

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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Circulation 2001;103;2994-3018

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1524-4539

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Guide to Anticoagulant Therapy: Heparin A Statement for Healthcare Professionals From the American Heart Association

Jack Hirsh, MD; Sonia S. Anand, MD; Jonathan L. Halperin, MD; Valentin Fuster, MD, PhD

Thrombi are composed of fibrin and blood cells and may form in any part of the cardiovascular system, including veins, arteries, the heart, and the microcirculation. Because the relative proportion of cells and fibrin depends on hemodynamic factors, the proportions differ in arterial and venous thrombi.^{1,2} Arterial thrombi form under conditions of high flow and are composed mainly of platelet aggregates bound together by thin fibrin strands.^{3–5} In contrast, venous thrombi form in areas of stasis and are predominantly composed of red cells, with a large amount of interspersed fibrin and relatively few platelets. Thrombi that form in regions of slow to moderate flow are composed of a mixture of red cells, platelets, and fibrin and are known as mixed platelet-fibrin thrombi.^{4,5} When a platelet-rich arterial thrombus becomes occlusive, stasis occurs, and the thrombus can propagate as a red stasis thrombus. As thrombi age, they undergo progressive structural changes.⁶ Leukocytes are attracted by chemotactic factors released from aggregated platelets² or proteolytic fragments of plasma proteins and become incorporated into the thrombi. The aggregated platelets swell and disintegrate and are gradually replaced by fibrin. Eventually, the fibrin clot is digested by fibrinolytic enzymes released from endothelial cells and leukocytes. The complications of thrombosis are caused either by the effects of local obstruction of the vessel, distant embolism of thrombotic material, or, less commonly, consumption of hemostatic elements.

Arterial thrombi usually form in regions of disturbed flow and at sites of rupture of an atherosclerotic plaque, which exposes the thrombogenic subendothelium to platelets and coagulation proteins; plaque rupture may also produce further narrowing due to hemorrhage into the plaque.^{7–11} Nonocclusive thrombi may become incorporated into the vessel wall and can accelerate the growth of atherosclerotic plaques.^{9,12,13} When flow is slow, the degree of stenosis is severe, or the thrombogenic stimulus is intense, the thrombi may become totally occlusive. Arterial thrombi usually occur in association with preexisting vascular disease, most commonly ath-

erosclerosis; they produce clinical tissue ischemia either by obstructing flow or by embolism into the distal microcirculation. Activation both of blood coagulation and of platelets is important in the pathogenesis of arterial thrombosis. These 2 fundamental mechanisms of thrombogenesis are closely linked in vivo, because thrombin, a key clotting enzyme generated by blood coagulation, is a potent platelet activator, and activated platelets augment the coagulation process. Therefore, both anticoagulants and drugs that suppress platelet function are potentially effective in the prevention and treatment of arterial thrombosis, and evidence from results of clinical trials indicates that both classes of drugs are effective.

Venous thrombi usually occur in the lower limbs; although often silent, they can produce acute symptoms due to inflammation of the vessel wall, obstruction of flow, or embolism into the pulmonary circulation. They can produce long-term complications due to venous hypertension by damaging the venous valves. Activation of blood coagulation is the critical mechanism in pathogenesis of venous thromboembolism, whereas platelet activation is less important. Anticoagulants are therefore very effective for prevention and treatment of venous thromboembolism, and drugs that suppress platelet function are of less benefit.

Intracardiac thrombi usually form on inflamed or damaged valves, on endocardium adjacent to a region of myocardial infarction (MI), in a dilated or dyskinetic cardiac chamber, or on prosthetic valves. They are usually asymptomatic when confined to the heart but may produce complications due to embolism to the cerebral or systemic circulation. Activation of blood coagulation is more important in the pathogenesis of intracardiac thrombi than platelet activation, although the latter plays a contributory role. Anticoagulants are effective for prevention and treatment of intracardiac thrombi, and in patients with prosthetic heart valves, the efficacy of anticoagulants is augmented by drugs that suppress platelet function.

Widespread microvascular thrombosis is a complication of disseminated intravascular coagulation or generalized platelet

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee in December 2000. A single reprint is available by calling 800-242-8721 (US only) or writing the American Heart Association, Public Information, 7272 Greenville Ave, Dallas, TX 75231-4596. Ask for reprint No. 71-0203. To purchase additional reprints: up to 999 copies, call 800-611-6083 (US only) or fax 413-665-2671; 1000 or more copies, call 214-706-1466, fax 214-691-6342, or e-mail pubauth@heart.org. To make photocopies for personal or educational use, call the Copyright Clearance Center, 978-750-8400.

Parts of this statement were originally published in *Circulation*. 1994;89:1449–1468. This publication is an update of the 1994 statement.

Parts of this statement are based on the Sixth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy and have been published previously in *Chest* (2001;119[suppl]:64S–94S).

This statement will also be published in the July 2001 issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*.

(*Circulation*. 2001;103:2994-3018.)

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aggregation. Microscopic thrombi can produce tissue ischemia, red cell fragmentation leading to a hemolytic anemia, or hemorrhage due to consumption of platelets and clotting factors. Anticoagulants are effective in selected cases of disseminated intravascular coagulation.

Clinical Consequences of Thrombosis

It has been estimated that venous thromboembolism is responsible for more than 300 000 hospital admissions per year in the United States¹⁴ and that pulmonary embolism (PE) causes or contributes to death in ≈12% of hospitalized patients and is responsible for 50 000 to 250 000 deaths annually in the United States. The burden of illness produced by venous thromboembolism includes death from PE (either acute or, less commonly, chronic), long-term consequences of the postthrombotic syndrome, the need for hospitalization, complications of anticoagulant therapy, and the psychological impact of a potentially chronic, recurrent illness.

Arterial thrombosis is responsible for many of the acute manifestations of atherosclerosis and contributes to the progression of atherosclerosis. The burden of illness from atherosclerosis is enormous. As a generalized pathological process, atherosclerosis affects the arteries supplying blood to the heart, brain, and abdomen or legs, causing acute and chronic myocardial ischemia, including sudden death, MI, unstable angina, stable angina, ischemic cardiomyopathy, chronic arrhythmia, and ischemic cerebrovascular disease (including stroke, transient ischemic attacks, and multi-infarct dementia). In addition, atherosclerosis can cause renovascular hypertension, peripheral arterial disease with resulting intermittent claudication and gangrene, and bowel ischemia, and it can compound the complications of diabetes mellitus and hypertension. Thromboembolism that originates in the heart can cause embolic stroke and peripheral embolism in patients with atrial fibrillation (AF), acute MI, valvular heart disease, and cardiomyopathy.

The second version of "A Guide to Anticoagulant Therapy" was published in 1994. Since then, the following important advances have been made: (1) low-molecular-weight heparin (LMWH) preparations have become established anticoagulants for treatment of venous thrombosis and have shown promise for the treatment of patients with acute coronary syndromes; (2) direct thrombin inhibitors have been evaluated in venous thrombosis and acute coronary syndromes; (3) important new information has been published on the optimal dose/intensity for therapeutic anticoagulation with coumarin anticoagulants; and (4) the dosing of heparin for adjunctive therapy in patients with acute coronary syndromes has been reduced because conventional doses cause serious bleeding when combined with thrombolytic therapy or glycoprotein (GP) IIb/IIIa antagonists.

Whenever possible, the recommendations in this review of anticoagulant therapy are based on results of well-designed clinical trials. For some indications or clinical subgroups, however, recommendations are of necessity based on less solid evidence and are therefore subject to revision as new information emerges from future studies.

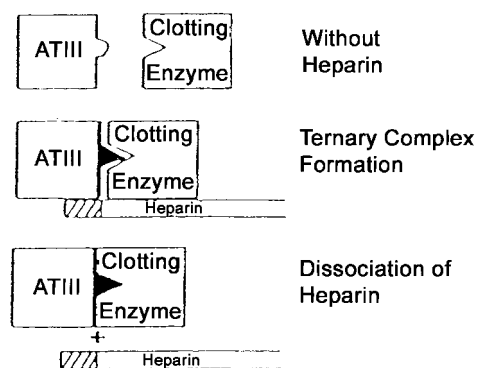


Figure 1. Inactivation of clotting enzymes by heparin. Top, AT-III is a slow inhibitor without heparin. Middle, Heparin binds to AT-III through high-affinity pentasaccharide (▨) and induces a conformational change in AT-III, thereby converting AT-III from a slow to a very rapid inhibitor. Bottom, AT-III binds covalently to the clotting enzyme, and the heparin dissociates from the complex and can be reused. Reprinted with permission from Hirsh J, Warkentin TE, Shaughnessy SG, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest*. 2001;119(1 suppl):64S–94S.

Historical Highlights

Heparin was discovered by McLean in 1916.¹⁵ More than 20 years later, Brinkhous and associates¹⁶ demonstrated that heparin requires a plasma cofactor for its anticoagulant activity; this was named antithrombin III by Abildgaard in 1968¹⁷ but is now referred to simply as antithrombin (AT). In the 1970s, Rosenberg, Lindahl, and others elucidated the mechanisms responsible for the heparin/AT interaction.^{18–20} It is now known that the active center serine of thrombin and other coagulation enzymes is inhibited by an arginine reactive center on the AT molecule and that heparin binds to lysine sites on AT, producing a conformational change at the arginine reactive center that converts AT from a slow, progressive thrombin inhibitor to a very rapid inhibitor.¹⁸ AT binds covalently to the active serine center of coagulation enzymes; heparin then dissociates from the ternary complex and can be reutilized¹⁸ (Figure 1). Subsequently, it was discovered^{18–20} that heparin binds to and potentiates the activity of AT through a unique glucosamine unit^{18–21} contained within a pentasaccharide sequence,²² the structure of which has been confirmed. A synthetic pentasaccharide has been developed and is undergoing clinical evaluation for prevention and treatment of venous thrombosis.^{23,24}

Mechanism of Action of Heparin

Only approximately one third of an administered dose of heparin binds to AT, and this fraction is responsible for most of its anticoagulant effect.^{25,26} The remaining two thirds has minimal anticoagulant activity at therapeutic concentrations, but at concentrations greater than those usually obtained clinically, both high- and low-affinity heparin catalyze the AT effect of a second plasma protein, heparin cofactor II²⁷ (Table 1).

The heparin-AT complex inactivates a number of coagulation enzymes, including thrombin factor (IIa) and factors Xa, IXa, XIa, and XIIa.¹⁸ Of these, thrombin and factor Xa

TABLE 1. Antihemostatic Effects of Heparin

Effect	Comment
Binds to AT-III and catalyzes inactivation of factors IIa, Xa, IXa, and XIIa	Major mechanism for anticoagulant effect, produced by only one third of heparin molecules (those containing the unique pentasaccharide binding AT-III)
Binds to heparin cofactor II and catalyzes inactivation of factor IIa	Anticoagulant effect requires high concentrations of heparin and occurs to the same degree whether the heparin has high or low affinity for AT-III
Binds to platelets	Inhibits platelet function and contributes to the hemorrhagic effects of heparin. High-molecular-weight fractions have greater effect than low-molecular-weight fractions

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are the most responsive to inhibition, and human thrombin is ≈10-fold more sensitive to inhibition by the heparin-AT complex than factor Xa (Figure 2). For inhibition of thrombin, heparin must bind to both the coagulation enzyme and AT, but binding to the enzyme is less important for inhibition of activated factor X (factor Xa; Figure 3).²¹ Molecules of heparin with fewer than 18 saccharides do not bind simultaneously to thrombin and AT and therefore are unable to catalyze thrombin inhibition. In contrast, very small heparin fragments containing the high-affinity pentasaccharide sequence catalyze inhibition of factor Xa by AT.²⁸⁻³¹ By inactivating thrombin, heparin not only prevents fibrin formation but also inhibits thrombin-induced activation of factor V and factor VIII.³²⁻³⁴

Heparin is heterogeneous with respect to molecular size, anticoagulant activity, and pharmacokinetic properties (Table 2). Its molecular weight ranges from 3000 to 30 000 Da, with a mean molecular weight of 15 000 Da (≈45 monosaccharide chains; Figure 4).³⁵⁻³⁷ The anticoagulant activity of heparin is heterogeneous, because only one third of heparin molecules administered to patients have anticoagulant function, and the anticoagulant profile and clearance of heparin are influenced

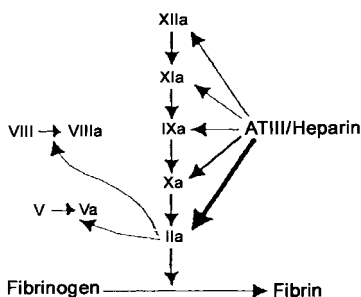


Figure 2. Heparin/AT-III complex inactivates the coagulation enzymes factor XIIa, factor XIa, factor IXa, factor Xa, and thrombin (IIa). Thrombin and factor Xa are most sensitive to the effects of heparin/AT-III. Reprinted with permission from Hirsh J, Warkentin TE, Shaughnessy SG, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest*. 2001;119(1 suppl):64S-94S.

