Drug Therapy

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LOW-MOLECULAR-WEIGHT HEPARINS

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AFTER almost two decades of intensive research, low-molecular-weight heparins have established their niche as an important class of antithrombotic compounds. The demonstration that these compounds are safe and effective for the prevention and treatment of venous thromboembolism has led to the licensing of several of them in Europe and North America. In addition, danaparoid sodium, which is a mixture of dermatan sulfate, heparan sulfate, and chondroitin sulfate, is often used for the treatment of heparin-induced thrombocytopenia.[1] Low-molecular-weight heparins have replaced unfractionated heparin in many parts of Europe but are only now finding their place in North America. Their use is likely to increase, however, because two recent studies show that about half of all patients with venous thrombosis can be safely treated with low-molecular-weight heparins without hospital admission,[2,3] and heparin-induced thrombocytopenia, a dangerous complication of unfractionated-heparin therapy, occurs less frequently with low-molecular-weight heparins.[4]

MECHANISMS OF ACTION OF LOW-MOLECULAR-WEIGHT HEPARINS

Like unfractionated heparin, low-molecular-weight heparins are glycosaminoglycans consisting of chains of alternating residues of D-glucosamine and uronic acid, either glucuronic acid or iduronic acid.[5] Unfractionated heparin is a heterogeneous mixture of polysaccharide chains ranging in molecular weight from about 3000 to 30,000. Low-molecular-weight heparins are fragments of unfractionated heparin produced by controlled enzymatic or chemical depolymerization processes that yield chains with a mean molecular weight of about 5000 (Table 1). Both unfractionated heparin and low-molecular-weight heparins exert their anticoagulant activity by activating antithrombin (previously known as antithrombin III). Their interaction with antithrombin is mediated by a unique pentasaccharide sequence that is randomly distributed along the heparin chains. Approximately one third of the chains of unfractionated heparin, but only 15 to 25 percent of the chains of low-molecular-weight heparins, contain the pentasaccharide sequence.[6]

Binding of the pentasaccharide to antithrombin causes a conformational change in antithrombin that accelerates its interaction with thrombin and activated factor X (factor Xa) by about 1000 times.[5] The chief difference between unfractionated heparin and low-molecular-weight heparins is in their relative inhibitory activity against factor Xa and thrombin.[6] Any pentasaccharide-containing heparin chain can inhibit the action of factor Xa simply by binding to antithrombin and causing a conformational change (Fig. 1). In contrast, to inactivate thrombin, heparin must bind to both antithrombin and thrombin, thereby forming a ternary complex.[7] This complex can be formed only by pentasaccharide-containing heparin chains composed of at least 18 saccharide units. Whereas most of the chains of unfractionated heparin are at least 18 saccharide units long, fewer than half of those of low-molecular-weight heparins are of sufficient length to bind to both antithrombin and thrombin.[8] Consequently, unlike unfractionated heparin, which has equivalent activity against factor Xa and thrombin, low-molecular-weight heparins have greater activity against factor Xa.

Tissue-factor-pathway inhibitor may also contribute to the inhibitory activity of low-molecular-weight heparins and unfractionated heparin against factor Xa.[9] First, tissue-factor-pathway inhibitor forms a complex with and inactivates factor Xa, and then the complex inactivates factor VIIa.[10] Both unfractionated heparin and low-molecular-weight heparins release tissue-factor-pathway inhibitor from endothelium[10,11] and enhance its inhibitory activity against factor Xa.[12]

The relative importance of inhibition of factor Xa and inhibition of thrombin in mediating the antithrombotic effect of unfractionated heparin and low-molecular-weight heparins is unclear, but there is evidence that both are necessary. In vitro, thrombin is the most important target, because inhibition of thrombin prevents feedback activation of factors V and VIII,[13,14] but inhibition of factor Xa also confers antithrombotic activity.[15]

PHARMACOKINETICS OF LOW-MOLECULAR-WEIGHT HEPARINS

Low-molecular-weight heparins produce a more predictable anticoagulant response than unfractionated heparin,[16] reflecting their better bioavailability, longer half-life, and dose-independent clearance. Thus, when low-molecular-weight heparins are given subcutaneously in low doses, the recovery of anti–factor Xa activity approaches 100 percent, as compared with about 30 percent with unfractionated

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Table 1. Comparison of Low-Molecular-Weight Heparin Preparations.

Preparation	Method of Preparation	Mean Molecular Weight	Anti-Xa: Anti-IIa Ratio*
Ardeparin (Normiflo)	Peroxidative depolymerization	6000	1.9
Dalteparin (Fragmin)	Nitrous acid depolymerization	6000	2.7
Enoxaparin (Lovenox)	Benzylation and alkaline depolymerization	4200	3.8
Nadroparin (Fraxiparine)	Nitrous acid depolymerization	4500	3.6
Reviparin (Clivarine)	Nitrous acid depolymerization, chromatographic purification	4000	3.5
Tinzaparin (Innohep)	Heparinase digestion	4500	1.9

*The ratios were calculated by dividing the anti–factor Xa (anti-Xa) activity by the antithrombin (anti-IIa) activity. The ratios are based on information provided by the manufacturers.

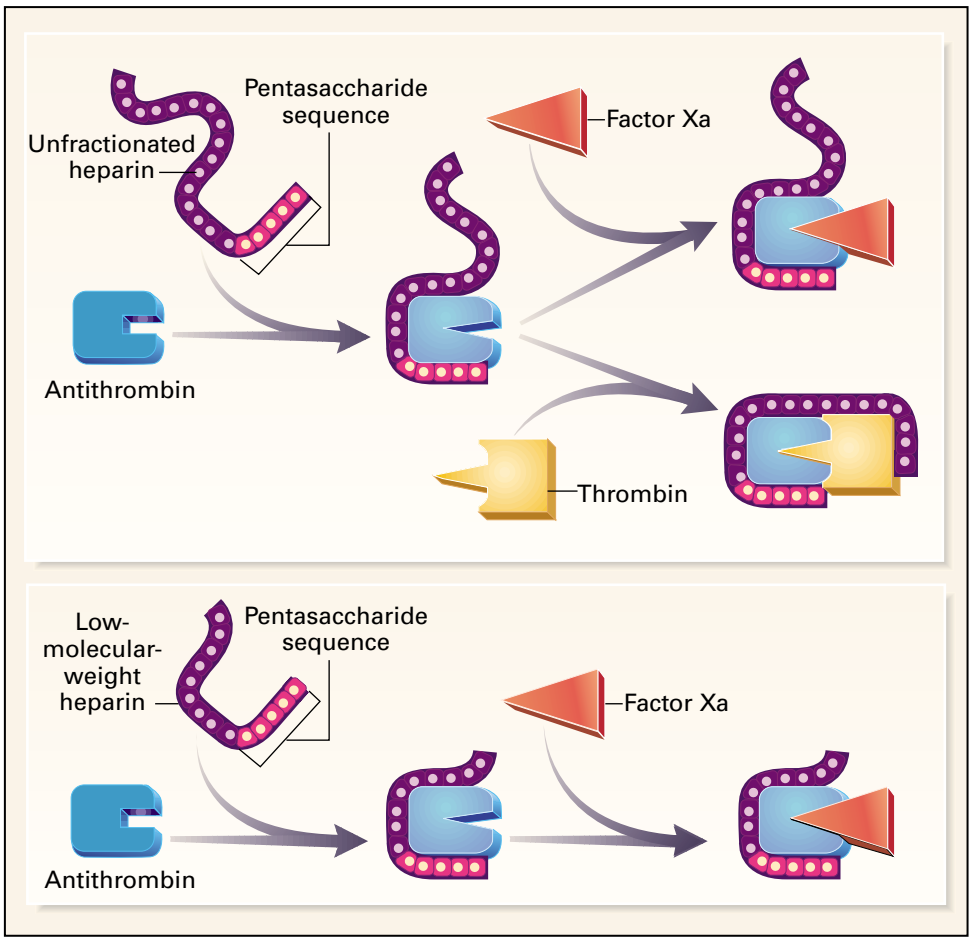

Figure 1. Catalysis of Antithrombin-Mediated Inactivation of Thrombin or Factor Xa by Unfractionated Heparin or Low-Molecular-Weight Heparins.

