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REVIEW ARTICLE

Low Molecular Weight Heparin

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THE IMPETUS for the development of low molecular weight heparins (LMWHs) as potential antithrombotic agents came from two observations in the mid 1970s and early 1980s. The first was the finding that LMWH fractions prepared from standard commercial grade heparin (SH) progressively lose their ability to prolong the activated partial thromboplastin time (APTT) while retaining their ability to inhibit activated factor X (factor Xa).[1,2] The second was the observation that, for an equivalent antithrombotic effect, LMWHs produce less bleeding in experimental models than SH.[3-8] Since then considerable progress has been made. The mechanism for the difference between the anticoagulant profiles of LMWHs and SH has been elucidated[9-15] and studies of platelet function[16-18,19] and vascular permeability[20] have provided plausible explanations for the reduced experimental bleeding observed with LMWHs. Important differences between LMWHs and SH have been found in their plasma recovery (bioavailability) at low doses,[21,22] in their pharmacokinetics,[23-27] and in the variability of their anticoagulant response to fixed doses.[28] 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, and at least five different LMWHs are licensed for clinical use in Europe. Large multicenter trials have been completed in Canada and the United States, but as yet LMWHs are not approved for routine clinical use in North America.

In this report, we review the anticoagulant, antithrombotic, hemorrhagic, pharmacokinetic, and clinical effects of LMWHs and, where appropriate, compare and contrast the properties of the LMWHs with SH.

BIOPHYSICAL PROPERTIES AND ANTICOAGULANT EFFECTS OF SH AND LMWHs

SH and LMWHs are glycosaminoglycans (GAGS) consisting of chains of alternating residues of D-glucosamine and a uronic acid, either gluconic acid or iduronic acid.[29] SH is a heterogeneous polydispersed mixture of sulfated polysaccharides ranging in molecular weight from 5,000 to 30,000, with an average molecular weight of 12,000 to 15,000.[30-32] The anticoagulant activity of SH is accounted for by a unique pentasaccharide with a high affinity binding sequence to antithrombin III (ATIII).[33-41] 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.[40,42] Only about one third of the SH molecules contain the unique pentasaccharide sequence, and its distribution along the heparin chain appears to be random.[9,40,43] The major anticoagulant effect of SH is through its interaction with ATIII.[43-46] This interaction produces a conformational change in ATIII[47-49] and so markedly accelerates the ability of ATIII to inactivate the coagulation enzymes thrombin (IIa), factor Xa, and factor IXa.[34] Of these enzymes, thrombin is most sensitive to inhibition by heparin, both because ATIII inhibits thrombin more rapidly than factor Xa[34,50,51] and because factor Xa is protected from inhibition by the ATIII/heparin when it is bound to phospholipid in the prothrombinase complex.[52-55] Heparin potentiates the inactivation of thrombin by serving as a template to which both ATIII and thrombin bind to form a ternary complex.[34,45,46,56,57] 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.[29,34,37,39,58] Heparin molecules with fewer than 18 saccharides (MW < 5,400) 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[10,11,57] (Fig 1 and Table 1). The anticoagulant activity of SH is also mediated by a second plasma cofactor, heparin cofactor II (HCII).[59] 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 (MW ~ 7,200).[60-63]

LMWHs are fragments of commercial grade SH produced by either chemical or enzymatic depolymerization.[64] Depolymerization of heparin invariably leads to partial loss

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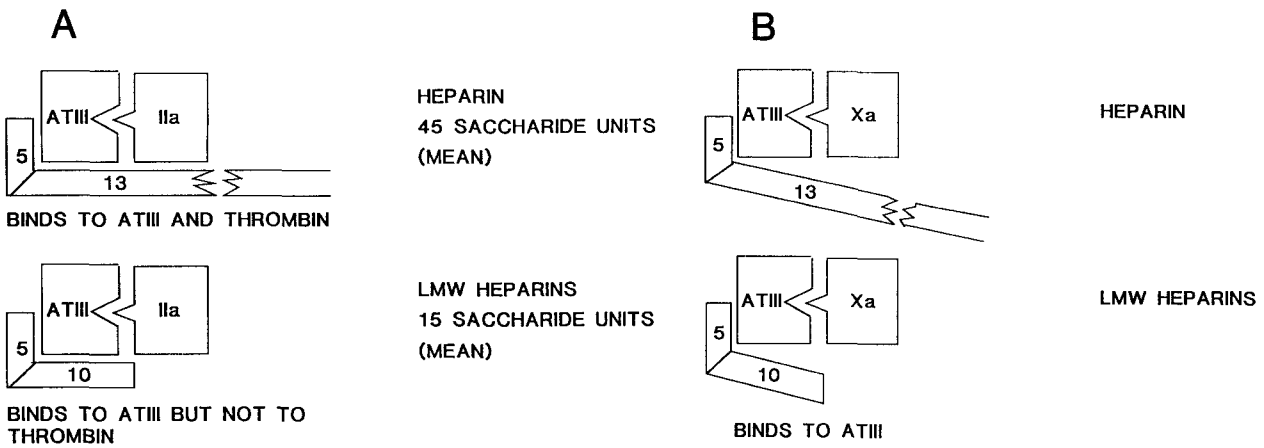

Fig 1. (A) Inactivation of thrombin. To inactivate thrombin, heparins must bind ATIII through the high-affinity pentasaccharide and to thrombin through an additional 13 saccharide U. LMWHs that contain less than 18 saccharide U cannot bind to thrombin and, therefore, are unable to inactivate thrombin. (B) Inactivation of factor Xa. To inactivate factor Xa, heparins must bind to ATIII through the high-affinity pentasaccharide but do not need to bind to factor Xa. Therefore, both SH and LMWHs are able to inactivate factor Xa.

of the original catalytic activity[45,57,65] 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.[30,64,66] Depolymerization is achieved by one of the following methods (Table 2): treatment with nitrous acid, treatment with the enzyme heparinase, by hydrolytic cleavage with hydrogen peroxide, or by β-elimination. The resulting LMWHs contain the unique pentasaccharide required for specific binding to ATIII, but in a lower proportion than is contained in their parent SH.[65] Two other glycosaminoglycans (commonly referred to as heparinoids) have also been developed for clinical use. These are dermatan sulfate and the Organon heparinoid which consists of a mixture of 80% of heparan sulfate and 20% of dermatan sulfate and chondroitan sulfates.

LMWHs developed commercially have different mean molecular weights that vary from 4,000 to 6,500.[67] LMWHs have reduced ability to catalyze the inactivation of thrombin relative to their ability to inhibit factor Xa because the inactivation of thrombin by heparin is critically dependent on molecular size.[10,11,12,13,40] Thus, compared with SH, 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. These ratios are based on assays performed in vitro using platelet-poor plasma and may not reflect the anticoagulant profiles of these GAGS in whole blood in vivo, because the anticoagulant effect of SH is impaired by platelets to a greater extent than LMWHs. Two mechanisms operate in whole blood or in platelet-rich plasma to reduce the anticoagulant potency of SH relative to LMWHs. The first is the release, during coagulation, of platelet factor 4 (PF4), a potent inhibitor of SH[78] but not of LMWHs.[11] The second is based on the observation that factor Xa bound to the platelet membrane in the prothrombinase complex is resistant to inactivation by SH[55,68,69] but is not resistant to inactivation by LMWHs.[52-54] These two properties of LMWHs, which have the potential to make them more effective anticoagulants than SH in whole blood, in vivo, are obscured when the anticoagulant activities of these GAGS are measured in vitro in platelet-free plasma. In addition observations from two laboratories indicate that, like SH, an important mechanism for the anticoagulant effect of many LMWHs is their ability to inactivate thrombin.[51-54,64,70,71] The most plausible explanation for this unexpected finding is that the inactivation of thrombin by LMWHs is mediated by the larger oligosaccharide chains in the polydispersed spectrum of each LMWH which contain at least 18 monosaccharides

