardiopulmonary bypass, hemodialysis, and preservation of graft patency, are presently under study.

Perhaps the most impressive benefits of LMWH will be realized when it is used for the treatment of venous thromboembolism. The meta-analysis presented in this review showed a trend toward greater efficacy with LMWH and fewer major bleeding events in comparison with adjusted-dose intravenous UFH. Also, during the months following the thrombotic event, there was significantly less mortality in patients receiving LMWH. A further advantage was the subcutaneous route of administration and lack of requirement for laboratory monitoring. Additional treatment trials are presently in progress and may establish LMWH as the treatment of choice for patients with thromboembolic disorders.

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