The interaction of unfractionated heparin and low-molecular-weight heparins with antithrombin is mediated by the pentasaccharide sequence of the drugs. Binding of either to antithrombin causes a conformational change at its reactive center that accelerates its interaction with factor Xa. Consequently, both unfractionated heparin and low-molecular-weight heparins catalyze the inactivation of factor Xa by antithrombin. In contrast to factor Xa inhibition, catalysis of antithrombin-mediated inactivation of thrombin requires the formation of a ternary heparin–antithrombin–thrombin complex. This complex can be formed only by chains at least 18 saccharide units long. This explains why low-molecular-weight heparins have less inhibitory activity against thrombin than unfractionated heparin.

TABLE 2. MECHANISMS RESPONSIBLE FOR THE PHARMACOKINETIC ADVANTAGES OF LOW-MOLECULAR-WEIGHT HEPARINS OVER UNFRACTIONATED HEPARIN.

ADVANTAGE	MECHANISM
More predictable anticoagulant response	Less binding to plasma proteins and to proteins released from activated platelets and endothelial cells
Better bioavailability at low doses	Less binding to endothelium
Dose-independent clearance mechanism	Less binding to macrophages
Longer half-life	Less binding to macrophages

TABLE 3. COMPARISON OF MONITORING REQUIREMENTS FOR CURRENTLY AVAILABLE ANTICOAGULANTS.

INDICATION	MONITORING REQUIREMENTS		
	UNFRACTIONATED HEPARIN	LOW-MOLECULAR-WEIGHT HEPARINS	ORAL ANTICOAGULANTS*
Prophylaxis	None	None	INR
Treatment	APTT or plasma heparin concentrations†	None‡	INR

*INR denotes international normalized ratio. For both prophylaxis and treatment, the dose of oral anticoagulant is usually adjusted to achieve an INR of 2.0 to 3.0.

†APTT denotes activated partial-thromboplastin time. Plasma heparin concentrations can be measured by a chromogenic anti–factor Xa assay or by protamine titration.

‡Plasma anti–factor Xa concentrations should be monitored in patients with renal insufficiency and possibly in those weighing less than 50 kg or more than 80 kg.

heparin.[17] The plasma half-life of low-molecular-weight heparins is two to four times as long as that of unfractionated heparin, ranging from two to four hours after intravenous injection and from three to six hours after subcutaneous injection.[6,18,19] The inhibitory activity of low-molecular-weight heparins against factor Xa persists longer than their inhibitory activity against thrombin, reflecting the more rapid clearance of longer heparin chains. In contrast, unfractionated heparin is eliminated in two phases in a dose-dependent fashion: a rapid, saturable phase reflecting hepatic uptake, and a slower phase corresponding to renal clearance.[20]

The pharmacokinetic differences between low-molecular-weight heparins and unfractionated heparin can be explained by the decreased propensity of the former to bind to plasma proteins, endothelial cells, and macrophages (Table 2). In contrast to low-molecular-weight heparins, unfractionated heparin binds to endogenous plasma proteins, such as histidine-rich glycoprotein, polymeric vitronectin, and fibronectin; to platelet factor 4,[21] which is released from activated platelets; and to high-molecular-weight multimers of von Willebrand factor,[22,23] the storage form of von Willebrand factor that is released from platelets and endothelial cells. Binding of unfractionated heparin to plasma proteins reduces its anticoagulant activity, because less is available to interact with antithrombin,[24] and the unpredictable anticoagulant response reflects the wide variability in plasma concentrations of heparin-binding proteins.[24] Some of these heparin-binding proteins are acute-phase reactants, the concentrations of which increase in ill patients, whereas others, like platelet factor 4 and von Willebrand factor, are released during the clotting process. Because of the unpredictable anticoagulant response,[25] careful laboratory monitoring is essential when unfractionated heparin is given in therapeutic doses (Table 3).

The reduced binding of low-molecular-weight heparins to plasma proteins[26,27] and endothelium[28] accounts for their better bioavailability. Their reduced binding to macrophages explains why they are not cleared by hepatic mechanisms to the same extent as unfractionated heparin and why renal clearance is slower than hepatic uptake, thereby accounting for the longer plasma half-life of low-molecular-weight heparins. The better bioavailability, dose-independent clearance, and decreased affinity for heparin-binding proteins make the anticoagulant response to low-molecular-weight heparins more predictable than that to unfractionated heparin. Consequently, laboratory monitoring is unnecessary except in patients with renal insufficiency[29] and possibly those with a body weight of less than 50 kg or more than 80 kg (Table 3).

Low-molecular-weight heparins cause less bleeding than unfractionated heparin in laboratory animals,[30] for several reasons. First, low-molecular-weight heparins inhibit platelet function less than unfractionated heparin[31] because they bind less to platelets.[32] Second, unlike unfractionated heparin, low-molecular-weight heparins do not increase microvascular permeability.[33] Third, because of their lower affinity for endothelial cells, high-molecular-weight forms of von Willebrand factor, and platelets,[22,23,30] low-molecular-weight heparins are less likely to interfere with the interaction between platelets and vessel walls.

CLINICAL STUDIES

Low-molecular-weight heparins are safe and effective for the prevention and treatment of venous thromboembolism (Table 4). They have also been used successfully in patients with unstable angina or acute thrombotic stroke. The key clinical studies of low-molecular-weight heparins are summarized below. On the basis of these studies, low-molecular-weight heparins are at least as safe and effective as

TABLE 4. ADVANTAGES OF LOW-MOLECULAR-WEIGHT HEPARINS AND RECOMMENDED DOSES FOR THE PREVENTION AND TREATMENT OF THROMBOSIS.

INDICATION	ADVANTAGES OF LOW-MOLECULAR-WEIGHT HEPARINS	RECOMMENDED DOSES*
Prevention		
General surgery	At least as effective as low-dose unfractionated heparin[34] but can be given once daily and cause fewer hematomas at injection sites[35,36]	Low risk† Dalteparin, 2500 U 1–2 hr before surgery and once daily after surgery Enoxaparin, 2000 U 1–2 hr before surgery and once daily after surgery Nadroparin, 3100 U 2 hr before surgery and once daily after surgery Tinzaparin, 3500 U 2 hr before surgery and once daily after surgery High risk‡ Dalteparin, 5000 U 10–12 hr before surgery and once daily after surgery Enoxaparin, 4000 U 10–12 hr before surgery and once daily after surgery
Orthopedic surgery	More effective than low-dose unfractionated heparin[34,37,38]; more effective than warfarin in patients undergoing total knee replacement[39-44]; no monitoring required	Ardeparin, 50 U/kg twice daily starting 12–24 hr after surgery Dalteparin, 5000 U 8–12 hr before surgery and once daily starting 12 hr after surgery Enoxaparin, 3000 U twice daily starting 12–24 hr after surgery or 4000 U once daily starting 10–12 hr before surgery Nadroparin, 40 U/kg starting 2 hr before surgery and once daily after surgery for 3 days; the dose is then increased to 60 U/kg once daily Tinzaparin, 50 U/kg 2 hr before surgery and once daily after surgery or 75 U/kg once daily starting 12–24 hr after surgery
Acute spinal injury	Apparently effective,[45,46] whereas low-dose unfractionated heparin[47] is not, and higher doses of unfractionated heparin cause excessive bleeding[48]	Enoxaparin, 3000 U twice daily
Multiple trauma	More effective than unfractionated heparin[49]	Enoxaparin, 3000 U twice daily
Medical conditions	As effective as low-dose unfractionated heparin but can be given once daily[50,51]	Dalteparin, 2500 U once daily Enoxaparin, 2000 U once daily
Treatment		
Venous thromboembolism	At least as safe and effective as unfractionated heparin[52-54] but can be given subcutaneously without laboratory monitoring, thereby allowing out-of-hospital treatment[2,3]	Dalteparin, 100 U/kg twice daily Enoxaparin, 100 U/kg twice daily Nadroparin, 90 U/kg twice daily Tinzaparin, 175 U/kg once daily
Unstable angina	At least as effective as unfractionated heparin[55-57] but can be given subcutaneously without monitoring	Dalteparin, 100 U/kg twice daily Enoxaparin, 100 U/kg twice daily