Table 1. MW and Anticoagulant Activity of Saccharide Fractions

Heparin Oligosaccharides	MR	Anticoagulant Activity Anti-Xa	Anticoagulant Activity Anti-IIa
8	2,400	1.30	Nil
12	3,600	1.58	Nil
16	4,800	1.60	Nil
18	5,400	0.95	0.51
24	7,200	1.30	1.21

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Table 2. Commercial LMWHs and Their Methods of Preparation

Agent	Manufacturer	Method of Preparation
CY 216 (Fraxiparin®)	Sanofi (France)	Nitrous acid depolymerization
PK 10169 (Enoxaparin) (Lovenox)	Rhone-Poulenc Rorer (France and United States)	Benzylation followed by alkaline depolymerization
Kabi 2165 (Fragmin)	KABI (Stockholm, Sweden)	Nitrous acid depolymerization
RD 11885	Wyeth (Philadelphia, PA)	Peroxidative depolymerization
Novo LMWH (Logiparin)	NOVO (Denmark)	Enzymatic (heparinase) depolymerization
ORG 10172 (Lomoparin)	Organon Inc (The Netherlands)	Prepared from porcine gut mucosa (contains dermatan sulfate [80%], heparan sulfate, chondroitin sulfate)

(equivalent to a molecular weight of approximately 5,400). Because the molecular weight distribution of LMWHs varies widely between preparations,[67] the anti-factor IIa activity of the different LMWHs with similar mean molecular weights will also vary between the different commercial preparations.[72] The different anticoagulant profiles (anti-factor Xa to anti-factor IIa activities) of commercially developed LMWHs also render the comparison of their anticoagulant potencies problematic. An International LMWH reference preparation has been established with a specific activity of 168 anti-Xa units/mg and 68 anti-IIa units/mg.[73,74] The reference preparation has shortcomings as a universal LMWH standard because the ratio of its anti-Xa to anti-IIa differs considerably from some LMWH preparations[75,76]; nevertheless, it provides the most practical means for verifying the stated potency of a given batch of LMWH and for comparing the clinical results obtained with different LMWHs.

PROTEIN BINDING AND PHARMACOKINETICS

In 1979, Andersson et al[30] made the observation that normal plasma contains components which neutralize the anti-factor Xa activity of SH but not 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 SH in their binding characteristics to plasma proteins.[77,78] SH binds to a number of plasma proteins including histidine-rich glycoprotein (HRGP),[78-80] PF4,[78,81] vitronectin,[82] fibronectin,[83] and von Willebrand factor (vWF).[84] The interaction of SH with HRGP and PF4 results in neutralization of its anticoagulant effect. Binding to plasma proteins could be responsible for the reduced bioavailability of SH at low concentrations, for the variability of its anticoagulant response to fixed doses in patients with thromboembolic disorders,[85] and for the laboratory phenomenon of heparin resistance.[86]

LMWHs have lower affinity for HRGP,[78] for fibronectin,[83] and for PF4[78] than SH, an observation that could explain the superior bioavailability of LMWHs at low doses and the more predictable anticoagulant response to high doses of LMWHs.[28] Both SH and LMWHs bind to vitronectin, but only after the adhesive protein has been modified by exposure to thrombin or a surface.[82] Binding of SH to vWF results in inhibition of vWF-dependent platelet function[84] and thus could contribute to the bleeding side effects of SH. LMWH preparations have a lower affinity for vWF,[84] a property that could contribute to their reduced enhancement[87] (relative to SH) of experimental microvascular bleeding.[3-8]

The molecular size of heparin and its fragments also influences their binding to endothelial cells. SH binds to endothelial cells and macrophages,[88] while LMWHs do not bind to endothelial cells in culture,[89,90] a feature that probably contributes to their reduced plasma clearance.

The pharmacokinetics of heparin and LMWHs differ in a number of important ways[21-27,29,91,92] After an intravenous (IV) injection of SH into healthy volunteers, there is a very rapid phase of elimination due to equilibration, which is followed by a more gradual disappearance due to a combination of a rapid saturable and a much slower first order mechanism of clearance.[93-95] The saturable phase of heparin clearance is thought to be due to heparin binding to receptors on endothelial cells,[89,90,96,97] and macrophages[98] where it is internalized, depolymerized, and metabolized into smaller and less sulfated forms.[99,100] The first order mechanism of heparin clearance is partly renal. Because of these kinetics the apparent biologic half-life of heparin is dose-dependent and increases from approximately 30 minutes with an IV bolus of 25 U/kg to 60 minutes with an IV bolus of 100 U/kg to 150 minutes with a bolus of 400 U/kg.[93-95]

The plasma recovery (bioavailability) and pharmacokinetics differ between LMWHs and SH,[26] possibly because of their different binding characteristics to plasma proteins and to endothelial cells.[89,90] Plasma recovery (measured as anti-Xa activity) of LMWHs is essentially complete at all concentrations, while the plasma recovery of SH is reduced markedly[26] when administered by subcutaneous injection in low (prophylactic) doses. However, at high therapeutic doses (>35,000 U/24 h) the plasma recovery of SH is high and essentially the same as LMWHs.[101] These differences between the plasma recovery and clearance of SH and LMWHs at low doses probably reflect the rapid binding of sub-saturating concentrations of SH to plasma proteins and endothelial cells. At high plasma concentrations of SH, binding sites on plasma proteins and endothelial cells are saturated, so plasma recovery of SH is increased and its rate of clearance reduced. Because LMWHs have much lower affinity for heparin-binding proteins and endothelial cells than SH, their plasma recovery and clearance is independent of dose and plasma concentration. The reduced binding of LMWHs to endothelial cells probably contributes to their longer plasma half-life, which is approximately twofold to fourfold longer than SH at therapeutic doses[21-27,91,92] (Table 3). LMWHs are cleared principally by the renal route and their biologic half-life is increased in patients with renal failure.[91,102,103]

ANTITHROMBOTIC AND HEMORRHAGIC EFFECTS OF LMWHs, HEPARINOIDS, AND STANDARD HEPARIN IN EXPERIMENTAL MODELS IN ANIMALS

The antithrombotic effects of SH has been compared with LMWHs and the heparinoids, Organon heparinoid, and dermatan sulfate in a variety of experimental animal models designed to simulate either the prevention or treatment of venous thrombosis.[3-8,87,104-108] Experimental thrombosis is achieved by producing temporary venous stasis and inducing activation of blood coagulation by injecting either serum, factor Xa, thrombin, or tissue factor.[87,104,106]

When compared on the basis of anti-Xa activity, SH is approximately twice as effective (range 1.3 to 3.5) as LMWHs with a mean MW of between 4,000 and 6,500[3,5,87,104] for preventing experimental thrombosis. Effective inhibition of experimental venous thrombosis is achieved with LMWHs at anti-factor Xa levels ex vivo of 0.2 U/mL to 0.3 U/mL.