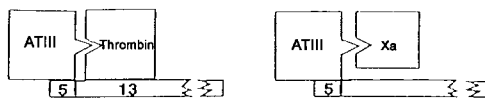


Figure 3. Inhibition of thrombin requires simultaneous binding of heparin to AT-III through the unique pentasaccharide sequence and binding to thrombin through a minimum of 13 additional saccharide units. Inhibition of factor Xa requires binding heparin to AT-III through the unique pentasaccharide without the additional requirement for binding to Xa. 5 indicates unique high-affinity pentasaccharide; 13, additional saccharide units. Reprinted with permission from Hirsh J, Warkentin TE, Shaughnessy SG, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest*. 2001;119(1 suppl):64S-94S.

by the chain length of the molecules, with the higher-molecular-weight species cleared from the circulation more rapidly than the lower-molecular-weight species. This differential clearance results in accumulation of the lower-molecular-weight species, which have a lower ratio of AT to anti-factor Xa activity, in vivo. This effect is responsible for differences in the relationship between plasma heparin concentration (measured in anti-factor Xa units) and the activated partial thromboplastin time (aPTT). The lower-molecular-weight species that are retained in vivo are measured by the anti-factor Xa heparin assay, but these have little effect on the aPTT.

In vitro, heparin binds to platelets and, depending on the experimental conditions, can either induce or inhibit platelet aggregation.^{38,39} High-molecular-weight heparin fractions with low affinity for AT have a greater effect on platelet function than LMWH fractions with high AT affinity⁴⁰ (Table 1). Heparin prolongs bleeding time in humans⁴¹ and enhances blood loss from the microvasculature in rabbits.⁴²⁻⁴⁴ The interaction of heparin with platelets⁴² and endothelial cells⁴³ may contribute to heparin-induced bleeding by a mechanism independent of its anticoagulant effect.⁴⁴

In addition to anticoagulant effects, heparin increases vessel wall permeability,⁴³ suppresses the proliferation of vascular smooth muscle cells,⁴⁵ and suppresses osteoblast formation and activates osteoclasts, effects that promote bone loss.^{46,47} Of these 3 effects, only the osteopenic effect is relevant clinically, and all 3 are independent of the anticoagulant activity of heparin.⁴⁸

Pharmacology of Unfractionated Heparin

The 2 preferred routes of administration of unfractionated heparin (UFH) are continuous intravenous (IV) infusion and

TABLE 2. Heterogeneity of Heparin

Attribute	Characteristics
Molecular size	Mean molecular weight=15 000 Da; range, 3000 to 30 000 Da
Anticoagulant activity	Only one third of heparin molecules contain the high-affinity pentasaccharide required for anticoagulant activity
Clearance	High-molecular-weight moieties are cleared more rapidly than lower-molecular-weight moieties

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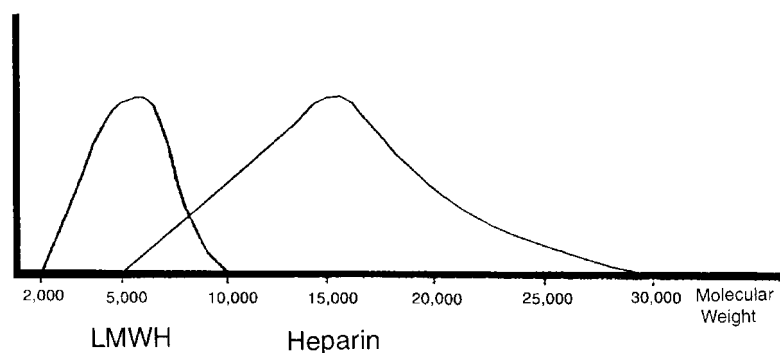


Figure 4. Molecular weight distributions (in daltons) of LMWHs and heparin. Reprinted with permission from Hirsh J, Warkentin TE, Shaughnessy SG, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest*. 2001;119(1 suppl):64S–94S.

subcutaneous (SC) injection. When the SC route is selected, the initial dose must be sufficient to overcome the lower bioavailability associated with this route of administration.⁴⁹ If an immediate anticoagulant effect is required, the initial dose should be accompanied by an IV bolus injection, because the anticoagulant effect of SC heparin is delayed for 1 to 2 hours.

After entering the bloodstream, heparin binds to a number of plasma proteins (Figure 5), which reduces its anticoagulant activity at low concentrations, thereby contributing to the variability of the anticoagulant response to heparin among patients with thromboembolic disorders⁵⁰ and to the laboratory phenomenon of heparin resistance.⁵¹ Heparin also binds to endothelial cells⁵² and macrophages, properties that further complicate its pharmacokinetics. Binding of heparin to von Willebrand factor also inhibits von Willebrand factor–dependent platelet function.⁵³

Heparin is cleared through a combination of a rapid saturable mechanism and much slower first-order mechanisms^{54–56} (Figure 6). The saturable phase of heparin clearance is attributed to binding to endothelial cell receptors^{57,58} and macrophages,⁵⁹ where it is depolymerized^{60,61} (Figure 5). The slower, unsaturable mechanism of clearance is largely renal. At therapeutic doses, a considerable proportion of heparin is cleared through the rapid saturable, dose-dependent mechanism (Figure 6). These kinetics make the anticoagulant response to heparin nonlinear at therapeutic doses, with both the intensity and duration of effect rising disproportionately

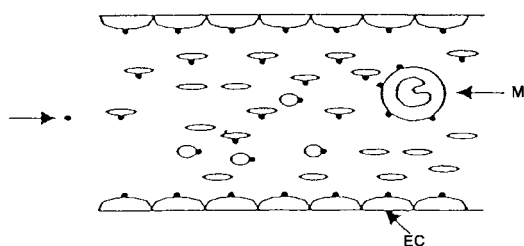


Figure 5. As heparin (●) enters the circulation, it binds to heparin-binding proteins (○), endothelial cells (EC), macrophages (M), and AT-III (◦). Only heparin with high-affinity pentasaccharide binds to AT-III, whereas binding to other proteins and to cells is nonspecific and occurs independently of the AT-III binding site. Reprinted with permission from Hirsh J, Warkentin TE, Shaughnessy SG, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest*. 2001;119(1 suppl):64S–94S.

with increasing dose. Thus, the apparent biological half-life of heparin increases from ≈30 minutes after an IV bolus of 25 U/kg to 60 minutes with an IV bolus of 100 U/kg and 150 minutes with a bolus of 400 U/kg.^{54–56}

The plasma recovery of heparin is reduced⁶² when the drug is administered by SC injection in low doses (eg, 5000 U/12 h) or moderate doses of 12 500 U every 12 hours⁶³ or 15 000 U every 12 hours.⁴⁹ However, at high therapeutic doses (>35 000 U/24 hours), plasma recovery is almost complete.⁶⁴ The difference between the bioavailability of heparin administered by SC or IV injection was demonstrated strikingly in a study of patients with venous thrombosis⁴⁹ randomized to receive either 15 000 U of heparin every 12 hours by SC injection or 30 000 U by continuous IV infusion; both regimens were preceded by an IV bolus dose of 5000 U. Therapeutic heparin levels and aPTT ratios were achieved at 24 hours in only 37% of patients given SC heparin compared with 71% of those given the same total dose by continuous IV infusion.

Dose-Response Relationships and Laboratory Monitoring

The risk of heparin-associated bleeding increases with dose^{65,66} and with concomitant thrombolytic^{67–70} or abcix-

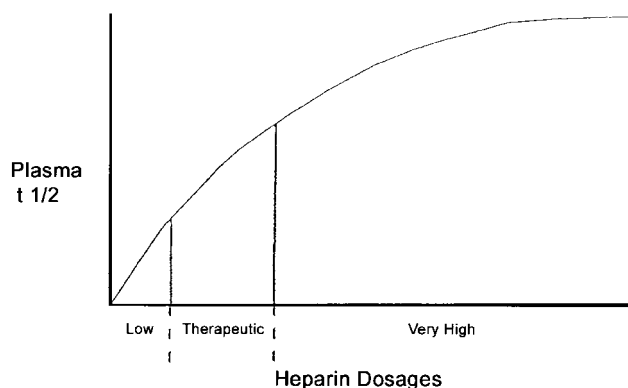


Figure 6. Low doses of heparin clear rapidly from plasma through saturable (cellular) mechanism of clearance. Therapeutic doses of heparin are cleared by a combination of rapid, saturable mechanism and slower, nonsaturable, dose-independent mechanism of renal clearance. Very high doses of heparin are cleared predominantly through slower, nonsaturable mechanism of clearance. $t_{1/2}$ indicates half-life. Reprinted with permission from Hirsh J, Warkentin TE, Shaughnessy SG, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest*. 2001;119(1 suppl):64S–94S.

TABLE 3. Relation Between Failure to Reach the Therapeutic Range for aPTT and Thromboembolic Events: Subgroup Analyses of Prospective Studies

Study	Condition	Outcome	Relative Risk
Hull et al ⁴⁹	DVT	Recurrent venous thromboembolism	15.0
Basu et al ⁷⁹	DVT	Recurrent venous thromboembolism	10.7
Turpie et al ⁶³	Acute MI	Left ventricular mural thrombosis	22.2
Kaplan et al ⁷⁶	Acute MI	Recurrent MI/angina pectoris	6.0
Camilleri et al ⁷⁵	Acute MI	Recurrent MI/angina pectoris	13.3

Relative risk refers to the increase in event rates when patients with subtherapeutic aPTTs are compared with those whose values were in the therapeutic range.

imab^{71,72} therapy. The risk of bleeding is also increased by recent surgery, trauma, invasive procedures, or concomitant hemostatic defects.⁷³ Randomized trials show a relationship between the dose of heparin administered and both its efficacy^{49,63,74} and its safety.^{71,72} Because the anticoagulant response to heparin varies among patients with thromboembolic disorders,^{75–78} it is standard practice to adjust the dose of heparin and monitor its effect, usually by measurement of the aPTT. This test is sensitive to the inhibitory effects of heparin on thrombin, factor Xa, and factor IXa. Because there is a relationship between heparin dose and both anticoagulant effect and antithrombotic efficacy, it follows that there should be a relationship between anticoagulant effect and antithrombotic efficacy.