*Doses are shown in anti–factor Xa units. Low-molecular-weight heparins are given subcutaneously for both prophylaxis and treatment. The prophylactic doses recommended for each low-molecular-weight heparin preparation are slightly different, but a common rationale underlies these regimens. Lower doses are used for low-risk general surgical or medical patients, whereas higher doses are used for high-risk general surgical or orthopedic surgical patients. When relatively large doses of low-molecular-weight heparins are started preoperatively, the dose is given 10 to 12 hours before surgery, to avoid excessive intraoperative bleeding. Lower doses of low-molecular-weight heparins can be given one to two hours before surgery. The doses used for the treatment of venous thromboembolism or for unstable angina are higher than those used for prophylaxis, and similar regimens are used for each of the low-molecular-weight heparins.

†Low-risk general surgical patients are those undergoing uncomplicated abdominal or pelvic surgery lasting 30 minutes or more.

‡High-risk general surgical patients are those undergoing abdominal or pelvic surgery for cancer or those with previous venous thromboembolism.

unfractionated heparin and are more convenient to use, because they can be given subcutaneously without laboratory monitoring.

PROPHYLAXIS AGAINST THROMBOEMBOLISM

General Surgery

Low-dose unfractionated heparin (5000 U given subcutaneously 2 hours before surgery and every 8 to 12 hours postoperatively) provides safe and effective prophylaxis for patients undergoing general surgery, reducing the risk of venous thromboembolism and fatal pulmonary embolism by 70 percent and 50 percent, respectively, with minimal bleeding.[58] Like unfractionated heparin, low-molecular-weight heparins also are given subcutaneously 2 to 12 hours before surgery but are given only once daily postoperatively. They are marginally better than low-dose unfractionated heparin at preventing venous thromboembolism[59] and cause fewer wound hematomas.[34,35]

Orthopedic Surgery of the Lower Limb

Without prophylaxis, deep-vein thrombosis occurs in 50 to 70 percent of patients undergoing total hip replacement, total knee replacement, or surgery for hip fractures. Low-molecular-weight heparins are safe and effective in these high-risk patients.

Total Hip Replacement

As compared with placebo in randomized clinical trials,[36,60] low-molecular-weight heparins significantly reduced the risk of deep-vein thrombosis (range of risk reduction, 31 percent to 79 percent) without increasing bleeding. Low-molecular-weight heparins were more effective than low-dose unfractionated heparin[59] and equal[61] or superior[62] to adjusted-dose unfractionated heparin (heparin started preoperatively at a dose of 5000 U subcutaneously and continued three times daily postoperatively, with the dose adjusted to maintain the activated partial-thromboplastin time near the upper range of normal).

In three studies that compared low-molecular-weight heparins with low-intensity warfarin (with the dose adjusted to reach an international normalized ratio of 2.0 to 3.0), there was no difference in the rates of thrombosis or bleeding.[39,40,63] A meta-analysis[41] comparing several prophylactic regimens found that low-molecular-weight heparins were the most effective, although their advantage over warfarin and adjusted-dose unfractionated heparin was small. Of these prophylactic options, however, low-molecular-weight heparins are the easiest to administer, because no monitoring is required.

Total Knee Replacement

Low-molecular-weight heparins given after total knee replacement are safe and effective, but the absolute incidence of deep-vein thrombosis remains high (25 to 30 percent, with one quarter of the thromboses being proximal). In all six trials in which low-molecular-weight heparins were compared with low-intensity warfarin,[37-40,42,63] low-molecular-weight heparins were superior. Warfarin was relatively ineffective, because the incidence of venous thrombosis was 45 to 50 percent (10 percent of thromboses were proximal). Two studies demonstrated a small but significant increase in postoperative bleeding with low-molecular-weight heparins as compared with warfarin,[38,63] which is not surprising, because the onset of anticoagulation with warfarin is delayed. A recent audit examining the cause of postoperative bleeding in patients treated with low-molecular-weight heparins suggests that up to 80 percent of bleeding episodes are associated with initiation of treatment too soon after surgery (Cooley M, Rhone–Poulenc Rorer: personal communication). Low-molecular-weight heparins should not be given for at least 12 hours after surgery.

Surgery for Hip Fracture

As compared with placebo, both low-dose unfractionated heparin[43] and low-molecular-weight heparins[44] result in a 45 percent reduction in the incidence of deep-vein thrombosis in patients undergoing surgery for hip fracture. Low-intensity warfarin decreases the incidence of venous thrombosis to a similar extent.[64] No trial has yet compared low-molecular-weight heparins with low-intensity warfarin. Low-molecular-weight heparins are a good choice for prophylaxis in patients undergoing surgery for hip fracture. Treatment should be started preoperatively if a delay in surgery is expected. Although warfarin is also effective in these patients, it is less convenient, because the timing of surgery is often difficult to predict.

Acute Spinal Cord Injury

Deep-vein thrombosis develops in about 40 percent of patients with acute spinal cord injuries. The period of greatest risk is within two weeks after injury,[65] when the incidence of symptomatic venous thrombosis and pulmonary embolism may be as high as 14.5 percent and 4.6 percent, respectively. Two small trials suggest that low-molecular-weight heparins are effective in patients with acute spinal cord injuries.[45,66] Adjusted-dose unfractionated heparin may also be effective when given in doses sufficient to produce an activated partial-thromboplastin time in the lower therapeutic range,[46] but this regimen causes an unacceptably high rate of bleeding. Although neither intermittent pneumatic compression[48] nor low-dose unfractionated heparin[67] is effective alone, intermittent pneumatic compression appears to be effective when combined with low-dose unfractionated heparin and the use of elastic stockings.[47]

Multiple Trauma

A prospective cohort study of patients with major trauma found a 50 percent incidence of deep-vein thrombosis documented by venography.[68] A recent randomized study of 344 patients with major trauma and without evidence of intracranial bleeding compared low-dose unfractionated heparin with low-molecular-weight heparin started within 36 hours after injury.[49] As compared with low-dose unfractionated heparin, low-molecular-weight heparin reduced the overall rate of venous thrombosis from 44 percent to 31 percent ($P=0.014$) and lowered the incidence of proximal thrombosis from 15 percent to 6 percent ($P=0.09$). Major bleeding occurred in six patients (1.7 percent), five of whom had received low-molecular-weight heparin.