Table 3. Anticoagulation Profiles, Molecular Weights, Plasma Half-Lives, and Recommended Doses of Commercial LMWHs

	Anti-Xa to Anti-IIa Ratio	MW (range) [saccharide units]	Plasma Half-Life (min)	Recommended Dose (converted into international anti-Xa units)		
				General Surgery	Orthopedic Surgery	Treatment
Enoxaparine (Rhone-Poulenc Rorer, France and United States)	2.7:1	4,500 (3,000-8,000) [10-27]	129-180	1,600 U s/c	3,200 U s/c OD or 2,400 U s/c BID	5,600 U s/c BID
Fragmin (KABI, Stockholm, Sweden)	2.0:1	5,000 (2,000-9,000) [7-30]	119-139	2,500 U s/c	2,500 U s/c BID or 5,000 U s/c OD	8,400 U s/c† (70 kg) BID
Fraxiparine (Sanofi, France)	3.2:1	4,500 (2,000-8,000) [7-27]	132-162	7,500 U/IC s/c* OD		31,500 U/IC† OD
Logiparin (NOVO, Denmark)	1.9:1	4,500 (3,000-6,000) [10-20]	111	3,500 U s/c OD	50 U/kg s/c OD	12,250 OD†
RD Heparin (Wyeth, Philadelphia, PA)	2.0:1	6,000 (2,000-15,000) [7-50]	200		50 U/kg s/c BID‡	
Lomoparin (Organon, The Netherlands)	20:1	6,500	1,100		750 U s/c BID	

Abbreviations: OD, once daily; BID, twice daily.
*U/IC (Institute Choay Units). 3 ICU = 1 International Unit.
†Weight adjusted dose–stated dose for 70 kg patient.
‡Dosage evaluated.

The ability of these GAGS to inhibit fibrin accretion onto experimental jugular vein thrombi in rabbits has also been compared in models designed to simulate the treatment of established venous thrombosis.[105] The minimum concentrations of GAGS required to produce effective inhibition of thrombus growth is equivalent to an anti-factor Xa activity of 0.4 to 0.7 U/mL, ie, approximately twofold to threefold higher than the optimal concentrations required to prevent experimental thrombosis.

The hemorrhagic effects of standard 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, SH produced more bleeding for an equivalent antithrombotic effect than the LMWHs and the heparinoids.[3,4,5,7,8,87,107,108] The differences in the relative antithrombotic to hemorrhagic effects of the SH and LMWHs could be due to the different effects of these GAGs on platelet function and vascular permeability. SH inhibits both collagen-induced platelet aggregation[17,18,109] and vWF-dependent platelet aggregation[86] more than LMWHs. SH has also been reported to increase vascular permeability at doses that produce experimental bleeding, while LMWHs and dermatan sulfate had no such effect[20]; these differential effects of SH and LMWHs on vascular permeability could also contribute to the greater hemorrhagic potential of SH.

CLINICAL STUDIES

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, while their use for other indications is limited to case reports and pilot studies.

Five different LMWHs (Enoxaparin [Rhone-Poulenc, France and United States], Fragmin [KABI, Stockholm, Sweden], Fraxiparin [Sanofi, France], Logiparin [NOVO, Denmark], and RD heparin [Wyeth, Philadelphia, PA]) and one heparinoid (Lomoparin; Organon, The Netherlands) have been evaluated in dose-finding studies and randomized clinical trials and definitive (although not necessarily optimal) dosage regimens have been established. Five of these new GAGS (Enoxaparin, Fragmin, Fraxiparin, Logiparin, and Lomoparin) have been approved for clinical use in Europe and three LMWHs (Enoxaparin, Logiparin, and RD heparin) and the heparinoid Lomoparin have been evaluated in North America in large-scale randomized trials.

LMWHs share a number of common properties but also differ from one another in a number of important ways; thus, 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 (Table 3). Therefore, until more information is available on their relative safety and efficacy, LMWHs should be considered to be distinct and separate compounds.

LMWHs have a number of potential and demonstrated advantages over SH. The potential advantage relates to the observation from experimental animal models that for an equivalent antithrombotic effect LMWHs produce less microvascular bleeding than SH.[3-5,7,8,87,107,108] If this property of LMWHs is transferable to the clinical situation, it would allow LMWHs to be administered to patients in higher anticoagulant doses than SH and so improve efficacy of antithrombotic therapy without compromising safety. The observation in experimental animal models that LMWHs produce less bleeding than SH for an equivalent antithrombotic effect has not been evaluated properly in humans,

because in all but one of the comparative prophylactic studies SH has been administered in lower anticoagulant doses than the LMWH. However, there is suggestive evidence that when compared with full-dose SH for the treatment of venous thrombosis, LMWHs produce less major bleeding than SH at a dose that produces at least an equivalent (and possibly superior) antithrombotic effect.

The demonstrated advantages of LMWHs are that they have a longer plasma half-life than SH and their anticoagulant response to weight-adjusted doses is less variable. These properties allow LMWHs to be administered once daily and without laboratory monitoring. Indeed, four studies have now reported that LMWHs administered subcutaneously in weight-adjusted fixed doses without any laboratory monitoring are at least as effective for the treatment of established deep venous thrombosis as SH administered IV with laboratory monitoring (see below). The main differences in properties between LMWHs and SH are summarized in Table 4.

Data on well-designed clinical trials comparing LMWHs with SH for the prevention and treatment of venous thrombosis are continuing to appear. A number of large multicentered studies in United States, Canada, and Europe are in their final stages of completion and new studies are in their planning stages. Because large numbers of patients have been entered into these unpublished and ongoing studies, their findings will add substantially to our present state of knowledge. Therefore, the conclusions on efficacy and safety reached in this review might have to be modified in the light of future reports.

A number of methodologic issues must be considered in a critical review of contemporary experience with LMWHs. The most important are the method of analysis and presentation of the accumulated data, and the criteria used to include studies in the analysis.

Because the LMWHs are distinct compounds with different properties, and because the dosage regimens differ between studies, the practice of pooling the results of studies that compare different LMWHs with either SH or placebo and presenting the data as a meta-analysis might not be appropriate. Accordingly in this review, the results of studies will be reported separately for each of the different LMWHs. Many of the early studies, including some randomized trials, were dose-finding and used dosage regimens that are no longer recommended. These early dosage regimens have been modified because in some cases they induced excessive bleeding. In addition, some of these published studies used inaccurate or nonvalidated outcome measures to detect thrombosis. These early exploratory studies were both important and necessary for the development of optimal dosage regimens, but their findings are not comparable with results of studies using contemporary dosage regimens. Accordingly, we have only included data from published randomized trials (either full-length reports or abstracts) that used currently accepted dosage regimens and that used appropriate outcome measures to assess the incidence of thromboembolism (see below).

Table 4. Comparisons Between Standard Heparin and LMWHs

	Standard Unfractionated Heparin	LMWHs
Mean MW	12,000-15,000	4,000-6,500
Saccharide units (mean)	40-50	13-22
Anti-Xa; anti-IIa activity	1:1	2:1 to 4:1
Inactivates factor Xa on platelet surface	Weak	Strong
Inhibitable by PF4	Yes	No
Inhibits thrombin generation in PRP	++	++++
Main action through inhibition of factor IIa	Yes	Yes
Protein binding	HRGP, Fn, Vn, PF4, VWF	Vn
Binds to endothelium	Yes	No (weak)
Dose-dependent clearance	Yes	No
Bioavailability at low doses	Poor	Good
Inhibits platelet function	++++	++
Increases vascular permeability	Yes	No
Augments microvascular bleeding	++++	++

Abbreviation: PRP, platelet-rich plasma.

PREVENTION OF VENOUS THROMBOSIS

General surgery. Studies were included in the analysis if either I^{125} fibrinogen leg scan-detected venous thrombosis or mortality were used as outcome measures. Thromboembolic mortality was accepted if the outcome assessment was blinded.

A number of very effective prophylactic approaches are available for the prevention of venous thrombosis in moderate-risk patients having general surgery. Of these, low-dose subcutaneous SH (5,000 U twice daily) and intermittent pneumatic compression produce a risk reduction of approximately 70%[110-112]; the risk of bleeding with low-dose heparin is minimal and confined to a slight excess of minor bleeding and wound hematoma.[110,112] Therefore, it would be difficult to demonstrate further true improvements in efficacy or safety in general surgical patients unless very large numbers of patients are included in the trial.