In the past, we were secure in the contention that a strong relationship existed between the *ex vivo* effect of heparin on the aPTT and its clinical effectiveness, but several lines of evidence have challenged the strength of such a relationship. First, the initial findings supporting a tight relationship between the effect of heparin on aPTT and its clinical efficacy were based on retrospective subgroup analysis of cohort studies and are therefore subject to potential bias^{49,63,75–79} (Table 3). Second, the results of a randomized trial⁸⁰ and 2 recent meta-analyses of contemporary cohort studies^{81,82} call into question the value of the aPTT as a useful predictor of heparin efficacy in patients with venous thrombosis. Third, no direct relationship between aPTT and efficacy was observed in the subgroup analysis of the GUSTO-I study (Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries) in patients with acute MI who were treated with thrombolytic therapy followed by heparin.⁸³ Fourth, even if the aPTT results were predictive of clinical efficacy, the value of this test would be limited by the fact that commercial aPTT reagents vary considerably in responsiveness to heparin.⁸⁴ Although standardization can be achieved by calibration against plasma heparin concentration (the therapeutic range is 0.2 to 0.4 U/mL based on protamine titration or 0.3 to 0.7 U/mL based on anti-factor Xa chromogenic assay), this is beyond the scope of many clinical laboratories. Heparin monitoring is likely to become less problematic in the future as LMWH replaces UFH for most indications.⁸⁵

TABLE 4. Protocol for Heparin Dose Adjustment

aPTT,* s	Repeat Bolus Dose, U	Stop Infusion, min	Change Infusion Rate (mL/h†) Dose (U per 24 h)	Time of Next aPTT
<50	5000	0	+3 (+2880)	6 h
50–59	0	0	+3 (+2880)	6 h
60–85‡	0	0	0 (0)	Next morning
86–95	0	0	–2 (–1920)	Next morning
96–120	0	30	–2 (–1920)	6 h
>120	0	60	–4 (–3840)	6 h

Starting dose of 5000 U IV bolus followed by 32 000 U per 24 hours as a continuous infusion (40 U/mL). First aPTT performed 6 hours after bolus injection, dosage adjustments made according to protocol, and aPTT repeated as indicated in the far right column.

*The normal range for aPTT using the Dade Actin FS reagent is 27 to 35 seconds.

†40 U/mL.

‡The therapeutic range of 60 to 85 seconds corresponds to a plasma heparin level of 0.2 to 0.4 U/mL by protamine titration or 0.35 to 0.7 U/mL in terms of anti-factor Xa activity. The therapeutic range varies with responsiveness of the aPTT reagent to heparin.

Adapted from Cruickshank et al.⁸⁶

Despite its limitations for monitoring heparin, aPTT remains the most convenient and most frequently used method for monitoring the anticoagulant response. aPTT should be measured ≈6 hours after the bolus dose of heparin, and the continuous IV dose should be adjusted according to the result. Various heparin dose-adjustment nomograms have been developed⁸⁶ (Tables 4 and 5), but none are applicable to all aPTT reagents,⁸⁴ and the therapeutic range must be adapted to the responsiveness of the reagent used. In addition, the dosage regimen should be modified when heparin is combined with thrombolytic therapy⁸⁷ or platelet GP IIb/IIIa antagonists.⁷² When heparin is given by SC injection in a dose of 35 000 U/24 hours in 2 divided doses,⁶⁴ the anticoagulant effect is delayed ≈1 hour, and peak plasma levels occur after ≈3 hours.

Limitations of Heparin

The limitations of heparin are based on its pharmacokinetic, biophysical, and nonanticoagulant biological properties.⁸⁸ All are caused by the AT-independent, charge-dependent binding properties of heparin to proteins and surfaces. Pharmacokinetic limitations are caused by AT-independent binding of heparin to plasma proteins,⁸⁹ proteins released from platelets,⁹⁰ and possibly endothelial cells, resulting in the variable anticoagulant response to heparin and the phenomenon of heparin resistance.⁸⁰ AT-independent binding to macrophages and endothelial cells also results in a dose-dependent mechanism of heparin clearance.

The biophysical limitations occur because the heparin-AT complex is unable to inactivate factor Xa in the prothrombinase complex and thrombin bound to fibrin or to subendothelial surfaces. The biological limitations of heparin include osteopenia and heparin-induced thrombocytopenia (HIT). Osteopenia is caused as a result of binding of heparin to osteoblasts,⁴⁶ which then release factors that activate osteoclasts, whereas HIT results from heparin binding to platelet

TABLE 5. Weight-Based Nomogram for Heparin Dosing

Initial dose	80 U/kg bolus, then 18 U · kg ⁻¹ · h ⁻¹
aPTT <35 seconds (<1.2× control)	80 U/kg bolus, then 4 U · kg ⁻¹ · h ⁻¹
aPTT 35 to 45 seconds (1.2 to 1.5× control)	40 U/kg bolus, then 2 U · kg ⁻¹ · h ⁻¹
aPTT 46 to 70 seconds (1.5 to 2.3× control)	No change
aPTT 71 to 90 seconds (2.3 to 3× control)	Decrease infusion rate by 2 U · kg ⁻¹ · h ⁻¹
aPTT >90 seconds (>3× control)	Interrupt infusion 1 hour, then decrease infusion rate by 3 U · kg ⁻¹ · h ⁻¹

Adapted from Raschke et al.⁷⁴

factor 4 (PF4), forming an epitope to which the HIT antibody binds.^{91,92} The pharmacokinetic and nonanticoagulant biological limitations of heparin are less evident with LMWH,⁹³ whereas the limited ability of the heparin-AT complex to inactivate fibrin-bound thrombin and factor Xa is overcome by several new classes of AT-independent thrombin and factor Xa inhibitors.⁹⁴

Platelets, fibrin, vascular surfaces, and plasma proteins modify the anticoagulant effect of heparin. Platelets limit the anticoagulant effect of heparin by protecting surface factor Xa from inhibition by the heparin-AT complex^{95,96} and by secreting PF4, a heparin-neutralizing protein.⁹⁷ Fibrin limits the anticoagulant effect of heparin by protecting fibrin-bound thrombin from inhibition by heparin AT.⁹⁸ Heparin binds to fibrin and bridges between fibrin and the heparin binding site on thrombin. As a result, heparin increases the affinity of thrombin for fibrin, and by occupying the heparin binding site on thrombin, it protects fibrin-bound thrombin from inactivation by the heparin-AT complex.^{99,100} Thrombin also binds to subendothelial matrix proteins, where it is protected from inhibition by heparin.¹⁰¹ These observations explain why heparin is less effective than the AT-independent thrombin and factor Xa inhibitors⁹⁴ for preventing thrombosis at sites of deep arterial injury in experimental animals^{102,103} and may explain why hirudin is more effective than heparin in patients with unstable angina or non-Q-wave MI.¹⁰⁴

Clinical Use of Heparin

Heparin is effective for the prevention and treatment of venous thrombosis and PE, for prevention of mural thrombosis after MI, and for treatment of patients with unstable

angina and MI. Although heparin is used to prevent acute thrombosis after coronary thrombolysis, recent reports question the benefits of heparin in this setting when patients are also treated with aspirin (see below).

In patients with venous thromboembolism or unstable angina, the dose of heparin is usually adjusted to maintain aPTT at an intensity equivalent to a heparin level of 0.2 to 0.4 U/mL as measured by protamine titration or an anti-factor Xa level of 0.30 to 0.7 U/mL. For many aPTT reagents, this is equivalent to a ratio (patient/control aPTT) of 1.5 to 2.5. The recommended therapeutic range^{49,79} is based on evidence from animal studies¹⁰⁵ and supported by subgroup analysis of prospective cohort studies involving treatment of deep vein thrombosis (DVT),⁴⁹ prevention of mural thrombosis after MI,⁶³ and prevention of recurrent ischemia after coronary thrombolysis.^{75,76} Recommended heparin regimens for venous and arterial thrombosis are summarized in Table 6.

Treatment of Venous Thromboembolism

Use of heparin for the treatment of venous thrombosis and PE is based on results of randomized studies.^{106,107} The effectiveness and safety of heparin administered by continuous IV infusion have been compared with intermittent IV injection in 6 studies^{108–113} and with high-dose SC heparin in 6 studies.^{64,114–118} It is difficult to determine the optimal route of heparin administration because different doses were used in these studies, most of the studies were small and underpowered, and different criteria were used to assess efficacy and safety. Nevertheless, the results indicate that heparin is safe and effective when appropriate doses are given. Thus, in a recent pooled analysis of 11 clinical trials in which ≈15 000

TABLE 6. Clinical Use of Heparin

Condition	Recommended Heparin Regimen
Venous thromboembolism	
Prophylaxis of DVT and PE	5000 U SC every 8 or 12 hours or adjusted low-dose heparin*
Treatment of DVT	5000 U IV bolus followed by 32 000 U per 24 hours by IV infusion or 35 000 to 40 000 U per 24 hours SC, adjusted to maintain aPTT* in the therapeutic range
Coronary heart disease	
Unstable angina or acute MI without thrombolytic therapy	5000 U IV bolus followed by 32 000 U per 24 hour IV infusion adjusted to maintain aPTT in the therapeutic range
Acute MI after thrombolytic therapy†	5000 U IV bolus followed by 24 000 U per 24 hours adjusted to maintain aPTT in the therapeutic range

*aPTT varies in responsiveness to heparin.

†The role of heparin is unproven.

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TABLE 7. Comparison of Short and Long Courses of Heparin for Treatment of Proximal Vein Thrombosis

	Gallus et al ¹²¹ (n=266)		Hull et al ¹²⁰ (n=199)	
	Short (4 d)	Long (9.5 d)	Short (5 d)	Long (10 d)
Recurrent VTE, %				
During heparin	3.6	4.7	7.7	7.7
During warfarin	3.3	1.6		
Total during treatment, %	6.9	6.3		

VTE denotes venous thromboembolism.

tk;2Reprinted with permission from Hirsh J, Warkentin TE, Shaughnessy SG, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest*. 2001;119(1 suppl):64S–94S.

patients were treated with either heparin (administered as an initial bolus of 5000 U followed by 30 000 to 35 000 U/24 hours with aPTT monitoring) or SC LMWH,¹¹⁹ the mean incidence of recurrent venous thromboembolism among patients assigned heparin was 5.4%. The rate of major bleeding was 1.9%, fatal recurrent venous thromboembolism occurred in 0.7%, and bleeding was fatal in 0.2% of heparin-treated patients. The initial dose of heparin is particularly critical when heparin is administered by SC injection, because an adequate anticoagulant response is not achieved in the first 24 hours unless a high starting dose is used (17 500 U SC).⁶⁴

Audits of heparin monitoring practices indicate that dosage adjustments are frequently inadequate, and dosing practices can be improved by use of a simple and effective weight-adjusted dosage regimen.⁷⁴ There is evidence that a 5-day course of heparin is as effective as a 10-day course^{120,121} (Table 7). The short-course regimen has obvious appeal, reducing hospital stay and the risk of HIT. Although the shorter course of treatment can be recommended for most patients with venous thromboembolism, this may not be appropriate in cases of extensive iliofemoral vein thrombosis or major PE, because such patients were underrepresented in these studies.^{120,121}

Prophylaxis of Venous Thromboembolism

Heparin in a fixed low dose of 5000 U SC every 8 or 12 hours is an effective and safe form of prophylaxis in medical and surgical patients at risk of venous thromboembolism. Low-dose heparin reduces the risk of venous thrombosis and fatal PE by 60% to 70%.^{122,123} Among general surgical patients, the incidence of fatal PE was reduced from 0.7% in controls to 0.2% in one study ($P<0.001$)¹²⁰ and from 0.8% to 0.3% ($P<0.001$) in a larger analysis that included orthopedic surgical patients.¹²³ There was also a small but statistically significant decrease in mortality from 3.3% to 2.4% with low-dose heparin prophylaxis ($P<0.02$).¹²³ The use of low-dose heparin is associated with a small excess incidence of wound hematoma^{122–124} and a minimal, statistically insignificant increase in major bleeding but no increase in fatal bleeding. Low-dose heparin also effectively prevents venous thromboembolism in patients with MI and in those with other serious medical disorders,¹²⁵ and it reduced in-hospital mortality by 31% ($P<0.05$) in a study of 1358 general medical

patients aged >40 years.¹²⁶ Although low-dose heparin is also effective in reducing DVT after hip surgery,¹²³ the incidence of thrombosis remains substantial (20% to 30%) and can be reduced further with either adjusted low-dose heparin¹²⁷ or fixed-dose LMWH.⁹³ Moderate-dose warfarin is effective in patients undergoing major orthopedic surgical procedures,^{128,129} but direct comparisons of low-dose heparin and warfarin have not been performed in major orthopedic surgery.