Medical Conditions

Patients with ischemic stroke have an overall incidence of deep-vein thrombosis of 42 percent in the paretic or paralyzed leg.[69] In a randomized trial, low-molecular-weight heparin was better than placebo in reducing the incidence of venous thrombosis, and it did not increase the incidence of bleeding.[70] In another trial, there was no difference in the rates of thrombosis between patients receiving once-daily low-molecular-weight heparin and those receiving placebo,[71] but the dose was very low. Finally, danap-

aroid sodium was superior to low-dose unfractionated heparin in reducing the incidence of deep-vein thrombosis in one trial.[72] On the basis of these data, low-molecular-weight heparins appear to be the best prophylaxis for patients with ischemic stroke.

In a study comparing low-molecular-weight heparin with placebo in medical patients older than 65 years,[73] low-molecular-weight heparin reduced the rate of thrombosis detected by fibrinogen leg scanning from 9.1 percent to 3.0 percent ($P = 0.03$) without any increase in bleeding. In two randomized studies comparing low-dose unfractionated heparin with low-molecular-weight heparins, the rates of venous thrombosis and bleeding were similar.[50,51] Thus, both therapies provide effective prophylaxis for medical patients.

Patency of Femoropopliteal Bypass Grafts

A recent study compared the effect of low-molecular-weight heparin with that of aspirin and dipyridamole on the patency of femoropopliteal bypass grafts.[74] Graft survival at one year was 78 percent in the patients given low-molecular-weight heparin, as compared with 64 percent in those given aspirin and dipyridamole ($P = 0.03$).

Restenosis after Angioplasty

Restenosis occurs in up to 40 percent of patients after successful coronary angioplasty. Two randomized trials evaluated the effect of short-term treatment with low-molecular-weight heparins on the incidence of restenosis.[75,76] As compared with placebo, neither low-molecular-weight heparin alone[75,76] nor the combination of low-molecular-weight heparin and fish oil[76] reduced the incidence of restenosis after coronary angioplasty.

TREATMENT OF THROMBOSIS

Venous Thrombosis

Low-molecular-weight heparins have been compared with unfractionated heparin for the treatment of patients with established deep-vein thrombosis. In eight trials, the effect of therapy on thrombus size was assessed by comparing pretreatment venograms with those obtained after 5 to 10 days of treatment. On the basis of meta-analyses of these studies,[52-54] low-molecular-weight heparins prevented thrombus growth more than unfractionated heparin. A reduction in thrombus size occurred in 64 percent of the patients treated with low-molecular-weight heparins, as compared with 50 percent of those given unfractionated heparin ($P<0.001$). Furthermore, only 6 percent of the patients treated with low-molecular-weight heparins had an increase in thrombus size, as compared with 12 percent of those given unfractionated heparin ($P<0.001$).

Although the clinical importance of changes in post-treatment thrombus size is uncertain, meta-analyses of trials comparing the effects of low-molecular-weight heparins and unfractionated heparin on the incidence of recurrent venous thromboembolism suggest that the former are more effective.[52-54] For example, in one overview analysis,[53] 2.7 percent of the patients treated with low-molecular-weight heparins had recurrences, as compared with 7.0 percent of those given unfractionated heparin ($P<0.001$). Pooled analyses also suggest that low-molecular-weight heparins are safer.[53,54] In the nine studies that could be evaluated, major bleeding occurred in 0.9 percent of the patients treated with low-molecular-weight heparins, as compared with 3.2 percent of those given unfractionated heparin ($P<0.005$). The pooled long-term mortality rate was lower in patients treated with low-molecular-weight heparins than in those given unfractionated heparin (4.3 percent vs. 8.1 percent, $P<0.03$). This effect was almost entirely attributable to differences in the subgroup of patients with cancer[53] and was heavily influenced by the results of two studies.[77,78] Nevertheless, the lower mortality in these trials may reflect superior antithrombotic activity of low-molecular-weight heparins in high-risk patients.

In most trials, low-molecular-weight heparins were given in fixed or weight-adjusted doses by subcutaneous injection either once or twice daily without laboratory monitoring. Two recent trials conducted among patients with deep-vein thrombosis took advantage of the predictable anticoagulant response to compare the effects of low-molecular-weight heparins given subcutaneously twice daily to outpatients with the effects of unfractionated heparin given by continuous intravenous infusion to inpatients.[2,3] The rates of recurrent thromboembolism and major bleeding were similar with both treatments (Table 5). On the basis of these results, unmonitored outpatient therapy with low-molecular-weight heparin appears to be as safe and effective as in-hospital intravenous unfractionated heparin in selected patients with proximal-vein thrombosis. Two recent studies indicate that unmonitored low-molecular-weight heparin is also as safe and effective as intravenous unfractionated heparin in patients with pulmonary embolism. The first study compared these agents in 1021 patients with venous thromboembolism, 26 percent of whom had pulmonary embolism, and reported similar rates of recurrent thromboembolism (5.3 percent and 4.9 percent, respectively) and major bleeding (3.1 percent and 2.3 percent).[79] In the second study, 912 patients with pulmonary embolism were randomly assigned to receive unfractionated heparin or low-molecular-weight heparin. The incidence of death, recurrent venous thromboembolism, or major bleeding was essentially the same in both groups (2.9 percent and 3.0 percent, respectively).[80] These findings may shift the management

TABLE 5. RATES OF RECURRENT THROMBOEMBOLISM, MAJOR BLEEDING, AND DEATH IN TWO RANDOMIZED TRIALS COMPARING LOW-MOLECULAR-WEIGHT HEPARIN GIVEN TO OUTPATIENTS WITH UNFRACTIONATED HEPARIN GIVEN TO INPATIENTS FOR PROXIMAL DEEP-VEIN THROMBOSIS.

EVENT	LEVINE ET AL.[2]		KOOPMAN ET AL.[3]	
	LOW-MOLECULAR-WEIGHT HEPARIN (N=247)	UNFRACTIONATED HEPARIN (N=253)	LOW-MOLECULAR-WEIGHT HEPARIN (N=202)	UNFRACTIONATED HEPARIN (N=198)
	percent			
Recurrent thromboembolism	5.3	6.7	6.9	8.5
Major bleeding	0.5	2.0	2.0	1.2
Death	6.9	8.0	4.0	6.3

of venous thromboembolism from the inpatient to the outpatient setting.

Once-daily subcutaneous low-molecular-weight heparin has also been compared with warfarin for secondary prophylaxis of venous thrombosis after a 10-day course of continuous intravenous unfractionated heparin.[81] The incidence of recurrent venous thromboembolism was similar in patients given low-molecular-weight heparin for three months and those given warfarin (6 percent and 4 percent, respectively), but bleeding was less frequent with low-molecular-weight heparin than with warfarin (4 percent and 13 percent, $P=0.04$). Thus, low-molecular-weight heparins may be a reasonable alternative to warfarin in patients at high risk for bleeding or in whom monitoring is difficult. Low-molecular-weight heparins may be better than unfractionated heparin for secondary prophylaxis, because monitoring is unnecessary and the risk of osteoporosis appears to be lower (see below).