We included nine randomized trials evaluating LMWHs that used currently recommended dosage regimens (Table 5). In two studies, LMWHs were compared with an untreated control group and in the other seven to low-dose SH. In all of the studies treatment was commenced preoperatively, the LMWHs were administered once daily and SH was administered either two or three times daily.

Both studies comparing LMWHs to an untreated group were placebo controlled.

Pezzuoli et al[113] randomized 4,498 patients to either Fraxiparin LMWH (7,500 anti-Xa U Institute Choay [IC] once daily) or placebo. There was a statistically significant difference in overall mortality between placebo and LMWH, 0.8% versus 0.36%, respectively ($P < .05$). There was also a statistically significant reduction in thromboembolic mortality in favor of LMWH, 0.36% to 0.09% ($P < .05$). Patients who received the LMWH had an increase in postoperative wound hematomas and transfusion requirements compared with placebo, but no difference was detected in major bleeding.

Ockelford et al[114] randomized 183 patients to either Fragmin LMWH (2,500 anti-Xa U once daily) or placebo; both regimens were commenced preoperatively and were

Table 5. Randomized Trials of LMWH Versus SH for the Prevention of Venous Thromboembolism in General Surgery

Study	Treatment	Dose (anti-Xa U)	No. Patients	DVT No. (%)	Bleeding No. (%)
Kakkar et al[115]*	Fraxiparin	7,500 I.C. OD	196	5 (2.6)	10 (5.1)
	SH	5,000 BID	199	15 (7.5)†	7 (3.5)
Encke and Breddin[116]	Fraxiparin	7,500 I.C. OD	960	27 (2.8)	47 (4.9)
	SH	5,000 TID	936	42 (4.5)†	42 (4.5)
Bergqvist et al[118]	Fragmin	5,000 pre-op, 5,000 OD	505	28 (5.5)	30 (6.0)
	SH	5,000 BID	497	41 (8.3)	15 (3.0)†
Caen[119]*	Fragmin	2,500 OD	195	6 (3.1)	4 (2.1)
	SH	5,000 BID	190	7 (3.7)	3 (1.6)
Hartle et al[120]*	Fragmin	2,500 OD	112	9 (8.0)	4 (3.6)
	SH	5,000 BID	115	9 (7.8)	4 (3.5)
Fricker et al[121]	Fragmin	2,500 pre-op, 5,000 OD	40	0	4 (10.0)
	SH	5,000 TID	40	0	12 (30.0)†
Leizorovicz et al[122]*	Logiparin	2,500 OD	431	34 (7.9)	9 (2.1)
	Logiparin	3,500 OD	430	16 (3.7)	13 (3.0)
	SH	5,000 BID	429	18 (4.2)	14 (3.3)
Samama et al[123]	Enoxaparin	1,600 OD	159	6 (3.8)	4 (2.5)
	SH	5,000 TID	158	12 (7.6)	4 (2.5)

Abbreviations: OD, once daily; BID, twice daily; TID, three times daily.

*Double blind trials.

†$P < .05$.

administered once daily. The rate of fibrinogen leg scan detected thrombosis was reduced from 15.9% in the placebo group to 4.2% in the LMWH group, $P = .008$. There were four major bleeds in each group, minor bleeding was not reported.

There have been seven randomized trials in general surgery in which LMWH has been compared with SH; two used Fraxiparin, three used Fragmin, one used Enoxaparin, and one used Logiparin. In all of these studies, the treatment was commenced preoperatively and radioactive fibrinogen leg scanning was used to detect postoperative thrombosis.

In the trial reported by Kakkar and Murray,[115] patients were randomly allocated to either Fraxiparin LMWH (7,500 anti-Xa IC U once a day or SH 5,000 U twice a day). There was a statistically significant reduction in thrombosis from 7.5% to 2.5% in favor of the LMWH. No difference was detected in bleeding between treatment groups. In the European Fraxiparin study reported by Encke and Breddin, 1,894 general surgery patients were randomized to either Fraxiparin LMWH (7,500 anti-Xa U IC once daily) or SH 5,000 U three times daily.[116] There was a 2.8% rate of deep vein thrombosis in the LMWH group compared with a 4.5% rate in the SH group, $P = .03$. No difference was detected in the rate of bleeding between groups.

Bergqvist et al[117,118] have conducted two trials comparing Fragmin with SH in patients undergoing general surgery. In the first study, 432 patients received either Fragmin 5,000 anti-Xa units 2 hours before the operation and then 5,000 U daily, or SH 5,000 U twice daily.[117] Thrombosis occurred in 6.4% of patients in the LMWH group compared with 4.3% in the SH group, a difference that was not statistically significant. However, there was a statistically significant increase in bleeding in patients who received the LMWH compared with SH, 11.6% versus 4.6%, respectively. In the second trial, the same dosage of Fragmin was used as in the first trial but the first dose of 5,000 anti-factor Xa units was administered the evening before surgery instead of 2 hours before surgery.[118] The rates of thrombosis were 5.5% in the 505 LMWH patients and 8.7% in the 497 SH patients. This difference was not statistically different. However, in this trial there was also a statistically significant increase in the rate of bleeding in patients who received Fragmin compared with SH, 6% compared with 3%; most of these bleeds were minor in nature. The first of these studies[117] resulted in a modification of the timing of the preoperative dose of heparin, from 2 hours before surgery to the evening before surgery, while the second study[118] led to a recommendation for a lower dose of Fragmin in patients having surgery for benign disorders.

The modified and currently recommended dosage regimen has now been used in two studies in which Fragmin has been compared with SH.

Caen[119] randomized 385 patients to either Fragmin LMWH, 2,500 anti-Xa U once daily or SH 5,000 U twice daily. The rate of thrombosis was 3.1% in the LMWH group compared with 3.7% in the SH group. No difference was detected in bleeding between groups.

Hartle et al[120] randomized 250 general surgery patients to either Fragmin LMWH 2,500 U once a day or SH 5,000 U twice daily. No difference was detected in deep vein thrombosis (8% *v* 7.8%, respectively) but patients who received the LMWH required fewer transfusions postoperatively, $P = .01$.

Fricker et al[121] randomized 80 patients undergoing oncologic surgery to either Fragmin LMWH or SH. The LMWH group received 2,500 anti-Xa U 2 hours before surgery and 12 hours after the first injection, and then 5,000 U daily while the SH group received 5,000 U 8 hourly. There were no thrombotic events in either group. Severe bleeding requiring withdrawal of treatment occurred in two Fragmin patients and in one SH patient, while moderate postoperative bleeding occurred in two Fragmin patients compared with 11 SH patients.

Thus, there have been five trials evaluating Fragmin in patients undergoing general surgery. Based on the results of these studies, the manufacturers of Fragmin have recommended a regimen of 2,500 anti-Xa U daily for low-risk or moderate-risk general surgical patients, and for high-risk patients either 5,000 anti-Xa U the evening before surgery and then 5,000 U daily postoperatively or 2,500 anti-Xa U 2 hours before surgery, then 2,500 anti-Xa U 12 hours postoperatively and then 5,000 anti-Xa U daily.

Leizorovicz et al[122] performed a double blind study on a total of 1,290 patients comparing two different doses of Logiparin (2,500 anti-Xa U and 3,500 anti-Xa U) administered once daily with SH 5,000 U twice daily. The incidence of thrombosis was 4.2% in the SH group and 3.7% in LMWH group who received 3,500 U (the recommended dose). The rates of major bleeding were similar in the two groups.

Samama et al[123] performed a dose ranging study in which Enoxaparin LMWH administered once daily was compared with SH 5,000 U three times daily in a series of three

consecutive randomized trials. Because it was concluded that all three dosages of Enoxaparin had equal efficacy, the lowest dose of Enoxaparin 20 mg (1,600 anti-Xa U) was recommended for general surgical patients. In this third trial, 334 patients were randomized to either Enoxaparin 20 mg or SH, the rate of thrombosis was 7.6% in the SH group compared with 3.8% in the LMWH group (ns).