Coronary Artery Disease

Coronary thrombosis is important in the pathogenesis of unstable angina, acute MI, and sudden cardiac death. It is also important in the pathogenesis of reinfarction and death in patients with acute MI treated with thrombolytic agents or percutaneous transluminal coronary angioplasty. In most patients, heparin ameliorates the thrombotic manifestations of acute coronary syndromes, but it is no longer used as the sole antithrombotic drug in these settings. Today, heparin is always used in combination with aspirin in potentially eligible patient groups with acute myocardial ischemia,¹³⁰ in those receiving thrombolytic therapy for evolving MI, in those treated with platelet GP IIb/IIIa antagonists for unstable angina,^{131,132} and in those undergoing high-risk coronary angioplasty.^{71,72,132} When combined with aspirin,^{130,133} thrombolytic agents, or GP IIb/IIIa antagonists, however, heparin in full doses increases the risk of bleeding, and the dose is usually reduced in these settings.⁷²

Unstable Angina and Non-Q-Wave MI

Heparin has been evaluated in a number of randomized, double-blind, placebo-controlled clinical trials for the short-term treatment of unstable angina or non-Q-wave MI.^{134–137} When given alone to patients with unstable angina, heparin is effective in preventing acute MI and recurrent angina,^{135–137} and when used in combination with aspirin, the results of a meta-analysis of 6 small trials suggest that the combination also reduces short-term rates of cardiovascular death and MI by $\approx 30\%$ over those achieved with aspirin alone.¹³⁴

Theroux et al¹³⁵ compared the relative efficacy and safety of heparin, aspirin, and their combination in 479 patients with unstable angina. Heparin was administered as an initial 5000-U IV bolus, followed by IV infusion of 1000 U/h, adjusted to maintain the aPTT at 1.5 to 2.0 times the control value. Treatment was initiated within 24 hours after the onset of chest pain and continued for ≈ 6 days. The incidence of MI during the acute period was 11.9% in the placebo group and was reduced to 3.3% in the aspirin groups ($P=0.012$), 0.8% in the heparin group ($P<0.0001$), and 1.6% in the group given the combination of aspirin and heparin ($P=0.001$). The incidence of refractory angina (22.9% in the placebo group) was significantly reduced to 8.5% ($P=0.002$) in the heparin group and 10.7% in the heparin-plus-aspirin group ($P=0.11$) but was 16.5% in the aspirin group. In a second study,¹³⁸ these investigators compared the efficacy and safety of heparin and aspirin. This was a continuation of the previous study in which the placebo and combination groups were discontinued and an additional 245 patients were randomized to receive either continuous IV heparin or oral aspirin twice

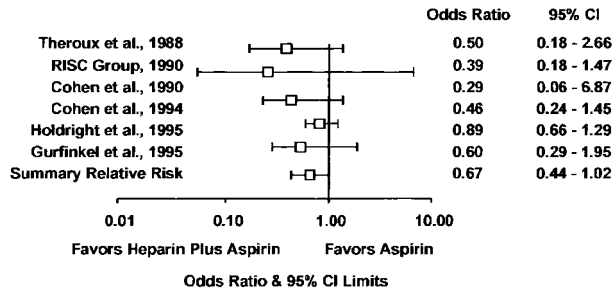


Figure 7. Heparin plus aspirin versus aspirin alone in unstable angina: relative risk of MI or death during hospitalization. Reprinted with permission from Oler et al.¹³⁰ Copyright 1996, American Medical Association.

daily during the in-hospital phase (≈6 days). Fatal or nonfatal MI occurred during the acute period in 4 of 362 heparin-treated patients compared with 23 of 362 patients who did not receive heparin (odds ratio [OR] 0.16, $P < 0.005$).

In contrast, the RISC (Research group in InStability in Coronary artery disease) investigators¹³⁴ did not show that heparin was more effective than aspirin. They compared low-dose aspirin (75 mg/d) with intermittent IV heparin (10 000 U bolus every 6 hours during the initial 24 hours followed by 7500 U every 6 hours for 5 days) in 796 men with unstable angina or non-Q-wave MI. Patients were randomized on the basis of a factorial design to treatment with heparin, aspirin, heparin plus aspirin, or placebo. The main outcome was a composite of MI or death evaluated 5 days after enrollment. The rate of this end point was 6.0% in the placebo group, 5.6% in the heparin group, 3.7% in the aspirin group, and 1.4% in the combined treatment group and was significantly reduced only with the combination ($P = 0.027$). At 30 and 90 days, both the aspirin and aspirin-plus-heparin groups showed significantly better results than the placebo group, but the outcome with heparin alone was no better than with placebo.

Cohen et al¹³⁹ performed a randomized, open-label study of 214 patients with unstable angina or non-Q-wave MI assigned to either aspirin (162.5 mg/d) or aspirin plus heparin for 3 to 4 days and warfarin for up to 12 weeks after enrollment. The main outcome measure was a composite of recurrent angina, MI, or death. After 12 weeks, the incidence of the main outcome was 28% for the aspirin group and 19% for the aspirin-plus-anticoagulation group ($P = 0.09$).

A meta-analysis of published data from 6 small randomized trials (n=1353 subjects), including the 3 described above, reported a risk reduction of 33% (95% confidence interval [CI] -2% to 56%) in cardiovascular death and MI with the combination of UFH and aspirin, which was of borderline significance (Figure 7).¹³⁰

Acute MI

Information on the benefit of heparin in patients with acute MI not given thrombolytic therapy is limited to those who were not treated with aspirin either, so the results may not be applicable to current clinical practice. An overview of randomized clinical trials performed before the reperfusion era reported a 17% reduction in mortality and a 22% reduction in

reinfarction in patients assigned heparin.¹⁴⁰ The control groups in these trials were not treated with aspirin, which is now considered routine.

The effect of heparin on the incidence of mural thrombosis has been evaluated in 2 randomized trials.^{141,142} One compared heparin in a fixed dose of 12 500 U SC every 12 hours with an untreated control group, and the other used low-dose heparin (5000 U SC every 12 hours) for comparison. In both studies, moderate-dose heparin (12 500 U SC every 12 hours) reduced the incidence of mural thrombosis detected by 2-dimensional echocardiography by 72% and 58%, respectively ($P < 0.05$ for each study).

Coronary Thrombolysis

Although in the past it was generally accepted that heparin was effective after coronary thrombolysis, the results of recent studies cast doubt on this view. In 3 studies that used angiographic patency as a usually surrogate end point, the combination of heparin and aspirin was not compared with aspirin alone. Topol et al¹⁴³ reported that a single IV bolus of 10 000 U of heparin did not improve coronary artery patency at 90 minutes. In another trial, in which heparin alone was compared with no treatment,¹⁴⁴ patency of the infarct-related artery at 2 days was 71% in the heparin group and 44% in the control group ($P < 0.023$). In the Heparin-Aspirin Reperfusion Trial,¹⁴⁵ coronary artery patency at 18 hours was 82% in patients treated with heparin and 52% in a group given aspirin 80 mg/d ($P < 0.0002$). The conclusion that heparin is more effective than aspirin in maintaining patency has been criticized because the aspirin dose was too low to completely suppress platelet thromboxane A₂ production. The results were less impressive when the combination of heparin and aspirin was compared with aspirin in a dose of 325 mg/d. In the sixth European Cooperative Study Group (ECSG-6) trial,⁷⁷ 687 patients receiving aspirin were randomized to heparin or no heparin. Patency at a mean of 81 hours was 80% in the heparin group and 75% in the comparison group ($P < 0.01$). In the Australian National Heart Study Trial,¹⁴⁶ 202 patients received heparin for 24 hours before randomization to either continuous IV heparin or a combination of aspirin (300 mg/d) and dipyridamole (300 mg/d). Patency after 1 week was 80% in both groups. Col et al¹⁴⁷ treated 128 patients with streptokinase and aspirin and randomized the patients to either an IV bolus of heparin or no heparin; the study reported no difference in coronary patency at 24 hours (86% versus 87%).¹⁴⁷ The DUCCS-1 (Duke University Clinical Cardiology Studies) investigators treated 250 patients with anisoylated plasminogen-streptokinase activator complex (APSAC) and aspirin and randomized patients to heparin or no heparin. There was a small difference in coronary artery patency (80% in the heparin group versus 74% in the control group).¹⁴⁸

Two large trials, the International Study Group¹⁴⁹ and the ISIS-3¹⁵⁰ (International Study of Infarct Survival) studies, assessed the value of adjunctive heparin in patients receiving thrombolytic therapy and aspirin. In both, heparin was given (12 500 U SC every 12 hours). In the International Study Group trial, heparin was begun 12 hours after randomization

TABLE 8. Effect of Heparin With or Without Aspirin in Coronary Thrombolysis: Overview of 26 Randomized Trials

	Risk Reduction per 1000 Patients Assigned Heparin			
	No Aspirin (n=5459)	<i>P</i>	Aspirin (n=68 090)	<i>P</i>
Death	35	0.002	5	0.03
Cardiac reinfarction	15	0.08	3	0.04
Stroke	10	0.01	1	0.01
Major bleeding	10 (more)	0.01	(3 more)	<0.001

Adapted from Collins et al.¹⁵³

to fibrinolytic therapy; in the ISIS-3 trial, heparin began 4 hours after randomization.

The International Study Group study¹⁴⁹ of 20 891 patients reported no difference in mortality between the heparin (8.5%) and no-heparin (8.9%) groups, whereas the risk of major bleeding was significantly increased by 0.5% in the heparin-treated group. The ISIS-3 study¹⁵⁰ of 41 299 patients reported a vascular mortality rate of 10.3% in the heparin group and 10.0% in the no-heparin control group at 35 days. During the 7-day treatment period, mortality was 7.4% in the heparin group and 7.9% in the control group ($P=0.06$). In-hospital rates of reinfarction with heparin were 3.2% compared with 3.5% in the no-heparin group ($P=0.09$); stroke rates were not different. Major bleeding requiring transfusion was slightly more frequent in the heparin group (1.0% versus 0.8%, $P<0.01$).

In both studies, moderate doses of heparin produced marginal benefits at the cost of increased bleeding. The issue of whether IV heparin would prove more effective and at least as safe as the SC regimen used in the ISIS-3 study was addressed in the GUSTO trial,¹⁵¹ in which patients receiving streptokinase were given either a high-dose heparin regimen (5000 U initial IV bolus, followed by an infusion of 1000 to 1200 U/h to maintain aPTT at 60 to 85 seconds) or the delayed SC heparin regimen used in the ISIS-3 trial. IV heparin was not superior to SC heparin among patients receiving streptokinase either in terms of mortality, reinfarction, major hemorrhage, cerebral hemorrhage, infarct-related artery patency, or arterial reocclusion.