Unstable Angina

The combination of unfractionated heparin and aspirin is the current treatment of choice for patients with unstable angina. In a small, open trial comparing low-molecular-weight heparin plus aspirin, unfractionated heparin plus aspirin, and aspirin alone, low-molecular-weight heparin reduced the risk of myocardial infarction.[82] These promising results prompted three large, randomized trials of low-molecular-weight heparins in patients with unstable angina who were treated with aspirin.[55-57] In the first study, low-molecular-weight heparin or placebo was given for 35 to 45 days.[55] At day 6, the incidence of death or myocardial infarction was lower in the patients given low-molecular-weight heparin than in those given placebo (1.8 percent vs. 4.7 percent, $P<0.001$). In the second and third studies, twice-daily subcutaneous low-molecular-weight heparin was compared with unfractionated heparin given by continuous intravenous infusion.[56,57] The treatment with low-molecular-weight heparin was not monitored, whereas the dose of unfractionated heparin was titrated to achieve a therapeutic activated partial-thromboplastin time. In one study,[56] the incidence of death, myocardial infarction, or recurrent angina in the patients receiving low-molecular-weight heparin was similar to that in the patients receiving unfractionated heparin (9.3 percent and 7.8 percent, respectively; $P=0.42$), as was the need for urgent revascularization procedures (5.2 percent and 5.8 percent, $P=0.48$). In contrast, in the other study,[57] the incidence of death, myocardial infarction, or recurrent angina was 17 percent lower in the patients given low-molecular-weight heparin than in those given unfractionated heparin (16.5 percent vs. 19.8 percent, $P<0.02$), whereas the incidence of major bleeding was similar in both groups (6.5 percent and 7.0 percent, respectively). On the basis of these data, low-molecular-weight heparins appear to be at least as effective as unfractionated heparin in patients with unstable angina, and they are more convenient, because no monitoring is necessary. The dose of low-molecular-weight heparin should not exceed 100 anti–factor Xa units per kilogram of body weight, because higher doses appear to cause excessive bleeding.[83]

Ischemic Stroke

In a study of 312 patients with acute ischemic stroke, patients were randomly assigned to one of two regimens of subcutaneous low-molecular-weight heparin (4100 anti–factor Xa units once or twice daily) or to placebo within 48 hours after the onset of symptoms.[84] The patients were treated for 10 days and followed for 6 months. Low-molecular-weight heparin was superior to placebo; 45 percent of the patients given low-molecular-weight heparin twice

daily and 52 percent of those given low-molecular-weight heparin once daily died or became dependent with regard to activities of daily living, as compared with 65 percent of the patients given placebo ($P = 0.005$). The rate of hemorrhagic transformation of the infarct during the 10-day treatment period was similar in the three groups.

REMAINING QUESTIONS

Preoperative or Postoperative Dosing with Low-Molecular-Weight Heparins

Although anticoagulant prophylaxis started postoperatively reduces the incidence of venous thromboembolism after hip or knee arthroplasty, breakthrough venous thromboembolism develops in about one fifth of patients. This probably occurs because thrombi form during surgery. Whether treatment with low-molecular-weight heparins started preoperatively is more effective is not known. Preoperative dosing may be a problem in patients undergoing spinal anesthesia, although spinal cord bleeding is rare.[85] Furthermore, preoperative low-molecular-weight heparins might increase intraoperative bleeding.

Once-Daily versus Twice-Daily Dosing

With its apparent half-life of three to four hours, administering low-molecular-weight heparins twice daily should be optimal. However, low-molecular-weight heparins are effective when treatment is started preoperatively and continued once daily postoperatively in patients undergoing general surgery or total hip replacement.[59] When started postoperatively, twice-daily treatment with low-molecular-weight heparin was more effective than once-daily therapy in patients undergoing orthopedic procedures.[39,86] On the basis of these results, twice-daily low-molecular-weight heparin is preferred for postoperative therapy in patients who have had orthopedic surgery.

For the treatment of venous thrombosis, low-molecular-weight heparins were given twice daily in most studies. However, once-daily low-molecular-weight heparin was at least as safe and effective as unfractionated heparin in one study,[77] and once-daily dosing is more convenient.

Risk of Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia, which can cause devastating thrombotic complications, is triggered by antibodies directed against complexes of heparin and platelet factor 4 that form on the surface of platelets and activate their Fc receptors.[87] In a recent randomized trial, the incidence of heparin-induced thrombocytopenia was significantly lower in patients given prophylaxis with low-molecular-weight heparin than in those receiving unfractionated heparin.[4] These findings may reflect the fact that low-molecular-weight heparins cause less activation of platelets and release of platelet factor 4 and that their lower affinity for platelet factor 4 results in the formation of fewer complexes.

Low-molecular-weight heparins should not be given to patients with established heparin-induced thrombocytopenia, because they have a high degree of in vitro cross-reactivity with the antibody that causes this disorder[1] and they can cause heparin-induced thrombocytopenia in patients with a history of it.[88-90] Danaparoid sodium, which cross-reacts minimally with heparin antibodies in vitro, has been used successfully in this setting.[1] Alternatively, direct thrombin inhibitors such as hirudin, bivalirudin, or argatroban can be used.

Neutralization of Low-Molecular-Weight Heparins with Protamine Sulfate

When given in equimolar concentrations, protamine sulfate neutralizes the anti-thrombin activity of low-molecular-weight heparins but only partially reverses their anti–factor Xa activity,[91] probably because it fails to bind to the very-low-molecular-weight heparin chains. Although protamine sulfate blocks bleeding induced by low-molecular-weight heparins in laboratory animals,[92] there have been no studies in humans.

Safety of Low-Molecular-Weight Heparins in Pregnancy

Unfractionated heparin is the anticoagulant of choice in pregnant women, because unlike warfarin, it does not cross the placenta. Low-molecular-weight heparins also do not cross the placenta,[93] and descriptive studies suggest that they are both safe and effective in pregnancy.[94]

Risk of Heparin-Induced Osteoporosis

When given for more than one month, unfractionated heparin can cause osteoporosis. This complication may be less frequent with low-molecular-weight heparins. In a case series, low-molecular-weight heparin was used successfully in patients with established heparin-induced osteoporosis,[94] and in a recent three-month trial of 80 patients, the incidence of osteoporosis was lower in patients given low-molecular-weight heparin than in those given unfractionated heparin (2.6 percent vs. 17.6 percent, $P = 0.05$).[95]

Comparability of Various Preparations of Low-Molecular-Weight Heparin

Although low-molecular-weight heparins have similar mechanisms of action, their molecular-weight distributions vary (Table 1), causing differences in their inhibitory activities against factor Xa and thrombin,[96] the extent to which they bind to plasma proteins,[26,27] and their plasma half-lives.[6,17,18] There are few studies comparing different low-molecular-weight heparins. In a study of enoxaparin and reviparin for the prevention of venous thromboembolism in 416 pa-

tients undergoing total hip replacement, the incidence of venous thrombosis was similar in both groups (9 percent and 10 percent, respectively), as was the rate of major bleeding (1 percent in both groups).[35] Thus, despite their different methods of preparation and small differences in their specific activities, the two agents were equally safe and effective when equivalent doses in terms of anti–factor Xa units were given. These results suggest that low-molecular-weight heparins with similar molecular-weight profiles, and hence similar specific activities, are equally effective.

Cost Effectiveness

In North America, low-molecular-weight heparins are 10 to 20 times as expensive as unfractionated heparin. Accordingly, from an economic viewpoint, it is difficult to justify their routine use in general surgical or medical patients, in whom their advantages over unfractionated heparin are minimal. Low-molecular-weight heparins are more effective than unfractionated heparin for patients undergoing orthopedic surgery[41,59] and more effective than warfarin for patients undergoing total knee replacement.[37-40,42,63]

Consequently, fewer patients require treatment for postoperative venous thrombosis, thereby explaining why analyses of cost effectiveness favor low-molecular-weight heparins over unfractionated heparin[97] or warfarin.[98,99] The validity of these studies is open to question, however, because venography was used to detect venous thrombosis. Since only 10 percent of patients with venographically detected thrombosis after orthopedic surgery have clinically evident thrombosis, and since venography is not routinely performed in this setting, these studies overestimate the cost differences between the treatments.