In summary for general surgery, the placebo-controlled studies show that the LMWHs tested are effective and safe. In one study, there was an increase in minor bleeding (compared with placebo) but in neither was there an increased incidence of major bleeding. Two studies reported that the same LMWH (Fraxiparin) was more effective than low-dose SH and the other six studies showed no significant difference in efficacy between the LMWHs and low-dose SH. Whether the observed difference in efficacy between Fraxiparin and SH and the lack of observed differences between the other LMWHs and SH represents a true difference in efficacy between Fraxiparin and the other LMWHs or whether it represents a type 2 error in the studies comparing SH with the other LMWHs is uncertain. In one study using Fragmin 2,500 anti-Xa U preoperatively,[121] bleeding was significantly less in the LMWH group. In a second study using Fragmin 5,000 U preoperatively,[118] bleeding was significantly more in the Fragmin group. In the other studies, there was no apparent difference in bleeding.

Orthopedic surgery. Venous thromboembolism is an important complication of major orthopedic surgical procedures with a postoperative incidence ranging from 40% to 50% for hip surgery to 60% to 70% for major knee surgery if prophylaxis is not used.[124-126] A number of effective prophylactic methods are available. Of these, LMWHs, adjusted-dose SH and oral anticoagulants appear to be most effective.[127-129] Low-dose heparin 5,000 U subcutaneously twice or three times daily, although effective, is still associated with about a 25% incidence of deep vein thrombosis and a 10% or greater incidence of proximal vein thrombosis.[130]

Recent studies have demonstrated that screening tests for postoperative venous thrombosis are very insensitive in orthopedic surgical patients.[131] Therefore, in this analysis we have only included studies in which mandatory venography was used as the outcome measure for postoperative venous thrombosis (Tables 6 and 7).

LMWHs have been compared with placebo in three trials in orthopedic surgical patients.[124-126] Two of the studies were performed with Enoxaparin administered twice daily with the first dose administered 12 hours postoperatively[124,125] and the other with Lomoparin that was administered twice daily commencing preoperatively.[126] In the study reported by Turpie et al,[124] 100 patients undergoing elective hip surgery were randomized to receive either Enoxaparin 30 mg (2,400 anti-Xa U) twice daily or placebo. There was a statistically significant reduction in deep vein thrombosis in the Enoxaparin group from 51% to 11%. No difference was detected in bleeding. Leclerc et al[125] performed a randomized study in 111 patients having knee surgery. Patients

Table 6. Randomized Trials of Prophylactic LMWH in Orthopedic Surgery

Study	Type	Treatment	Dose (anti-Xa U)	No. Patients	DVT No. (%)
Turpie et al[124]*†	Elective hip	Enoxaparin	2,400 BID	37	4 (10.8)
		Placebo		39	20 (51.3)‡
Leclerc et al[125]*†	Elective knee	Enoxaparin	2,400 BID	41	8 (19.5)
		Placebo		54	35 (64.8)‡
Hoek et al[126]*	Elective hip	Lomoparin	750 BID	97	15 (15.5)
		Placebo		99	56 (56.6)‡
Planes et al[130]*	Elective hip	Enoxaparin	3,200 OD	120	15 (12.5)
		SH	5,000 TID	108	27 (25.0)‡
Levine et al[132]*†	Elective hip	Enoxaparin	2,400 BID	258	50 (19.4)
		SH	7,500 BID	263	61 (23.2)
Estoppey et al[133]*	Elective hip	Lomoparin	750 BID	146	25 (17.1)
		SH/DHE	5,000/0.5 BID	149	48 (32.2)‡
Leyvraz et al[134]	Elective hip	Fraxiparin	Adjusted dose	174	22 (12.6)
		SH	Adjusted dose	175	28 (16)
Dechavanne et al[135]	Elective hip	Fragmin	2,500 BID	38	2 (5.3)
		Fragmin	2,500 BID/5,000 OD	39	3 (7.7)
		SH	Adjusted dose	38	4 (10.5)
Eriksson et al[136]*	Elective hip	Fragmin	5,000 OD	63	19 (30.2)
		SH	5,000 TID	59	25 (42.4)
Lassen et al[137]	Elective hip	Enoxaparin	3,200 OD	108	7 (6.5)
		Dextran 70	500 mL × 5	111	24 (21.6)‡
Spiro et al[138]*	Elective hip	Enoxaparin	800 OD	116‡	36 (31)
		Enoxaparin	3,200 OD	149	21 (14)
		Enoxaparin	2,400 BID	143	16 (11)
Bergqvist et al[140]	Fractured hip	Lomoparin	750 BID	107	14 (13)
		Dextran 70	500 mL × 5	115	40 (35)‡

Abbreviations: OD, once daily; BID, twice daily; TID, three times daily.

*Double blind trials.

†Prophylaxis commenced postoperatively.

‡$P < .05$.

Table 7. Randomized Trials of Prophylactic LMWH in Orthopedic Surgery

Study	Treatment	Dose (anti-Xa U)	No. Patients	Bleeding No. (%)
Turpie et al[124]*	Enoxaparin	2,400 BID	50	2 (4.0)
	Placebo		50	2 (4.0)
Leclerc et al[125]*	Enoxaparin	2,400 BID	66	4 (6.1)
	Placebo		65	5 (7.6)
Hoek et al[126]*	Lomoparin	750 BID	97	6 (6.1)
	Placebo		99	0†
Planes et al[130]*	Enoxaparin	3,200 OD	124	3 (2.4)
	SH	5,000 TID	112	2 (1.8)
Levine et al[132]*	Enoxaparin	2,400 BID	333	17 (5.1)
	SH	7,500 BID	332	31 (9.3)†
Leyvraz and Postel[134]	Fraxiparin	Adjusted dose	198	1 (0.5)
	SH	Adjusted dose	199	3 (1.5)
Dechavanne et al[135]	Fragmin	2,500 BID	41	7 (17.1)
	Fragmin	2,500 BID/5,000 OD	41	4 (10.0)
	SH	Adjusted dose	39	4 (10.3)
Eriksson et al[136]*	Fragmin	5,000 OD	67	1 (1.5)
	SH	5,000 TID	68	5 (7.4)
Lassen et al[137]	Enoxaparin	3,200 OD	108	15 (13.9)
	Dextran 70	500 mL × 5	111	26 (23.4)
Spiro et al[138]*	Enoxaparin	800 OD	161	8 (5.0)
	Enoxaparin	3,200 OD	199	21 (10.6)
	Enoxaparin	2,400 BID	208	27 (13.0)
Bergqvist et al[140]	Lomoparin	750 BID	143	6 (4.2)
	Dextran 70	500 mL × 5	146	3 (2.1)

Abbreviations: OD, once daily; BID, twice daily; TID, three times daily.

*Double blind trials.

†$P < .05$.

received either Enoxaparin 30 mg (2,400 anti-Xa U) twice daily or placebo. The rate of deep vein thrombosis was reduced from 65% in the placebo group to 20% in the LMWH group, $P < .01$. No difference was detected in bleeding between groups. In the study reported by Hoek et al,[126] 196 patients having hip replacement were randomized to receive either Lomoparin 750 anti-Xa U twice daily or placebo. The rate of deep vein thrombosis was 57% in the placebo control group compared with 16% in the heparinoid group, $P = .001$. There was no difference in major bleeding between groups but there were six minor wound hematomas in the heparinoid group compared with none in the placebo group.

LMWHs have been compared with a variety of other methods of prophylaxis, including low-dose SH (two studies), low-dose SH and dihydroergotamine (DHE), (one study), adjusted-dose heparin (two studies), dextran (two studies), and warfarin (one study).