In a much smaller study, O'Connor et al¹⁵² randomized 250 patients who had received APSAC to either aspirin alone or aspirin plus weight-adjusted IV heparin beginning 4 hours after APSAC infusion. There were no differences in ischemic outcomes, but bleeding was significantly greater with heparin (32% versus 17.2%; $P=0.006$). From a meta-analysis composed largely of the International Study Group and ISIS-3 studies, Collins and associates¹³³ reported that in the presence of aspirin, heparin produced a relative risk reduction of mortality of only 6% (95% CI 0% to 10%; $P=0.03$), representing just 5 fewer deaths per 1000 patients treated (Table 8). There were 3 fewer reinfarctions per 1000 ($P=0.04$) and 1 fewer PE per 1000 patients ($P=0.01$). This small beneficial effect was associated with an insignificant excess incidence of stroke but a definite excess of 3 major bleeding incidents per 1000 patients ($P<0.0001$). In trials using high-dose heparin, there was an ≈ 2 -fold increase in the

absolute risk of major extracranial bleeding (31 per 1322 [2.3%] versus 14 per 1321 [1.1%]; $P=0.01$).¹⁵³

Data on the role of adjunctive heparin in patients treated with tissue plasminogen activator are limited. From contemporary studies, Kruse and associates¹⁵⁴ concluded that the role of heparin as adjunctive treatment to accelerated tissue plasminogen activator is still an open issue. A pooled analysis by Mahaffey et al¹⁵⁵ of 6 randomized trials exposed a trend toward reduced in-hospital mortality with heparin (9% reduction; OR 0.91, 95% CI 0.59 to 1.39) but a significantly higher rate of hemorrhagic complications when adjunctive heparin was used in tissue plasminogen activator-treated patients.¹⁵⁶

Recommendations for use of heparin in patients with acute MI are provided in the American College of Cardiology/American Heart Association guidelines.^{87,156} The intensity of the suggested heparin regimen is influenced by whether thrombolytic therapy is given, the type of thrombolytic agent used, and the presence or absence of risk factors for systemic embolism.

Coronary Angioplasty

Percutaneous transluminal coronary angioplasty can be complicated by early thrombotic occlusion in the instrumented artery. It is standard practice to give heparin, commencing with either an IV bolus of 10 000 U with repeated smaller bolus injections as required or as a weight-adjusted-dose regimen of 100 to 175 U/kg followed by 10 to 15 U/kg per hour. The dose is adjusted to maintain the activated clotting time (ACT) greater than 300 to 350 seconds, because there is some evidence that the complication rate is higher with lower ACT values.¹⁵⁷ When these high-dose regimens are used in combination with abciximab and aspirin, however, heparin increases the risk of major bleeding.^{77,78} The risk can be reduced without compromising efficacy by lowering the bolus dose of heparin to 70 U/kg and giving bolus doses as needed to achieve an ACT of >200 seconds and by removing arterial sheaths when the ACT falls below 150 to 180 seconds.⁷⁸ After coronary angioplasty, postprocedural heparin infusions are not needed for most patients who are treated with a combination of aspirin and ticlopidine.

A beneficial role for heparin has not been established when unstable angina develops within the first 6 months after coronary angioplasty. In a recent randomized trial, 200 patients who had undergone angioplasty without intracoronary stenting were randomized to IV nitroglycerin, heparin, the combination of both agents, or placebo for 63 ± 30 hours. Recurrent angina developed in 75% of patients in the placebo and heparin-alone groups compared with 42.6% of patients in the nitroglycerin-alone group and 42% of patients in the nitroglycerin-plus-heparin group ($P<0.003$). Refractory angina occurred in 23%, 29%, 4%, and 4% of patients, respectively ($P<0.002$). The OR for being event free was 0.98 (95% CI -0.55 to 1.73, $P=NS$) for heparin versus no heparin in this study.¹⁵⁸

Atrial Fibrillation

The role of heparin for prevention of ischemic stroke and systemic embolism in high-risk patients with nonvalvular AF has been less thoroughly investigated than oral anticoagula-

tion with warfarin. It is likely that heparin represents an effective alternative to warfarin for antithrombotic prophylaxis, because both anticoagulants decrease hemostatic activation associated with atrial stasis in patients with this cardiac rhythm disturbance.¹⁵⁹ Heparin is sometimes given as an alternative to oral anticoagulation perioperatively in patients with chronic AF who are undergoing elective surgery, but no consensus has emerged regarding when and how to substitute heparin in this situation.¹⁶⁰

Patients with AF who have sustained recent cerebral ischemic events are among those at highest risk of thromboembolism ($\approx 12\%$ per year). Oral anticoagulation reduces the risk by two thirds, similar to the benefit achieved in primary prevention. When oral anticoagulation is contraindicated, aspirin is a much less effective alternative.¹⁶¹ How rapidly and intensively to initiate anticoagulation after a cerebral ischemic event is controversial, however, considering that hemorrhagic transformation might worsen the neurological deficit.^{162,163}

In a study of 231 patients with nonvalvular AF and acute stroke, heparin was administered IV or SC in doses adjusted to an aPTT 1.5 to 2.0 times control values.¹⁶⁴ Delay before the initiation of heparin therapy was <6 hours from the onset of symptoms in 74 patients and 6 to 48 hours in 157 patients. In-hospital mortality was 9%, hemorrhagic worsening occurred in 3% of patients, and stroke recurred early in 2% of patients. Neurological recovery was associated with age younger than 70 years (OR 0.2), normal baseline computed tomography (CT)-scan findings (OR 8.9), and early heparin treatment (OR 1.7, 95% CI 1.1 to 2.5), even though targeted aPTT ratios were achieved at 24 hours in fewer than 50% of patients. Stroke recurrence was associated with lower mean aPTT ratios, but higher ratios were observed in patients with symptomatic bleeding, especially on the day bleeding occurred. Neither age, initial stroke severity, blood pressure, or baseline CT findings predicted hemorrhagic worsening. Functional recovery was improved sooner when heparin was administered early, but close monitoring of aPTT was necessary to lessen the risk of hemorrhagic complications.

Hemorrhagic transformation after acute ischemic stroke is compounded by thrombolytic therapy, but the impact of heparin can only be inferred. The Multicenter Acute Stroke Trial-Europe (MAST-E) study¹⁶⁵ evaluated the safety and efficacy of streptokinase administered IV within 6 hours of stroke onset. Among 310 patients, 159 (51%) had evidence of hemorrhagic transformation on CT scan, but only 23% of these were symptomatic. The relative risk of hemorrhagic transformation after streptokinase in this trial was in the same range as in other trials of thrombolytic therapy for acute stroke. Multivariate secondary analysis found that patients with symptomatic hemorrhagic transformation were more likely to have AF and less likely to have received heparin treatment.¹⁶⁵

To minimize the risk of thromboembolism after electrical cardioversion of AF or flutter, therapeutic anticoagulation should be established for at least 3 weeks before and for 4 weeks after cardioversion when the dysrhythmia has persisted longer than 2 days or when the duration is unknown. Warfarin is usually used during the outpatient phase.^{166,167} A more

recent approach uses transesophageal echocardiography to demonstrate the absence of thrombi in the left atrium and left atrial appendage. If no thrombus is evident, heparin anticoagulation may be initiated before pharmacological or electrical cardioversion, followed by warfarin therapy for 1 month after cardioversion. This treatment algorithm has a safety profile similar to that of conventional therapy and minimizes both the period of anticoagulation and the duration of AF before cardioversion, but no outcome superiority has been established.¹⁶⁸

A similar rationale underlies the use of heparin in conjunction with radiofrequency catheter ablation of cardiac tachyarrhythmias. A review of the literature over the last 10 years found an overall incidence of reported thromboembolic complications of 0.6% associated with radiofrequency catheter ablation. The risk is increased (to 1.8% to 2%) when ablation is performed in the left heart, but this increase is less than when the indication is ventricular tachycardia (2.8%).¹⁶⁹ For the ablation of AF, creation of extensive left atrial lesions has been associated with a high rate of thromboembolic stroke, despite administration of IV heparin and modulated electromagnetic energy. Adjuvant platelet inhibitor therapy to reduce the risk of thromboembolism in this specialized situation is under investigation.¹⁷⁰

Heparin-Induced Thrombocytopenia

HIT is an antibody-mediated adverse reaction to heparin that can result in venous or arterial thrombosis. Diagnosis of HIT is based on both clinical and serological features.^{171,172} Manifestations of the HIT syndrome include an otherwise unexplained fall in platelet count $\geq 50\%$, even if the nadir remains above $150 \times 10^9/L$, or skin lesions at heparin injection sites^{173,174} accompanied by HIT antibody formation. The fall in platelet count almost always occurs between day 5 and day 15 after introduction of heparin but can develop earlier in patients exposed to heparin during the previous 3 months. The frequency of HIT varies in different clinical settings^{175,176} such that the risk of venous thrombosis from HIT is higher in high-risk surgical patients¹⁷⁵ than in medical patients.¹⁷⁶

The HIT antigen is a multimolecular complex between PF4 and heparin.^{91,92,177-179} HIT antibodies bind to regions of the PF4 molecule that have been conformationally modified by its interaction with heparin. The increased propensity to thrombosis in HIT is probably mediated by thrombin generated as a result of *in vivo* platelet activation,^{180,181} as a consequence of interaction between heparin/PF4/IgG immune complexes with Fc receptors on platelets.¹⁸² A minimum of 12 to 14 saccharides are required to form the antigenic complex with PF4,^{178,179} so heparin molecules with a molecular weight greater than ≈ 4000 Da have the potential to cause HIT, and HIT occurs less commonly with LMWH than with UFH.^{183,184}

Diagnosis

Two main classes of laboratory assays have been developed to detect HIT antibodies,^{185,186} activation assays and antigen assays. The use of washed platelets rather than platelet-rich plasma derived from normal donors increases the reliability

TABLE 9. Treatment Protocol for Lepirudin (Recombinant Hirudin) in HIT

For rapid therapeutic anticoagulation (IV infusion):	
Loading dose	0.4 mg/kg bolus IV
Maintenance	0.15 mg · kg ⁻¹ · h ⁻¹ IV, with adjustments to maintain aPTT 1.5–2.5 times median normal range

of activation assays. Of the various activation assays available, those that use washed platelets and platelet serotonin release¹⁸⁷ or heparin-induced platelet activation^{188,189} are most accurate.¹⁷³ Antigen assays, now commercially available, that are based on detecting antibodies against PF4 bound to heparin¹⁸⁸ or polyvinylsulfonate¹⁹⁰ respond to clinically insignificant antibodies more often than do activation assays.¹⁷⁵

Treatment

If HIT is suspected on clinical grounds and the patient either has thrombosis or is at risk of developing thrombosis, heparin should be stopped and replaced with lepirudin (Refludan). Although the diagnosis should be confirmed as soon as practical, treatment should not be delayed. Warfarin should not be used alone, because a recent report suggests this can aggravate the thrombotic process. Lepirudin is a hirudin derivative that does not exhibit cross-reactivity and is manufactured by recombinant technology.¹⁹¹ Its use in HIT has been approved by the Food and Drug Administration on the basis of 2 prospective cohort studies^{192,193} that compared treatment of HIT-associated thrombosis with lepirudin versus historical controls. An IV infusion is used for rapid therapeutic anticoagulation, beginning with a bolus loading dose of 0.4 mg/kg IV followed by a maintenance dose of 15 mg · kg⁻¹ · h⁻¹, with adjustments to maintain aPTT at 1.5 to 2.5 times the median of the normal laboratory range.

In the absence of overt thrombosis, cessation of heparin has long been the cornerstone of management of HIT, but several studies have shown that simply stopping heparin may be inadequate because of the high risk of overt thrombosis in the week after interruption of heparin.^{192–197} Treatment with hirudin should therefore be considered in all patients with HIT who remain at risk of thrombosis, including postoperative patients and those with sepsis. Recombinant hirudin (lepirudin) should be used until the platelet count has recovered (Table 9). This should also be considered for patients with acute HIT without thrombosis (isolated HIT), because there is a high risk for subsequent clinically evident thrombosis in these patients. Warfarin should not be used alone to treat acute HIT complicated by DVT because of the risk of venous limb gangrene. When given to patients adequately anticoagulated with lepirudin, warfarin appears safe in acute HIT, but it is prudent to delay starting warfarin until the platelet count has risen above 100 × 10⁹/L.