The use of low-molecular-weight heparins to treat selected patients with venous thromboembolism outside the hospital has the potential to dramatically reduce the cost of health care. If other studies confirm the effectiveness of low-molecular-weight heparins for the outpatient management of venous thromboembolism,[2,3] and if these findings can be extrapolated to patients with arterial thrombosis, enormous cost savings may be realized.

SUMMARY

Low-molecular-weight heparins have proved to be both safe and effective for the prophylaxis and treatment of venous thromboembolism and show promise for prophylaxis and treatment of arterial thrombosis. Their pharmacokinetic advantages over unfractionated heparin have obviated the need for laboratory monitoring and have set the stage for the outpatient management of venous thrombosis. Although low-molecular-weight heparins have largely replaced unfractionated heparin in many parts of Europe, they are only beginning to find their niche in North America. Because they cause less heparin-induced thrombocytopenia and possibly less osteoporosis, the use of low-molecular-weight heparins is likely to increase over the coming years.

There still is room for anticoagulants that are more potent. Like unfractionated heparin, low-molecular-weight heparins are unable to inactivate thrombin bound to fibrin,[100] which may be an important trigger for clot extension at sites of vascular injury. This may explain why it has been difficult to show an advantage of low-molecular-weight heparins over unfractionated heparin in patients with unstable angina.[53-57] The limitations of both low-molecular-weight heparins and unfractionated heparin have stimulated the development of new antithrombotic drugs, including hirudin, factor Xa inhibitors, tissue-factor-pathway inhibitor, and antagonists of glycoprotein IIb/IIIa, the platelet fibrinogen receptor. With these and newer drugs on the horizon, our ability to prevent and treat thrombotic diseases is likely to improve substantially.

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REFERENCES

1. Chong BH, Ismail F, Cade J, Gallus AS, Gordon S, Chesterman CN. Heparin-induced thrombocytopenia: studies with a new low molecular weight heparinoid, Org 10172. Blood 1989;73:1592-6.
2. Levine M, Gent M, Hirsh J, et al. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. N Engl J Med 1996;334:677-81.
3. Koopman MMW, Prandoni P, Piovella F, et al. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. N Engl J Med 1996;334:682-7.
4. Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. N Engl J Med 1995;332:1330-5.
5. Rosenberg RD, Bauer KA. The heparin–antithrombin system: a natural anticoagulant mechanism. In: Colman RW, Hirsch J, Marder VJ, Salzman EW, eds. Hemostasis and thrombosis: basic principles and clinical practice. 3rd ed. Philadelphia: J.B. Lippincott, 1994:837-60.
6. Harenberg J. Pharmacology of low molecular weight heparins. Semin Thromb Hemost 1990;16:Suppl:12-8.
7. Danielsson A, Raub E, Lindahl U, Bjork I. Role of ternary complexes, in which heparin binds both antithrombin and proteinase, in the acceleration of the reactions between antithrombin and thrombin or factor Xa. J Biol Chem 1986;261:15467-73.
8. Jordan RE, Oosta GM, Gardner WT, Rosenberg RD. The kinetics of hemostatic enzyme-antithrombin interactions in the presence of low molecular weight heparin. J Biol Chem 1980;255:10081-90.
9. Abildgaard U, Lindahl AK, Sandset PM. Heparin requires both antithrombin and extrinsic pathway inhibitor for its anticoagulant effect in human blood. Haemostasis 1991;21:254-7.
10. Sandset PM, Abildgaard U, Larsen ML. Heparin induces release of extrinsic coagulation pathway inhibitor (EPI). Thromb Res 1988;50:803-13.