Planes et al[130] randomized 237 patients undergoing elective hip replacement to either Enoxaparin LMWH 40 mg (3,200 anti-Xa U) once daily or SH 5,000 U three times daily; both regimens commenced preoperatively. The rate of deep vein thrombosis was reduced from 25% with SH to 12.5% with LMWH, $P = .01$. No difference in bleeding was detected between groups. Levine et al[132] randomized 665 patients undergoing hip replacement to either Enoxaparin 30 mg twice daily or SH 7,500 U twice daily; both regimens commenced 12 hours postoperatively. The rate of deep vein thrombosis was 23% in the SH heparin group compared with 19% in the LMWH group, a difference that was not statistically significant. However, the incidence of clinically important bleeding was significantly higher (9%) in the SH group than in the LMWH group (5%), $P < .05$.

Estoppey et al[133] compared Lomoparin 750 U twice daily with SH 5,000 U twice daily plus DHE in 295 patients undergoing elective hip surgery; both regimens were commenced preoperatively. The incidence of venous thrombosis was 17% in the Lomoparin group and 32% in the SH/DHE group ($P = .003$). There was no difference in the incidence of bleeding between the two groups.

Leyvraz et al[134] randomized 349 patients having elective hip surgery to adjusted-dose Fraxiparin once daily or adjusted-dose heparin three times daily commencing preoperatively. The incidence of thrombosis was 13% in the LMWH group and 16% in the SH group (not significant). There was no difference in the incidence of bleeding between the two groups.

Dechavanne et al[135] randomized 124 patients undergoing hip replacement to Fragmin 2,500 anti-Xa U twice daily (group 1), Fragmin 2,500 anti-Xa U twice daily during the first 48 hours postoperatively and then 5,000 anti-Xa U daily (group 2), or adjusted-dose heparin. The first dose was administered 2 hours before surgery in all groups. The rate of deep vein thrombosis was 4.9% in Fragmin group 1, 7.3% in Fragmin group 2, and 10% in the SH group. These rates were not statistically significantly different. No difference was detected in bleeding.

Eriksson et al[136] compared the LMWH Fragmin with SH in 136 patients who had elective total hip replacement. Patients received either LMWH 5,000 U once daily or SH 5,000 U 8 hourly. LMWH was commenced 12 hours before operation, and SH was commenced 2 hours preoperatively;

both regimens were continued for 10 days. Deep vein thrombosis was diagnosed in 19 (30%) of 63 in the LMWH group and in 25 (42%) of the 59 who received SH ($P = .189$). Pulmonary embolism was detected by routine ventilation-perfusion scanning in eight patients (12.3%) who received LMWH and 19 (30.6%) who received SH ($P = .016$). Only three patients had clinical signs of embolism. Total loss of blood and the total amount of blood that was transfused were significantly reduced in the patients who received LMWH.

Lassen et al[137] randomized 219 patients undergoing hip replacement to either Enoxaparin 40 mg (3,200 anti-Xa U) once daily commencing preoperatively or Dextran. The rate of deep vein thrombosis was 6.5% in the LMWH group compared with 21.6% in the Dextran group, $P < .01$. No difference was detected in bleeding between groups.

Spiro et al[138] reported on a double blind randomized trial in 572 patients who had elective hip replacement. Patients received one of the following dosage regimens of Enoxaparin; 10 mg (800 anti-Xa U) once daily, 40 mg (3,200 anti-Xa U) once daily, or 30 mg (2,400 anti-Xa U) twice daily. Treatment was initiated postoperatively within 24 hours of surgery. Although there was no untreated control group, this study provides useful information on efficacy because the incidence of thrombosis was significantly higher in the lowest dose group than in the other two groups. The incidence of venous thrombosis was 31% in the group receiving 10 mg once daily, 14% in the group receiving 40 mg once daily, and 11% in those receiving 30 mg twice daily. There was no difference in the incidence of bleeding between the three groups.

Heit et al[139] reported the results of a multicentered randomized trial comparing RD LMWH with warfarin in 936 patients undergoing either elective total hip arthroplasty (THA) or total knee arthroplasty (TKA). The patients were allocated to receive one of three treatments: group 1, LMWH 50 anti-Xa U/kg subcutaneously (sc) twice daily; group 2, LMWH 90 anti-Xa U/kg sc once daily; or group 3, warfarin at a dose targeted to maintain the prothrombin time at a ratio of 1.2 to 1.5 (International Normalized Ratio of ~2.0 to 3.0). LMWH was commenced approximately 12 hours postoperatively and warfarin was commenced the night before surgery. Efficacy was evaluated by unilateral venography performed on the side of surgery. Therefore, although the results of comparisons of the incidence of thrombosis between groups in this study are valid, the absolute rates of thrombosis are underestimates of the true rates by approximately 20% to 30%. The overall incidence of thrombosis in group 1 was 16%; in group 2, 21%; and in group 3, 27%. The differences between the LMWH group 1 and the warfarin group was significant ($P < .001$). For patients undergoing THA, the incidence of thrombosis was 7% in group 1 (n = 169); 14% in group 2 (n = 168); and 13% in group 3 (n = 166). These differences were not statistically significant ($P = .063$ for the comparison of group 1 with warfarin). For patients undergoing TKA, the incidence of thrombosis was 25% in group 1 (n = 145); 29% in group 2 (n = 145); and 43% in group 3 (n = 143). The differences between each of the LMWH groups and the warfarin group was statistically significant ($P = .002$ between groups 1 and 3; and $P = .025$ between groups 2 and 3). There were no differences in bleeding between the three groups.

There has only been one randomized trial performed in patients with hip fracture. In this study reported by Bergqvist et al,[140] 308 patients were randomly allocated to receive Lomoparin 750 U twice daily or Dextran, both regimens commencing preoperatively. The incidence of thrombosis was 10% in the Lomoparin group and 30% in the Dextran group ($P < .001$). The number of units of blood transfused was significantly higher in the Dextran group.

Thus, LMWHs are very effective, safe, and convenient to use in high-risk patients undergoing major orthopedic surgical procedures. Compared with placebo the relative risk reduction for all thrombi and for proximal vein thrombi is approximately 70%. This impressive reduction occurs without an increase in clinically important bleeding. Although the number of studies comparing LMWHs with other forms of prophylaxis is small, the limited findings suggest that LMWHs are approximately 50% more effective than standard low-dose heparin 5,000 U three times daily without any apparent difference in bleeding. However, when the dose of SH is increased to 7,500 U the difference in efficacy is lost, but the incidence of bleeding is increased in the SH group. From the limited data available, LMWHs appear to be as effective and safe as adjusted-dose heparin and warfarin and more effective than Dextran in THA and more effective than warfarin in TKA.

Medical patients. Experience with LMWHs in medical patients is less than with surgical patients, but the results are impressive both in terms of efficacy and safety. In all of the reported studies, radioactive fibrinogen leg scanning was used to detect venous thrombosis.

LMWHs have been compared to placebo in two studies of patients with ischaemic stroke[141,142] and in one study in undifferentiated high-risk medical patients over the age of 65[143] (Table 8).

Turpie et al[141] randomized 75 patients with stroke to either Lomoparin (750 anti-Xa U) or placebo, both administered twice daily. There was a statistically significant reduction in deep vein thrombosis from 28% to 4% in the patients who received the heparinoid. Prins et al[142] randomized 60 patients with stroke to either Fragmin 2,500 anti-Xa U twice daily or placebo; there was a statistically significant reduction in deep vein thrombosis in patients who received the LMWH from 50% to 20%. In both of these trials no difference was detected in bleeding between treatment groups. Dahan et al[143] randomized 275 medical patients over 65 years to Enoxaparin LMWH 60 mg (4,800 anti-Xa U) once daily or placebo. The incidence of venous thrombosis was 9.1% in the placebo group and 3% in the LMWH group ($P = .03$). There was no difference in bleeding, but there was a significant increase in the incidence of injection site hematomas in the LMWH group.