Low-Molecular-Weight Heparins

Historical Perspective

The development of LMWHs for clinical use was stimulated by 3 main observations. These are that compared with UFH, LMWH has reduced anti-factor IIa activity relative to anti-factor

TABLE 10. Relationship Between Molecular Weight of Heparin Fractions and Anticoagulant Activity

Heparin Oligosaccharides	Molecular Weight, Da	Anticoagulant Activity (Anti-Xa)	Anticoagulant Activity (Anti-IIa)
8	2400	1.30	Nil
12	3600	2.58	Nil
16	4800	1.60	Nil
18	5400	0.95	0.51
24	7200	1.30	1.21

Data from Lane et al.²⁹

Xa activity,^{26,198} more favorable benefit-risk ratios^{199–204} in experimental animals, and superior pharmacokinetic properties.^{205–210} Of these potential advantages, only the pharmacokinetic properties are of clear clinical importance.^{93,211}

LMWH fractions prepared from standard commercial-grade heparin have progressively less effect on the aPTT as they are reduced in molecular size, while still inhibiting activated factor X (factor Xa).^{26,198} The aPTT activity of heparin reflects mainly its anti-factor IIa activity. The dissociation of anti-factor Xa activity from AT (IIa) activity (expressed as an aPTT measurement), described in 1976,²⁶ challenged the prevailing biophysical model for the anticoagulant effect of heparin, which predicted that any heparin molecule, irrespective of chain length, would catalyze the inactivation of serine protease coagulation enzymes equally provided it contained the high-affinity binding site for AT. The explanation for the difference in anticoagulant profile between LMWH and heparin was elucidated in subsequent studies (Table 10).^{29,30,212–216}

Bleeding in Experimental Animals

Early evidence that LMWH produces less microvascular bleeding than heparin in experimental models^{199–204} has not been borne out by recent large randomized trials in the prevention and treatment of venous thrombosis, treatment of PE, or treatment of unstable angina. In these studies, LMWH and heparin have shown similar low rates of bleeding (see below).

Pharmacokinetic Properties

In the 1980s, a number of investigators^{205–210} reported that LMWH preparations had a longer plasma half-life and better bioavailability at low doses than heparin, as well as a more predictable dose response.²¹⁷ These findings provided the rationale for comparing unmonitored weight-adjusted LMWH with aPTT-monitored heparin in patients with established DVT and in patients with unstable angina.

Structure and Pharmacology

LMWHs are derived from heparin by chemical or enzymatic depolymerization to yield fragments approximately one third the size of heparin. The various LMWHs approved for use in Europe, Canada, and the United States are shown in Table 11. Because they are prepared by different methods of depolymerization, they differ to some extent in pharmacokinetic properties and anticoagulant profile and are not clinically

TABLE 11. Commercial LMWH and a Heparinoid: Methods of Preparation

Agent	Manufacturer	Method of Preparation
Nadroparin calcium (Fraxiparin)	Sanofi	Nitrous acid depolymerization
Enoxaparin sodium (Lovenox/Clexane)	Rhône-Poulenc Rorer	Benzylation followed by alkaline depolymerization
Dalteparin (Fragmin)	Kabi	Nitrous acid depolymerization
Ardeparin (Normiflo)	Wyeth-Ayerst	Peroxidative depolymerization
Tinzaparin (Innohep)	Leo Laboratories	Enzymatic depolymerization with heparinase
Reviparin (Clivarine)	Knoll	Nitrous acid depolymerization
Danaparoid sodium (Orgaran)	NV Organon	Prepared from animal gut mucosa; contains heparin sulfate (84%), dermatan sulfate (12%), and chondroitin sulfate (4%)

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interchangeable. LMWHs have a mean molecular weight of 4500 to 5000 Da with a distribution of 1000 to 10 000 Da.

Depolymerization of heparin yields low-molecular-weight fragments with reduced binding to proteins or cells (Table 12). Indeed, all of the anticoagulant, pharmacokinetic, and other biological differences between UFH and LMWH can be explained by the relatively lower binding properties of LMWH. Thus, compared with UFH, LMWHs have reduced ability to inactivate thrombin because the smaller fragments cannot bind simultaneously to AT and thrombin. On the other hand, because bridging between AT and factor Xa is less critical for anti-factor Xa activity, the smaller fragments inactivate factor Xa almost as well as larger molecules.^{35,218–220} Reduced binding to plasma proteins is responsible for the more predictable dose-response relationship of LMWHs.⁸⁹ Less binding to macrophages and endothelial cells increases the plasma half-life²¹¹ of LMWH compared with UFH, whereas reduced binding to platelets and PF4 may explain the lower incidence of HIT.^{40,90,183} Finally, reduced binding of LMWH to osteoblasts results in less activation of osteoclasts and less bone loss.^{46,47} LMWHs are cleared principally by the renal route, and their biological half-life is prolonged in patients with renal failure.^{221–223}

Anticoagulant Effects

Like UFH, LMWHs produce their major anticoagulant effect by activating AT. The interaction with AT is mediated by a unique pentasaccharide sequence^{21,224} found on fewer than one third of LMWH molecules. Because a minimum chain length of 18 saccharides (including the pentasaccharide sequence) is required for the formation of ternary complexes between heparin chains, AT, and thrombin, only the 25% to 50% of LMWH species that are above this critical chain

length are able to inactivate thrombin. In contrast, all LMWH chains containing the high-affinity pentasaccharide catalyze the inactivation of factor Xa (Figure 3). Because virtually all heparin molecules contain at least 18 saccharide units,^{213,214} heparin has an anti-factor Xa to anti-factor IIa ratio of 1:1. In contrast, commercial LMWHs have anti-factor Xa to anti-IIa ratios between 2:1 and 4:1, depending on their molecular size distribution.

LMWHs have been evaluated in a large number of randomized clinical trials and have been found to be safe and effective for prevention and treatment of venous thrombosis. More recently, LMWH preparations have also been evaluated in patients with acute PE and those with unstable angina.

Prevention of Venous Thrombosis

LMWHs were first evaluated for the prevention of venous thrombosis in high-risk surgical patients in the mid-1980s, and there is now extensive experience with their use for this indication. In patients undergoing general surgery and in high-risk medical patients, low doses of LMWH administered SC once daily are at least as effective and safe as low-dose UFH administered SC 2 or 3 times daily. LMWH has become the anticoagulant of choice for the prevention of venous thrombosis during major orthopedic surgery and in anticoagulant-eligible patients after major trauma. The risk of bleeding with LMWH is small and comparable to that with low-dose heparin.

General Surgery

LMWHs were effective and safe in 2 well-designed randomized trials. One trial²²⁵ in 4498 patients showed a statistically significant reduction in thromboembolic mortality in favor of LMWH (0.07%) compared with a UFH control group

TABLE 12. Biological Consequences of Reduced Binding of LMWH to Proteins and Cells

Binding Target	Biological Effects	Clinical Consequences
Thrombin	Reduced anti-IIa to anti-Xa ratio	Unknown
Proteins	More predictable anticoagulant response	Monitoring of anticoagulant effect unnecessary
Macrophages	Cleared through renal mechanism	Longer plasma half-life. Once-daily SC treatment effective
Platelets	Reduced incidence of heparin-dependent antibody	Reduced incidence of HIT
Osteoblasts	Reduced activation of osteoclasts	Lower incidence of osteopenia

Reprinted with permission from Hirsh J, Warkentin TE, Shaughnessy SG, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest*. 2001;119(1 suppl):64S–94S.

TABLE 13. Meta-Analysis of Randomized Studies Comparing LMWH With UFH in Patients Undergoing Elective Hip Surgery

Factor	Proximal Venous Thrombosis	Total Venous Thrombosis	Major Bleeding	Minor Bleeding	PE
Common OR*	0.40	0.70	0.64	0.90	0.30
95% CI	0.28–0.59	0.53–0.92	0.34–1.23	0.61–1.33	0.09–1.02

*A common OR <1.0 favors LMWH over heparin.

Data from Anderson et al.²³⁸

(0.36%). A meta-analysis²²⁶ of randomized trials comparing low-dose heparin with LMWH concluded that there were minimal differences between the 2 forms of prophylaxis.

Orthopedic Surgery

Compared with placebo, LMWH produced a risk reduction for all thrombi and for proximal vein thrombi between 70% and 79%. This reduction occurred without an increase in major bleeding in 2 studies^{227,228} and with a small increase in minor bleeding in a third,²²⁹ but all were too small to exclude a modest increase in major bleeding with LMWH. LMWH has been compared with a variety of other methods of prophylaxis, including low-dose heparin,^{230–232} adjusted-dose heparin,^{233,234} dextran,^{235,236} and warfarin.²³⁷ In most studies performed in North America, the LMWH was started 12 to 24 hours postoperatively, increasing the acceptance of prophylaxis among orthopedic surgeons and anesthesiologists concerned about the risk of spinal cord hematoma with prophylactic LMWH in patients undergoing spinal anesthesia. In such cases, the first dose of LMWH should be delayed until after the epidural catheter has been removed; when this is not feasible, the catheter should be removed at least 8 hours after the last dose of LMWH. In addition, other drugs that impair hemostasis (such as nonsteroidal anti-inflammatory agents) should be avoided.

Anderson et al²³⁸ performed a meta-analysis of randomized studies comparing LMWH with either fixed low-dose or adjusted-dose heparin. The observed incidence of venous thrombosis was 15.9% in the LMWH group and 21.7% in the heparin group ($P=0.01$), and there was a significant reduction in the incidence of proximal venous thrombosis in the LMWH group (5.4% versus 12.5%; $P<0.0001$). There was no difference in the incidence of bleeding between the 2 groups (Table 13). These results are comparable to those of an earlier meta-analysis.²²⁶

Two studies compared LMWH and low-dose heparin for prevention of venous thrombosis after elective total knee

arthroplasty. In one, LMWH was more effective than heparin²³⁹; the incidence of venous thrombosis was 24.6% in the LMWH group and 34.2% in the heparin group ($P=0.02$). In the other,²⁴⁰ the incidence of venous thrombosis was 23% in the LMWH group and 27% in the heparin group. There was no difference in the incidence of bleeding in either study.

LMWH preparations have been compared with warfarin and other oral anticoagulants in 6 studies involving high-risk orthopedic surgical patients.^{241–246} The LMWH preparations tested showed efficacy equal to warfarin in patients undergoing elective hip replacement, but LMWHs appeared more effective than oral anticoagulants in patients undergoing major knee surgery (Table 14). In a number of these studies, LMWH was associated with a small but significant increase in major bleeding.

Hip Fracture

Two randomized trials have been performed with danaparoid sodium in patients with hip fracture. In one,²⁰⁴ the incidence of thrombosis was 13% in patients given danaparoid sodium (Orgaran) and 35% in patients given dextran ($P<0.001$). Blood transfusion requirements were significantly higher in the dextran group. In the other,²⁴⁷ venous thrombosis occurred in 27.8% of the patients treated with danaparoid sodium and in 44.8% of patients in the aspirin group ($P=0.028$). There was no difference in bleeding between the 2 groups.