11. Broze GJ Jr. Tissue factor pathway inhibitor. Thromb Haemost 1995; 74:90-3.
12. Huang ZF, Wun T-C, Broze GJ Jr. Kinetics of factor Xa inhibition by tissue factor pathway inhibitor. J Biol Chem 1993;268:26950-5.
13. Ofosu FA, Hirsh J, Esmon CT, et al. Unfractionated heparin inhibits thrombin-catalysed amplification reactions of coagulation more efficiently than those catalysed by factor Xa. Biochem J 1989;257:143-50.
14. Beguin S, Mardiguian J, Lindhout T, Hemker HC. The mode of action of low molecular weight heparin preparation (PK10169) and two of its major components on thrombin generation in plasma. Thromb Haemost 1989;61:30-4.
15. Barrowcliffe TW, Merton RE, Havercroft SJ, Thunberg L, Lindahl U, Thomas DP. Low-affinity heparin potentiates the action of high-affinity heparin oligosaccharides. Thromb Res 1984;34:125-33.
16. Handeland GF, Abildgaard U, Holm HA, Arnesen K-E. Dose adjusted heparin treatment of deep venous thrombosis: a comparison of unfractionated and low molecular weight heparin. Eur J Clin Pharmacol 1990;39: 107-12.
17. Bara L, Billaud E, Gramond G, Kher A, Samama M. Comparative pharmacokinetics of a low molecular weight heparin (PK 10 169) and unfractionated heparin after intravenous and subcutaneous administration. Thromb Res 1985;39:631-6.
18. Bara L, Samama MM. Pharmacokinetics of low molecular weight heparins. Acta Chir Scand Suppl 1988;543:65-72.
19. Matzsch T, Bergqvist D, Hedner U, Ostergaard P. Effects of an enzymatically depolymerized heparin as compared with conventional heparin in healthy volunteers. Thromb Haemost 1987;57:97-101.
20. Bjornsson TO, Wolfram KM, Kitchell BB. Heparin kinetics determined by three assay methods. Clin Pharmacol Ther 1982;31:104-13.
21. Lane DA. Heparin binding and neutralizing proteins. In: Lane DA, Lindahl U, eds. Heparin: chemical and biological properties, clinical applications. Boca Raton, Fla.: CRC Press, 1989:363-91.
22. Sobel M, McNeill PM, Carlson PL, et al. Heparin inhibition of von Willebrand factor-dependent platelet function in vitro and in vivo. J Clin Invest 1991;87:1787-93.
23. de Romeuf C, Mazurier C. Heparin binding assay of von Willebrand factor (vWF) in plasma milieu — evidence of the importance of the multimerization degree of vWF. Thromb Haemost 1993;69:436-40.
24. Young E, Prins M, Levine MN, Hirsh J. Heparin binding to plasma proteins, an important mechanism for heparin resistance. Thromb Haemost 1992;67:639-43.
25. Hirsh J, van Aken WG, Gallus AS, Dollery CT, Cade JF, Yung WL. Heparin kinetics in venous thrombosis and pulmonary embolism. Circulation 1976;53:691-5.
26. Young E, Wells P, Holloway S, Weitz J, Hirsh J. Ex-vivo and in-vitro evidence that low molecular weight heparins exhibit less binding to plasma proteins than unfractionated heparin. Thromb Haemost 1994;71: 300-4.
27. Young E, Cosmi B, Weitz J, Hirsh J. Comparison of the non-specific binding of unfractionated heparin and low molecular weight heparin (enoxaparin) to plasma proteins. Thromb Haemost 1993;70:625-30.
28. Barzu T, Molho P, Tobelem G, Petitou M, Caen J. Binding and endocytosis of heparin by human endothelial cells in culture. Biochem Biophys Acta 1985;845:196-203.
29. Cadroy Y, Pourrat J, Baladre MF, et al. Delayed elimination of enoxaparin in patients with chronic renal insufficiency. Thromb Res 1991;63: 385-90.
30. Carter CJ, Kelton JG, Hirsch J, Cerskus AL, Santos AV, Gent M. The relationship between the hemorrhagic and antithrombotic properties of low molecular weight heparin in rabbits. Blood 1982;59:1239-45.
31. Salzman EW, Rosenberg RD, Smith MH, Lindon JN, Favreau L. Effect of heparin and heparin fractions on platelet aggregation. J Clin Invest 1980;65:64-73.
32. Horne MK III, Chao ES. The effect of molecular weight on heparin binding to platelets. Br J Haematol 1990;74:306-12.
33. Blajchman MA, Young E, Ofosu FA. Effects of unfractionated heparin, dermatan sulfate and low molecular weight heparin on vessel wall permeability in rabbits. Ann N Y Acad Sci 1989;556:245-54.
34. Kakkar W, Cohen AT, Edmonson RA, et al. Low molecular weight versus standard heparin for prevention of venous thromboembolism after major abdominal surgery. Lancet 1993;341:259-65.
35. Boneu B. An international multicentre study: Clivarin in the prevention of venous thromboembolism in patients undergoing general surgery: report of the International Clivarin Assessment Group. Blood Coagul Fibrinolysis 1993;4:Suppl 1:S21-S22.
36. Turpie AGG, Levine MN, Hirsh J, et al. A randomized controlled trial of a low-molecular-weight heparin (enoxaparin) to prevent deep-vein thrombosis in patients undergoing elective hip surgery. N Engl J Med 1986;315:925-9.
37. Leclerc JR, Geerts WH, Desjardins L, et al. Prevention of venous thromboembolism after knee arthroplasty: a randomized, double-blind trial comparing enoxaparin with warfarin. Ann Intern Med 1996;124:619-26.
38. Spiro TE, Fitzgerald RH, Trowbridge AA, et al. Enoxaparin a low molecular weight heparin and warfarin for the prevention of venous thromboembolic disease after elective knee replacement surgery. Blood 1994;84: Suppl 1:246A. abstract.
39. RD Heparin Arthroplasty Group. RD heparin compared with warfarin for prevention of venous thromboembolic disease following total hip or knee arthroplasty. J Bone Joint Surg Am 1994;76:1174-85.
40. Hamulyak K, Lensing AWA, van der Meer J, Smid WM, van Ooy A, Hoek JA. Subcutaneous low-molecular weight heparin or oral anticoagulants for the prevention of deep-vein thrombosis in elective hip and knee replacement? Thromb Haemost 1995;74:1428-31.
41. Imperiale TF, Speroff T. A meta-analysis of methods to prevent venous thromboembolism following total hip replacement. JAMA 1994;271: 1780-5. [Erratum, JAMA 1995;273:288.]
42. Heit JA, Berkowitz SD, Bona R, et al. Efficacy and safety of low molecular weight heparin (ardeparin sodium) compared to warfarin for the prevention of venous thromboembolism after total knee replacement surgery: a double-blind, dose-ranging study. Thromb Haemost 1997;77:32-8.
43. Moskovitz PA, Ellenberg SS, Feffer HL, et al. Low-dose heparin for prevention of venous thromboembolism in total hip arthroplasty and surgical repair of hip fractures. J Bone Joint Surg Am 1978;60:1065-70.
44. Barsotti J, Gruel Y, Rosset P, et al. Comparative double-blind study of two dosage regimens of low-molecular weight heparin in elderly patients with a fracture of the neck of the femur. J Orthop Trauma 1990;4:371-5.
45. Green D. Prophylaxis of thromboembolism in spinal cord-injured patients. Chest 1994;102:Suppl A:649S-651S.
46. Green D, Lee Y, Ito VY, et al. Fixed- vs adjusted-dose heparin in the prophylaxis of thromboembolism in spinal cord injury. JAMA 1988;260: 1255-8.
47. Merli GJ, Crabbe S, Doyle L, Ditunno JF, Herbision GJ. Mechanical plus pharmacological prophylaxis for deep vein thrombosis in acute spinal cord injury. Paraplegia 1992;30:558-62.
48. Green D, Rossi EC, Yao JST, Flinn WR, Spies SM. Deep vein thrombosis in spinal cord injury: effect of prophylaxis with calf compression, aspirin, and dipyridamole. Paraplegia 1982;20:227-34.
49. Geerts WH, Jay RM, Code KI, et al. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. N Engl J Med 1996;335:701-7.
50. Bergmann JF, Neuhart E. A multicenter randomized double-blind study of enoxaparin compared with unfractionated heparin in the prevention of venous thromboembolic disease in elderly in-patients bedridden for an acute medical illness. Thromb Haemost 1996;76:529-34.
51. Harenberg J, Kallenbach B, Martin U, et al. Randomized controlled study of heparin and low molecular weight heparin for prevention of deep-vein thrombosis in medical patients. Thromb Res 1990;59:639-50.
52. Leizorovicz A, Simonneau G, Decousus H, Boissel JP. Comparison of efficacy and safety of low molecular weight heparins and unfractionated heparin in initial treatment of deep venous thrombosis: a meta-analysis. BMJ 1994;309:299-304.
53. Siragusa S, Cosmi B, Piovella F, Hirsh J, Ginsberg JS. Low-molecular-weight heparins and unfractionated heparin in the treatment of patients with acute venous thromboembolism: results of a meta-anlysis. Am J Med 1996;100:269-77.
54. Lensing AWA, Prins MH, Davidson BL, Hirsh J. Treatment of deep venous thrombosis with low-molecular-weight heparins: a meta-analysis. Arch Intern Med 1995;155:601-7.
55. Fragmin during Instability in Coronary Artery Disease (FRISC) Study Group. Low-molecular-weight heparin during instability in coronary artery disease. Lancet 1996;347:561-8.
56. Klein W. Low molecular weight heparin in the initial and prolonged treatment of unstable coronary artery disease — the fragmin in unstable coronary heart disease study (FRIC). Eur Heart J 1996;17:Suppl:306. abstract.
57. Cohen M, Demers C, Gurfinkel EP, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disese. N Engl J Med 1997;337:447-52.
58. Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin: overview of results of randomized trials in general, orthopedic, and urologic surgery. N Engl J Med 1988;318:1162-73.
59. Nurmohamed MT, Rosendaal FR, Buller HR, et al. Low-molecular-weight heparin versus standard heparin in general and orthopaedic surgery: a meta-analysis. Lancet 1992;340:152-6.
60. Torholm C, Broeng L, Jorgensen PS, et al. Thromboprophylaxis by low-molecular-weight heparin in elective hip surgery: a placebo controlled study. J Bone Joint Surg Br 1991;73:434-8.
61. The German Hip Arthroplasty Trial (GHAT) Group. Prevention of deep vein thrombosis with low molecular-weight heparin in patients un-