LMWHs have been compared with low-dose SH in two studies. Turpie et al[144] randomized patients with ischaemic stroke to either Lomoparin 750 anti-Xa U administered twice daily or SH 5,000 U administered twice daily. Thirty-

Table 8. Randomized Trials of Prophylactic LMWH in Medical Patients

Study	Condition	Treatment	Dose (anti-Xa U)	No. Patients	DVT No. (%)	Bleeding No. (%)
Turpie et al[141]*	Stroke	Lomoparin	750 BID	50	2 (4.0)	1 (2.0)
		Placebo		25	7 (28.0)†	2 (8.0)
Prins et al[142]*	Stroke	Fragmin	2,500 BID	30	6 (30)	4 (13.3)
		Placebo		30	15 (50)†	2 (6.7)
Dahan et al[143]*	Elderly	Enoxaparin	4,800 OD	132	4 (3.0)	1 (1.0)
		Placebo		131	12 (9.1)†	3 (2.3)
Turpie et al[144]*	Stroke	Lomoparin	750 BID	45	4 (8.9)	5 (11.1)
		SH	5,000 BID	42	13 (31)†	3 (7.1)
Green et al[145]	Spinal cord injury	Logiparin	3,500 OD	20	0	0
		SH	5,000 TID	21	5 (23.8)†	2 (9.5)

Abbreviations: OD, once daily; BID, twice daily; TID, three times daily.
*Double blind trial.
†$P < .05$.

one percent of SH patients developed fibrinogen leg scan-detected thrombosis compared with 8.9% of the heparinoid patients, $P = .02$. There was no difference detected in hemorrhagic complications between groups. Green et al[145] randomized 41 patients with spinal cord injury to either Logiparin 3,500 anti-Xa U once daily or SH 5,000 U three times daily. No patients who received Logiparin experienced thromboembolism compared with five who received SH, $P = .02$. No statistically significant difference was detected in bleeding between the two groups.

Thus, LMWHs produce a relative risk reduction in venous thrombosis of between 60% and 90% compared to placebo in patients with stroke and in high-risk medical patients without an increase in clinically important bleeding. In both of the studies that compared LMWHs with low-dose SH in medical patients, patients randomized to receive LMWH showed an impressive (>70%) risk reduction in thrombosis that was statistically significant.

TREATMENT OF ESTABLISHED THROMBOSIS

LMWHs have been compared with SH for the treatment of established venous thrombosis in a number of large studies (Tables 9 and 10). The early small pilot trials[146-148] and four of the larger more recent trials[149-153] compared the size of the thrombus in a pretreatment and 5- to 10-day posttreatment venogram and used the change in size as the outcome measure (Table 9). Two recent large studies used the more clinically relevant endpoints of confirmed symptomatic recurrent thromboembolism.[152,154] In the early trials, the LMWH tested showed a trend toward superiority over SH in terms of reduction in thrombus size; and this impression was confirmed in the larger randomized trials.

In the first of the six larger trials, Bratt et al[149] reported on 119 patients who were randomly allocated to receive either Fragmin LMWH 120 anti-Xa U/kg subcutaneously twice daily or SH as a continuous IV infusion. The dosage was adjusted in each treatment group to maintain a test of coagulation within a defined therapeutic range. At repeat venography performed after 5 to 7 days of treatment 76% of patients in the LMWH group compared with 61% in the SH group showed improvement in the venographic score. No difference was detected in bleeding. On long-term follow-up, no difference was detected in the rates of rethrombosis between groups (7.2% *v* 10.9%, respectively).

Albada et al[153] performed a randomized double blind trial in 194 patients with symptomatic venous thromboem-

Table 9. LMWH for Established Venous Thrombosis: Change in Clot Size

Study	Treatment	Dose (anti-Xa U)	Patient No.	Venogram		
				Imp	UC	Worse
Faivre et al[146]	CY222	750 IC/kg BID subcu	33	19	11	0
	SH	500/kg BID subcu	35	19	8	2
Bratt et al[147]	Fragmin	240/kg BID subcu	12	6	6	0
	Fragmin	120/kg BID subcu	13	10	3	0
	SH	240/kg BID IV	29	14	12	3
Holm et al[148]	Fragmin	7,500 BID subcu	29	10	14	1
	SH	15,000 BID subcu	27	12	11	2
Bratt et al[149]	Fragmin	120/kg subcu BID	45	34	9	2
	SH	30,000/24 h IV	49	30	16	3
Duroux and Beclere[150]	Fraxiparin	255 IC/kg BID subcu	77	54	23	
	SH	20/kg/h IV	71	44*	27	
Simonneau[151]	Enoxaparin	1 mg/kg BID subcu	67	28		
	SH	Continuous IV	67	18		
Prandoni[152]	Fraxiparin	12,500-17,500 IC BID subcu	85	50	28	5
	SH	Continuous IV	85	36	35	14

Abbreviations: Imp, improved; UC, unchanged; IC, Institute Choay units; BID, twice daily; subcu, subcutaneously.
*$P < .05$.

Table 10. LMWH for Established Venous Thrombosis

Study	Treatment	Dose (anti-Xa U)	No. Patients	Recurrent VTE No. (%)	Bleeding
Bratt et al[149]	Fragmin	120/kg subcu BID	55	4 (7.2)	0
	SH	30,000/24 h IV	55	6 (10.9)	2 (3.6)
Albada et al[153]*	Fragmin	15,000/24 h IV	96	—	37 (38.5)
	SH	30,000/24 h IV	98	—	48 (48.9)
Duroux and Beclere[150]	Fraxiparin	255 IC/kg/12 h subcu	85	3 (3.5)	2 (2.4)
	SH	20/kg/h IV	81	2 (2.5)	4 (4.9)
Simonneau[151]	Enoxaparin	1 mg/kg BID subcu	134	0	0
	SH	Continuous IV		1	0
Prandoni[152]	Fraxiparin	<55 kg 12,500 IC BID subcu 50-80 kg 15,000 IC BID subcu >80 kg 17,500 IC BID subcu	85	6 (7.1)	4 (4.7)
	SH	Continuous IV	85	11 (12.9)	9 (10.6)
Hull et al[154]*	Logiparin	175/kg OD subcu	213	7 (3.3)	7 (3.3)
	SH	Continuous IV	213	13 (6.1)	16 (7.5)

Abbreviations: VTE, venous thromboembolism; OD, once daily; BID, twice daily.
*Double blind trials.

bolism confirmed by either impedance plethysmography or ventilation-perfusion lung scanning. Patients received either SH (30,000 U) or Fragmin (15,000 anti-Xa U) by continuous infusion and the dose of each agent was adjusted to maintain the anti-factor Xa level in a defined therapeutic range. Efficacy was assessed by a second lung scan (which, however, was performed on less than 50% of the patients) and by improvement in the impedance plethysmographic result (an outcome measure of uncertain clinical relevance). Safety was assessed by recording bleeding complications. There was a 21% reduction in bleeding in the LMWH group; this trend was not statistically significant.

In the trial reported by Duroux and Beclere,[150] 166 patients with proximal deep vein thrombosis were randomized to receive either Fraxiparin 255 anti-Xa IC U/kg subcutaneously twice daily in a fixed dose or SH administered by continuous IV infusion. The initial dose of Fraxiparin was based on body weight and then not altered, while the dose of SH was adjusted to maintain the APTT within the therapeutic range. Patients had venography at diagnosis and after 10 days of therapy. There was a statistically significant reduction in clot size in both groups by day 10, but the improvement in the LMWH group was statistically significantly greater than in the SH group. No difference was detected in bleeding between the groups nor in recurrent thrombosis during the 3 months after randomization.