Multiple Trauma

Geerts and colleagues²⁴⁸ compared LMWH (enoxaparin sodium [Lovenox/Clexane]; 30 mg SC every 12 hours) with low-dose heparin (5000 U SC every 12 hours), started within 36 hours of injury in victims of multiple trauma. The incidence of venous thrombosis was 44% in the 136 patients allocated to the low-dose heparin group and 31% among 129 patients in the LMWH group ($P=0.014$). The incidence of proximal venous thrombosis was 15% in the low-dose hepa-

TABLE 14. Controlled Trials With LMWH in Patients Undergoing Elective Total Knee Arthroplasty

Author	LMWH	DVT	Proximal DVT	Major Hemorrhage	Control	DVT	Proximal DVT	Major Hemorrhage
Hull et al ²⁴⁴	Tinzaparin (Innohep)	116/258 (45%)	20/258 (18%)	9/317 (3%)	Warfarin	152/277 (55%)	34/277 (12%)	3/324 (1%)
RD Heparin Group ²⁴¹	Ardeparin (Normiflo)	41/149 (28%)	7/149 (5%)	N/A	Warfarin	60/147 (41%)	15/147 (10%)	NA
Leclerc et al ²⁴⁵	Enoxaparin sodium (Lovenox/Clexane)	8/41 (19%)	0/41 (0%)	0/66 (0%)	Placebo	35/54 (65%)	11/54 (20%)	1/65 (2%)
Spiro et al ²⁴²	Enoxaparin sodium (Lovenox/Clexane)	41/108 (38%)	3/108 (3%)	9/173 (5%)	Warfarin	72/122 (59%)	16/122 (13%)	4/176 (2%)
Fauno et al ²⁴⁰	Enoxaparin sodium (Lovenox/Clexane)	29/92 (23%)	3/92 (3%)	NA	Heparin	25/93 (27%)	5/93 (5%)	NA
Colwell et al ²³⁹	Enoxaparin sodium (Lovenox/Clexane)	54/145 (37%)	4/145 (2%)	3/28 (1%)	Heparin	74/143 (52%)	22/143 (15%)	3/225 (1%)

Adapted from Colwell et al.²³⁹

TABLE 15. LMWH vs Heparin for Treatment of DVT: Symptomatic Recurrent Venous Thromboembolism During Initial Treatment and After 3 to 6 Months

Agent	Patients, n (%)		Relative Risk Reduction (95% CI)	P
	LMWH	UFH		
Nadroparin (Fraxiparin)	20/361 (5.5)	32/355 (9.0)	40 (−5–66)	0.07
Tinzaparin (Logiparin)	6/213 (2.8)	15/219 (6.9)	59 (−1–83)	0.07
Enoxaparin (Clexane)	13/314 (4.1)	20/320 (6.3)	35 (−32–68)	0.23
Dalteparin (Fragmin)	16/322 (5.0)	8/339 (2.4)	−110 (−374–7)	0.07

Data from Kuijter et al.²⁵⁵

rin group and 6% in the LMWH group ($P=0.09$).²⁴⁹ Major bleeding occurred in 0.6% of patients treated with heparin and 2.9% of those treated with LMWH.

Summary of LMWH in Orthopedic Surgery and Trauma

Overall, LMWHs appear effective for prevention of venous thromboembolism, and they appear safe for 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 $\approx 70\%$. LMWHs are more effective than low-dose heparin, at least as effective as warfarin, and more effective than dextran or aspirin in patients undergoing total hip arthroplasty, and they are more effective than warfarin, aspirin, or dextran in patients undergoing major knee surgery. Similarly, LMWHs are more effective than aspirin in patients with hip fracture. The risk of bleeding with LMWH is comparable to that with low-dose heparin or warfarin.

Neurosurgery

In a recent study²⁵⁰ comparing LMWH plus compression stockings with compression stockings alone, those assigned to the LMWH group had a risk reduction of 48%. There was no difference in major bleeding.

Medical Patients

LMWHs have been compared with placebo in 2 studies of patients with ischemic stroke^{251,252} and have been compared with low-dose heparin in 2 studies.^{253,254} Compared with placebo, LMWHs reduce the risk of venous thrombosis between 40% and 86% without an increase in clinically important bleeding. In studies comparing LMWHs with heparin, patients randomized to receive LMWH showed a statistically significant $>70\%$ relative risk reduction in thrombosis.^{118,259}

Treatment of Venous Thromboembolism

A number of LMWH preparations have been compared with heparin in patients with venous thrombosis and/or PE in well-designed studies. The results of studies published before 1995 that used 4 different preparations have been summarized in a meta-analysis²⁵⁵ in which the data for each of the 4 LMWHs were pooled separately (Tables 15 and 16). All 4 LMWH preparations were as effective and safe as IV heparin, and the rates of recurrent thromboembolism and major bleeding were similar with all of the LMWHs. It is noteworthy that the LMWHs were administered by SC injection in unmonitored, weight-adjusted doses, whereas heparin was monitored by the aPTT.

Since publication of the pooled analysis in 1995, 5 additional large randomized trials have been completed,^{256–260} 2 in patients with venous thrombosis,^{257,258} 1 in patients with venous thrombosis or PE,²⁵⁹ 1 in patients with PE,²⁵⁶ and 1 in patients with proximal vein thrombosis who were also randomized to inferior vena cava filter insertion.²⁶⁰ The design of 2 of the studies^{257,258} capitalized on the more predictable anticoagulant response to LMWH by encouraging patients assigned to LMWH treatment at home, whereas those assigned to heparin were treated conventionally in the hospital with a continuous IV infusion. The results, shown in Table 17, indicate that out-of-hospital administration of LMWH to eligible patients with DVT is as effective and safe as IV heparin administered in the hospital. Both studies excluded patients with symptomatic PE or a history of recent previous venous thrombosis. To address this study deficiency, the investigators collaborated in the COLUMBUS study,²⁵⁹ in which 1021 patients with venous thrombosis or PE were randomly assigned to treatment with either SC LMWH (rivariparin sodium) or adjusted-dose IV UFH for 8 days. Warfarin was started concomitantly and continued for 3 months. The mean hospital stay was 3 days shorter in patients assigned to LMWH, whereas the incidence of recurrent thromboembolism, bleeding, and mortality was similar in both groups.

TABLE 16. Incidence of Major Bleeding Complications During Initial Treatment and for 48 Hours After Heparin Cessation: UFH vs LMWH

Agent	Patients, n (%)		Relative Risk Reduction (95% CI)	P
	LMWH	UFH		
Nadroparin (Fraxiparin)	4/446 (0.9)	10/436 (2.3)	59 (−16–86)	0.09
Tinzaparin (Logiparin)	1/213 (0.5)	11/219 (5.0)	91	<0.01
Enoxaparin (Clexane)	5/314 (1.6)	3/320 (0.9)	−70 (−580–58)	>0.2
Dalteparin (Fragmin)	2/433 (0.5)	5/464 (1.0)	55 (−99–90)	>0.2

Data from Kuijter et al.²⁵⁵

TABLE 17. Efficacy and Safety of Outpatient LMWH in Patients With Venous Thrombosis

Study	Treatment	n	Recurrent Thrombosis, %	Major Bleeding, %	Mean Hospital Stay, d
Levine et al ²⁵⁷	UFH	253	6.7	1.2	6.5
	LMWH	247	5.3	2.0	1.1
Koopman et al ²⁵⁸	UFH	198	8.6	2.0	8.1
	LMWH	202	6.9	0.5	2.2

The relative efficacy and safety of LMWH and heparin for treatment of patients with acute PE have also been investigated in a larger population. Patients who did not require thrombolytic therapy or pulmonary embolectomy (n=612) were randomly assigned to receive LMWH (tinzaparin, 175 anti-factor Xa U/kg SC once daily) or heparin (50 U/kg bolus followed by a continuous infusion of 500 U · kg⁻¹ · d⁻¹ adjusted to an aPTT ratio of 2.0 to 3.0). The outcome measure, a composite of recurrent thromboembolism, major bleeding, and death, was assessed on days 8 and 90. By day 8, 9 (2.9%) of 308 patients assigned to UFH and 9 (3.0%) of 304 patients assigned to LMWH developed at least 1 of the primary events; by day 90, 22 patients (7.1%) assigned to UFH and 18 (5.9%) assigned to LMWH developed events ($P=0.54$; Table 18). The rate of major bleeding was similar in both groups (2.6% and 2.0%, respectively; $P=NS$). There were 3 deaths at 8 days and 14 deaths (4.5%) at 90 days in those assigned to UFH, and there were 4 deaths at 8 days and 12 (3.9%) at 90 days in patients assigned to LMWH. Five of the deaths in the heparin group were treatment related (3 from PE and 2 from major bleeding) compared with 4 in the LMWH group (3 from PE and 1 from bleeding). The findings of this study combined with those of the COLUMBUS study indicate that SC weight-adjusted LMWH is as effective and safe as IV heparin.

A meta-analysis¹¹⁹ of 11 randomized studies comparing IV heparin and SC LMWH in ≈3500 patients with acute DVT (Table 19) found major bleeding to be less frequent in patients treated with LMWH (OR 0.57; $P=0.05$). The frequency of recurrent thromboembolic events did not differ significantly between treatment groups (OR 0.85; $P=0.28$), but the mortality rate was lower in those assigned LMWH (OR 0.71; $P=0.02$). Most of the deaths were not ascribed to PE, so the mechanism for this mortality reduction is uncertain.

Most studies evaluating LMWH preparations for treatment of venous thromboembolism evaluated a twice-daily, weight-adjusted regimen. However, 2 studies using tinzaparin, 1 in

patients with acute venous thrombosis²⁶¹ and the other in patients with acute PE,²⁵⁶ used once-daily dosing (175 anti-factor Xa U/kg). Results of comparisons of the efficacy and safety of LMWH administered once or twice daily^{262,263} found once-daily administration of 2 different LMWH preparations as effective and safe as twice-daily dosing.

Unstable Angina and Non-Q-Wave MI

Although the combination of heparin and aspirin is effective for short-term treatment of patients with unstable angina, between 6% and 15% progress to MI or death within 1 month despite continuing aspirin therapy.^{67,264} The recent success of LMWH for the treatment of venous thromboembolism and the feasibility and safety of out-of-hospital use have led to the evaluation of LMWH preparations administered SC without laboratory monitoring in the setting of unstable angina and non-Q-wave MI. To date, 7 randomized trials evaluating LMWH in patients with unstable angina and non-Q-wave MI have been reported (Table 20). Short- and long-term relative risk reductions compared with UFH are shown in Figures 8 and 9. The first small trial²⁶⁵ (n=219) compared nadroparin plus aspirin versus UFH plus aspirin versus aspirin alone using an open-label design. The rate of acute MI, recurrent angina, and urgent coronary revascularization was significantly lower with the LMWH and aspirin combination than with UFH and aspirin or aspirin alone. Subsequent to this, a large, double-blind, placebo-controlled trial in 1506 patients with unstable angina or non-Q-wave MI (FRISC; FRagmin during InStability in Coronary artery disease)²⁶⁶ compared 120 U/kg of dalteparin twice daily for 6 days followed by 7500 anti-factor Xa U once daily for 35 to 45 days with placebo; all patients received aspirin. Compared with placebo, LMWH reduced the risk of death or MI by ≈80% at 6 days. In addition, the composite end point of death, MI, and need for revascularization was significantly lower in patients treated with LMWH (10.3% versus 5.4%). However, no additional benefit was observed with long-term lower-dose LMWH (7500 anti-factor Xa U of dalteparin once daily)

TABLE 18. Relative Safety and Efficacy of LMWH and UFH in Patients With PE

Study	Treatment	n	Recurrent Thrombosis, %	Major Bleeding, %	Mortality, %
COLUMBUS ²⁵⁹	UFH	511	4.9	1.6	7.6
	LMWH	510	5.3	2.0	7.1
Simonneau et al ²⁵⁶	UFH	308	1.9	1.6	4.5
	LMWH	304	1.6	1.0	3.9

In the COLUMBUS trial, only one third of the patients had PE; the other two thirds had DVT.

TABLE 19. LMWH vs Heparin for Treatment of DVT: Meta-Analysis

	Total Subjects, n	Summary Odds Reduction*	NNT, n	Frequency With UFH, %
Major bleeding	3674	0.57†	164	1.9
RTE	3566	0.85	114	5.4
Mortality (overall)	3566	0.7†	61	6.8

NNT indicates number of patients needed to treat to prevent 1 event that would occur during alternate treatment; RTE, recurrent thromboembolism.

*A summary odds reduction <1.0 favors LMWH; odds reduction >1.0 favors UFH.