dergoing total hip replacement: a randomized trial. Arch Orthop Trauma Surg 1992;111:110-120.
62. Dechavanne M, Ville D, Berruyer M, et al. Randomized trial of a low-molecular-weight heparin (Kabi 2165) versus adjusted-dose subcutaneous standard heparin in the prophylaxis of deep-vein thrombosis after elective hip surgery. Haemostasis 1989;19:5-12.
63. Hull R, Raskob G, Pineo G, et al. A comparison of subcutaneous low-molecular-weight heparin with warfarin sodium for prophylaxis against deep-vein thrombosis after hip or knee implantation. N Engl J Med 1993; 329:1370-6.
64. Powers PJ, Gent M, Jay RM, et al. A randomized trial of less intense postoperative warfarin or aspirin therapy in the prevention of venous thromboembolism after surgery for fractured hip. Arch Intern Med 1989; 149:771-4.
65. Waring WP, Karunas RS. Acute spinal cord injuries and the incidence of clinically occurring thromboembolic disease. Paraplegia 1991;29:8-16.
66. Green D, Lee MY, Lim AC, et al. Prevention of thromboembolism after spinal cord injury using low-molecular-weight heparin. Ann Intern Med 1990;113:571-4.
67. Frisbie JH, Sasahara AA. Low dose heparin prophylaxis for deep venous thrombosis in acute spinal cord injury patients: a controlled study. Paraplegia 1981;19:343-6.
68. Geerts WH, Code KI, Jay RM, Chen E, Szalai JP. A prospective study of venous thromboembolism after major trauma. N Engl J Med 1994;331: 1601-6.
69. Clagett GP, Anderson FA Jr, Heit J, Levine MN, Wheeler HB. Prevention of venous thromboembolism. Chest 1995;108:Suppl:312S-334S.
70. Prins MH, Gelsema R, Sing AK, van Heerde LR, den Ottolander GJ. Prophylaxis of deep venous thrombosis with a low-molecular-weight heparin (Kabi 2165/Fragmin) in stroke patients. Haemostasis 1989;19:245-50.
71. Sandset PM, Dahl T, Stiris M, Rostad B, Scheel B, Abildgaard U. A double-blind and randomized placebo-controlled trial of low molecular weight heparin once daily to prevent deep-vein thrombosis in acute ischemic stroke. Semin Thromb Hemost 1990;16:Suppl:25-33.
72. Turpie AGG, Levine MN, Powers P, et al. A double blind randomized trial of ORG 10172 low molecular weight heparinoid versus unfractionated heparin in the prevention of deep vein thrombosis in patients with thrombotic stroke. Thromb Haemost 1991;65:753. abstract.
73. Dahan R, Houlbert D, Caulin C, et al. Prevention of deep vein thrombosis in elderly medical in-patients by a low molecular weight heparin: a randomized double-blind trial. Hemostasis 1986;16:159-64.
74. Edmondson RA, Cohen AT, Das SK, Wagner MB, Kakkar VV. Low-molecular weight heparin versus aspirin and dipyridamole after femoropopliteal bypass grafting. Lancet 1994;344:914-8. [Erratum, Lancet 1994; 344:1307.]
75. Faxon DP, Spiro TE, Minor S, et al. Low molecular weight heparin in prevention of restenosis after angioplasty: results of Enoxaparin Restenosis (ERA) Trial. Circulation 1994;90:908-14.
76. Cairns JA, Gill J, Morton B, et al. Fish oils and low-molecular-weight heparin for the reduction of restenosis after percutaneous transluminal coronary angioplasty: the EMPAR Study. Circulation 1996;94:1553-60.
77. Hull RD, Raskob GE, Pineo GF, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. N Engl J Med 1992;326:975-82.
78. Prandoni P, Lensing AWA, Buller HR, et al. Comparison of subcutaneous low-molecular-weight heparin with intravenous standard heparin in proximal deep-vein thrombosis. Lancet 1992;339:441-5.
79. The Columbus Investigators. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. N Engl J Med 1997; 337:657-62.
80. Simonneau G, Sors H, Charbonnier B, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. N Engl J Med 1997;337:663-9.
81. Pini M, Aiello S, Manotti C, et al. Low molecular weight heparin versus warfarin in the prevention of recurrences after deep vein thrombosis. Thromb Haemost 1994;72:191-7.
82. Gurfinkel EP, Manos EJ, Mejail RI, et al. Low molecular weight heparin versus regular heparin or aspirin in the treatment of unstable angina and silent ischemia. J Am Coll Cardiol 1995;26:313-8.
83. The Thrombolysis in Myocardial Infarction (TIMI) 11A Trial Investigators. Dose-ranging trial of enoxaparin for unstable angina: results of TIMI 11A. J Am Coll Cardiol 1997;29:1474-82.
84. Kay R, Wong KS, Yu YL, et al. Low-molecular-weight heparin for the treatment of acute ischemic stroke. N Engl J Med 1995;333:1588-93.
85. Bergqvist D, Lindblad B, Matzsch T. Risk of combining low molecular weight heparin for thromboprophylaxis and epidural or spinal anesthesia. Semin Thromb Hemost 1993;19:Suppl 1:147-51.
86. Spiro TE, Johnson GJ, Christie MJ, et al. Efficacy and safety of enoxaparin to prevent deep venous thrombosis after hip replacement surgery. Ann Intern Med 1994;121:81-9.
87. Amiral J, Bridey F, Wolf M, et al. Antibodies to macromolecular platelet factor 4-heparin complexes in heparin-induced thrombocytopenia: a study of 44 cases. Thromb Haemost 1995;73:21-8.
88. Leroy J, Leclerc MH, Delahousse B, et al. Treatment of heparin-associated thrombocytopenia and thrombosis with low molecular weight heparin (CY 216). Semin Thromb Hemost 1985;11:326-9.
89. Vitoux JF, Mathieu JF, Roncato M, Fiessinger JN, Aiach M. Heparin-associated thrombocytopenia treatment with low molecular weight heparin. Thromb Haemost 1986;55:37-9.
90. Horellou MH, Conard J, Lecrubier C, et al. Persistent heparin induced thrombocytopenia despite therapy with low molecular weight heparin. Thromb Haemost 1984;51:134.
91. Holst J, Lindblad B, Bergqvist D, et al. Protamine neutralization of intravenous and subcutaneous low-molecular-weight heparin (tinzaparin, Logiparin): an experimental investigation in healthy volunteers. Blood Coagul Fibrinolysis 1994;5:795-803.
92. Van Ryn-McKenna J, Cai L, Ofosu FA, Hirsh J, Buchanan MR. Neutralization of enoxaparine-induced bleeding by protamine sulfate. Thromb Haemost 1990;63:271-4.
93. Forestier F, Daffos F, Capella-Pavlovsky M. Low molecular weight heparin (PK 10169) does not cross the placenta during the second trimester of pregnancy: study by direct fetal blood sampling under ultrasound. Thromb Res 1984;34:557-60.
94. Melissari E, Parker CJ, Wilson NV, et al. Use of low molecular weight heparin in pregnancy. Thromb Haemost 1992;68:652-6.
95. Monreal M, Lafoz E, Olive A, del Rio L, Vedia C. Comparison of subcutaneous unfractionated heparin with a low molecular weight heparin (Fragmin) in patients with venous thromboembolism and contraindications to coumarin. Thromb Haemost 1994;71:7-11.
96. Fareed J, Walenga JM, Hoppensteadt D, Huan X, Racanelli A. Comparative study on the in vitro and in vivo activities of seven low-molecular-weight heparins. Haemostasis 1988;18:Suppl 3:3-15. [Erratum, Haemostasis 1988;18:389a.]
97. Anderson DR, O'Brien BJ, Levine MN, Roberts R, Wells PS, Hirsh J. Efficacy and cost of low-molecular-weight heparin compared with standard heparin for the prevention of deep vein thrombosis after total hip arthroplasty. Ann Intern Med 1993;119:1105-12.
98. O'Brien BJ, Anderson DR, Goeree R. Cost-effectiveness of enoxaparin versus warfarin prophylaxis against deep-vein thrombosis after total hip replacement. Can Med Assoc J 1994;150:1083-90.
99. Menzin J, Colditz GA, Regan MM, Richner RE, Oster G. Cost-effectiveness of enoxaparin vs low-dose warfarin in the prevention of deep-vein thrombosis after total hip replacement surgery. Arch Intern Med 1995; 155:757-64.
100. Weitz JI, Hudoba M, Massel D, Maraganore J, Hirsh J. Clot-bound thrombin is protected from inhibition by heparin-antithrombin III but is susceptible to inactivation by antithrombin III-independent inhibitors. J Clin Invest 1990;86:385-91.