Simonneau[151] randomized 134 patients with proximal vein thrombosis into 10 days of treatment with either Enoxaparin (2 mg/kg/d in two daily injections sc) or SH by continuous infusion that was adjusted to maintain the APTT in the therapeutic range. At 10 days 42.5% of patients in the LMWH group and 27.3% in the SH group showed an improvement in their venographic score, $P < .007$. Two thromboembolic complications occurred in the SH group and none in the LMWH group. There were no serious bleeding complications in either group. The mean anti-factor Xa levels were approximately 0.9 U/mL in the LMWH group.

Prandoni[152] randomized 170 patients with venographically confirmed proximal deep vein thrombosis to either Fraxiparin (using a weight adjusted regimen of between 12,500 and 17,000 anti-Xa IC U twice daily) or SH administered by continuous IV infusion adjusted to maintain the APTT at 1.5 to 2 times control. The outcome measures were symptomatic recurrence at 10 days and 6 months. At 10 days, 4 of 85 (4.7%) patients receiving SH developed recurrence compared with 1 of 85 (1.2%) receiving LMWH. At 6 months, 11 of 85 (12.9%) of SH patients developed recurrent thromboembolism compared with 6 of 85 LMWH patients (7.1%), $P = .2$. All patients underwent repeat venography after 7 days of therapy. In the SH patients, the second venogram was improved in 36 patients, unchanged in 35, and worse in 14 patients. In contrast, in the LMWH group the second venogram was improved in 50 patients, unchanged in 28, and worse in 5 patients, $P = .3$. Bleeding occurred in 10.6% of the SH patients compared with 3.5% in the LMWH patients, $P = .1$. The mortality at 6 months was 12 of 85 (14.1%) in the SH group and 6 of 85 (7.1%) in the LMWH group (not significant). Most deaths were cancer related.

Hull et al[154] reported the results of their double blind randomized study comparing Logiparin 175 anti-factor Xa U/kg daily sc with SH in patients with proximal vein thrombosis. The LMWH was administered in a fixed dose and the SH by continuous infusion adjusted to maintain the APTT in the therapeutic range. The main outcome measure was symptomatic recurrence at 3 months. The incidence of recurrent venous thromboembolism was 6.1% in the SH group and 3.3% in the LMWH group, $P = .3$. The mortality at 3 months was 9.9% in the LMWH group and 21% in the SH group ($P = .04$); most deaths were cancer related. At 10 days there were 16 bleeding events in the SH group (10 major) and seven in the LMWH group (one major). The difference in major bleeding was significantly greater in the SH group ($P < .05$).

The results of these studies suggest that in patients with proximal vein thrombosis LMWHs administered in either a fixed or weight adjusted dose sc are more effective and

produce less bleeding than conventional APTT-adjusted SH administered by continuous infusion. Thus, when compared on the basis of improvement in a second venogram performed after 5 to 10 days of treatment, there was either a significantly greater improvement or trend for a greater improvement in the quantitative venographic score in patients treated with LMWHs compared to those treated with SH. The two most recent studies that were relatively large and used clinically relevant outcome measures reported similar findings; namely, a strong trend (50%) in reduction of recurrent venous thromboembolism in the LMWH group; a greater than 50% reduction in bleeding in the LMWH group that was significant for major bleeding in one study[154]; and a surprising 50% or greater reduction in mortality, which was mainly associated with malignancy. This latter observation could be a chance finding unrelated to antithrombotic treatment, though, because the antimortem diagnosis of major embolism in sick patients is notoriously insensitive and autopsies were not usually performed, these deaths could have been thromboembolic in nature. Further studies with the power to detect true differences of approximately 50% are required before a definitive conclusion can be reached that some LMWHs are both safer and more effective than SH in the treatment of proximal vein thrombosis, but the present findings are very suggestive of this conclusion. The greater efficacy of LMWHs (based on significant differences in the venographic score and strong trends in symptomatic recurrences) has biologic plausibility. Thus, LMWHs are administered in much greater anticoagulant doses than SH, but because they produce less marked nonanticoagulant hemostatic effects, these higher anticoagulant doses of LMWHs are not accompanied by increased bleeding.

UNRESOLVED ISSUES

A number of unresolved issues remain and need to be addressed. For prophylactic use, postoperative dosing of LMWHs is effective[124,125,129,132,138,139] but it is unknown whether it is as effective as preoperative administration. This question can only be answered by an appropriately designed randomized trial. The use of postoperative prophylaxis is particularly applicable when spinal anesthesia is used, and after major trauma. Once-daily administration of LMWHs is highly effective when prophylaxis is started preoperatively, but twice-daily administration may be preferable if postoperative administration is used; this question is being addressed in a number of ongoing studies.

A major issue that has probably been resolved, but because of its great importance requires further study, is the relative efficacy and safety of fixed dose LMWHs and SH for the treatment of venous thrombosis. If LMWHs can replace SH, then for many patients (we have estimated 50%) with venous thrombosis out-of-hospital treatment might be possible, a radical change from current practice that would reduce cost and improve patient convenience. Other unresolved issues related to the use of LMWHs are: (1) their neutralization with protamine; (2) the safety of their use in pregnancy; (3) the risk of osteoporosis with their long-term use; and (4) the risk of thrombocytopenia relative to the risk with SH.

The anticoagulant and hemorrhagic effects of standard heparin are neutralized by an equimolar concentration of protamine sulfate. Equimolar concentrations of protamine sulfate neutralize the anti-factor IIa activity but result in only partial neutralization of the anti-factor Xa of LMWHs,[155-158] probably because protamine sulfate does not bind to the very low molecular weight components. However, studies in experimental animal models indicate that increased microvascular bleeding produced by very high concentrations of LMWHs is neutralized by protamine sulfate.[158] Whether protamine sulfate will neutralize clinically important bleeding is uncertain.

Heparin is the anticoagulant of choice in pregnancy because it does not cross the placenta and therefore does not affect fetal coagulation.[159] Studies in humans indicate that LMWHs also do not cross the placental barrier,[160-162] and descriptive studies suggest they might be safe and effective.[163] In contrast, there is a report that treatment of pregnant sheep with an LMWH results in the release a dermatan sulfate-like molecule into the fetal circulation[164]; whether this phenomenon occurs in humans is unknown.

The long-term use of heparin can be complicated with osteoporosis.[165] Although there is a case report of successful use of an LMWH in a patient whose treatment with SH was complicated with symptomatic osteoporosis,[163] there is experimental evidence that both LMWH and SH inhibit type 1 collagen and DNA synthesis in fetal rat calvariae, suggesting that both affect bone metabolism.[166] More information from appropriately designed studies will be required before it can be concluded that this troublesome side effect of SH will be avoided by using LMWHs.

When they were developed initially, it was hoped that the use of LMWHs would not be complicated by heparin-induced thrombocytopenia (HIT), and that these new preparations could be used safely to replace SH in patients with HIT. This expectation has not been realized. Although there is an impression that the incidence of thrombocytopenia might be less with LMWHs than SH, this view has not been investigated in a properly designed clinical study. There are reports that the administration of LMWHs can be associated with the development of thrombocytopenia both in previously unexposed individuals[167] and in those with a history of HIT.[168] There is also evidence that LMWH preparations cross-react with plasma from patients with recent HIT.[169] In contrast to the LMWHs, the heparinoid Lomoparin, which is said to be free of contaminating heparin, has minimal cross-reactivity in in vitro assays for HIT[170] and has been used successfully in patients with a history of heparin-induced thrombocytopenia.[170] However, there have been rare reports of thrombocytopenia developing in patients treated with Lomoparin; whether these reported associations are causal or coincidental is unclear.

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