† $P < 0.05$.

Adapted from Gould et al.¹¹⁹

compared with placebo. After 4 to 5 months of follow-up, the rates of death and MI in the placebo and dalteparin groups was 15.3% and 14.0%, respectively ($P=0.41$), and the rates of death, MI, or revascularization were 43.6% and 42.7%, respectively ($P=0.18$). This study established the short-term value of LMWH (dalteparin) for treatment of unstable angina and non-Q-wave MI and added to the data in support of a beneficial effect of heparin and aspirin over aspirin alone in this patient population. However, no effect of moderate-dose LMWH was observed over the long term.

In a third study (FRIC; FRagmin In unstable Coronary artery disease),²⁶⁷ which used an open, randomized design, dalteparin (120 anti-factor Xa U/kg twice daily) was compared with heparin (5000-U bolus followed by 1000-U/h continuous infusion for 6 days) in 1492 patients with unstable angina or non-Q-wave infarction. This was followed in a second phase by a double-blind study comparing LMWH at a dose of 7500 U/d with placebo. All patients received aspirin. Both treatment regimens were equivalent in terms of efficacy and safety. At 6 days, the composite outcome of death, MI, or recurrent angina occurred in 7.6% of the heparin group and 9.3% of the LMWH group, whereas the corresponding rates of the composite of death or MI were 3.6% and 3.9%, respectively. Between days 6 and 45, the rate of death, MI, or

recurrent angina was 12.3% in both groups. There was no difference in major bleeding, which was infrequent.

The ESSENCE trial (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events)²⁶⁸ is 1 of 2 studies that compared enoxaparin with heparin. Patients ($n=3171$) with unstable angina or non-Q-wave MI were randomized in a double-blind fashion to 1 mg/kg SC (100 anti-factor Xa U) of enoxaparin every 12 hours or UFH, administered as an IV bolus followed by a continuous infusion, for 2 to 8 days; the median duration of treatment in both groups was 2.6 days (Table 20). There was a significant 17% risk reduction in the primary end point of death, MI, or recurrent angina at 14 days with LMWH ($P=0.019$) and a 15% risk reduction at 30 days ($P=0.016$). This difference was accounted for mainly by a lower incidence of recurrent angina in patients assigned to LMWH. There was no difference in the incidence of major bleeding at 30 days (6.5% with LMWH versus 7.0% with heparin), but total bleeding was more frequent with the LMWH group (18.4% versus 14.2%), primarily because of bruising at injection sites. At 1 year, the difference in the composite end point remained significant ($P=0.022$).²⁶⁹

TIMI-11B (Thrombolysis In Myocardial Infarction 11B)²⁷⁰ was a double-blind study comparing enoxaparin (bolus followed by SC injections every 12 hours for 3 to 8 days) and IV heparin (administered for at least 3 days) in 3910 patients with unstable angina or non-Q-wave MI. The primary outcome was death, MI, or urgent revascularization at 43 days. Patients assigned to LMWH continued SC treatment at a lower dose until day 43, whereas patients assigned initially to heparin received placebo. There was an 18% relative risk reduction in events at 14 days ($P=0.029$) and a 12% risk reduction at 43 days ($P=0.048$). The absolute risk reductions were 2.4% and 2.3% at 14 and 43 days, respectively. The difference in treatment duration between UFH (3 days) and enoxaparin (43 days) and the validity of comparing event rates at 14 days render these data questionable. In addition, the lack of effectiveness of enoxaparin beyond 14 days is surprising and fails to establish a role for long-term use of LMWH in this patient population.²⁷¹

TABLE 20. Trials of LMWH in Patients With Acute Coronary Syndromes Without ST-Segment Elevation on the ECG

Trial	n	Short-Term Comparison*	Long-Term Comparison†
Gurfinkel et al ²⁶⁵	219	Nadroparin 214 U SC BID vs placebo	N/A
FRISC ²⁶⁶	1506	Dalteparin 120 U/kg SC BID vs placebo	Dalteparin 7500 U SC QD vs placebo
Klein et al (FRIC) ²⁶⁷	1482	Dalteparin 120 U/kg SC BID vs UFH 5000 U B, 1000 U/h IV then 12 500 U SC BID	Dalteparin 7500 U SC QD vs placebo
Cohen et al (ESSENCE) ²⁶⁸	3171	Enoxaparin 1 mg/kg SC BID 2–8 d vs UFH 5000 U aPTT 55–85 seconds	N/A
Antman et al (TIMI-11B) ²⁷⁰	3912	Enoxaparin 3000 U B, 100 U/kg BID vs UFH 70 U B, 15 U/kg aPTT 1.5–2.0×	Enoxaparin 4500–6000 U SC BID vs placebo
Leizorivich (FRAXIS) ²⁷²	3468	Nadroparin 86 U SC BID vs UFH 5000 B 1250 U/h target local aPTT	Nadroparin 86 U SC vs placebo
FRISC-II ²⁷³	2457	Dalteparin 120 U/kg BID vs placebo	Dalteparin 5000 or 7500 U SC BID vs placebo

B indicates bolus.

*In-hospital phase.

†One to 3 months.

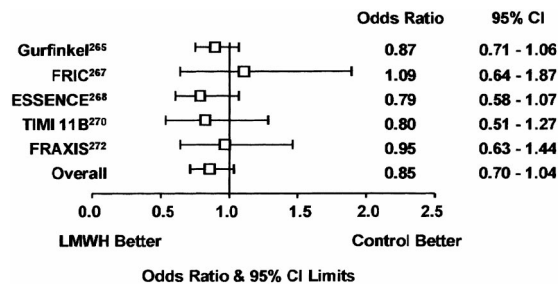


Figure 8. Unstable angina in LMWH vs UFH meta-analysis of short-term trials for death/recurrent MI.

Nadroparin was also evaluated in the FRAXIS (FRAXiparine in Ischaemic Syndrome) trial.²⁷² Patients with unstable angina or non-Q-wave infarction were randomly assigned to receive full-dose SC nadroparin (every 12 hours on days 1 through 6, then placebo from day 7 to day 14), sustained SC nadroparin (every 12 hours for 14 days), or initial IV heparin (on days 1 through 6, followed by placebo until day 14). The incidence of the primary outcome (cardiovascular death, MI, and refractory or recurrent angina) was no different among the 3 groups at 6 days, and there was no difference between short- and long-term treatment with LMWH by 14 days.

Another recent trial evaluated long-term administration of LMWH compared with placebo. FRISC-II (Fragmin and Fast Revascularisation during InStability in Coronary artery disease) was a randomized, placebo-controlled trial of dalteparin in 2267 patients with unstable angina and non-Q-wave-MI.²⁷³ All patients received dalteparin 120 IU/kg every 12 hours for the acute phase (5 to 7 days) and then were randomized to dalteparin 5000 to 7500 IU every 12 hours or placebo for 90 days. The primary outcome was the composite of death and MI at 3 months. The primary outcome rates did not differ significantly between the dalteparin and placebo groups (6.7% versus 8.0%, $P=0.17$), but the rates of major and minor bleeding were significantly higher in patients who received dalteparin (3.3% versus 1.5%, $P<0.01$ and 23.0% versus 8.4%, $P<0.001$), respectively. A meta-analysis of the 2 trials of enoxaparin (ESSENCE²⁶⁸ and TIMI-11B²⁷⁰) showed that compared with UFH, enoxaparin produced a 20% relative reduction in rates of death and MI during the first 7 to 14 days of treatment.

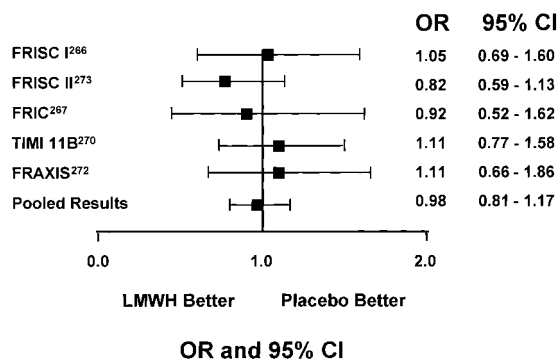


Figure 9. Long-term trials comparing LMWH vs UFH in patients with acute coronary syndromes and outcome of death/MI.

The reason for the observed differences across trials that evaluated short-term LMWH compared with UFH in the presence of aspirin (the FRIC and FRAXIS versus ESSENCE and TIMI-11B studies) is not clear. Potential explanations include true therapeutic differences between the LMWH agents and differences in trial design, administration of UFH, and patient population, or the play of chance. To determine definitively whether enoxaparin is superior to other LMWH preparations would require head-to-head comparisons within 1 or more trials.

When all trials that compared short-term LMWH with UFH were pooled ($n=12\ 171$), an OR of 0.85 (95% CI 0.70 to 1.04) was derived, which suggests a modest 15% reduction with LMWH over UFH (Figure 8). Data from $\approx 10\ 000$ patients in long-term trials do not indicate a benefit of LMWH over placebo in reducing MI or death (OR 1.04; 95% CI 0.79 to 1.37; Figure 9). It is of interest to consider these results with LMWH in unstable angina and non-Q-wave MI in light of experience with platelet GP IIb/IIIa antagonists and direct thrombin inhibitors. Because LMWH has not been compared directly with either of these classes of antithrombotic agents, however, only indirect inferences are possible, and these may be misleading.

Heparin has been compared with the synthetic GP IIb/IIIa blocker, iabipfiban, in the PARAGON trial (Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network)²⁷⁴ and with tirofiban in the PRISM trial (Platelet Receptor Inhibition in Ischemic Syndrome Management).²⁷⁵ When used alone, neither GP IIb/IIIa antagonist was more effective than heparin. The PURSUIT trial (Platelet Glycoprotein IIb/IIIa in Unstable Angina Receptor Suppression Using Integrilin Therapy)²⁷⁶ evaluated 9450 patients and showed that a 72-hour infusion of Integrilin was associated with a 15% to 20% relative reduction in death and MI. Both the CAPTURE trial (C7E3 fab AntiPlatelet Therapy in Unstable REfractory angina),¹³² which evaluated abciximab in 1265 patients, and the PRISM-PLUS trial,¹³¹ which evaluated tirofiban in 1915 patients, focused on high-risk patients with unstable coronary artery disease. In both studies, GP IIb/IIIa inhibitors produced a 30% to 50% relative reduction in death or MI with treatment before and during revascularization.

Hirudin, a bivalent direct thrombin inhibitor, was evaluated in the OASIS-2 (Organization to Assess Strategies for Ischemic Syndromes) trial,¹⁰⁴ a randomized study of 10 141 patients with unstable coronary artery disease assigned to either 72 hours of IV hirudin or standard heparin. There was a 10% to 20% relative reduction in the incidence of death or MI with hirudin in the first 3 to 7 days, but this was associated with an increase in bleeding (major bleeding in 1.2% versus 0.7% of patients and minor bleeding in 7.6% versus 4.5% of patients with hirudin and heparin, respectively).

Thus, 3 new classes of antithrombotic agents—LMWH (such as enoxaparin), platelet GP IIb/IIIa antagonists (such as abciximab), and thrombin inhibitors (such as hirudin)—are available for treatment of patients with unstable angina and non-Q-wave infarction. It appears that it is necessary to combine GP IIb/IIIa antagonists with heparin to achieve optimal efficacy. Because the efficacy of these new anti-

thrombotic agents is limited to the initial period of acute treatment, the challenge is to develop safe and effective regimens that require simple or no monitoring and that are convenient for outpatient use to reduce the 15% risk of new MI over 3 months.

Q-Wave MI

Experience with LMWH in patients with acute Q-wave MI is limited to 2 small studies in which the majority of patients received thrombolytic therapy. The Fragmin in Acute Myocardial Infarction (FRAMI) study²⁷⁷ enrolled 776 patients with acute anterior MI in a randomized, double-blind comparison of LMWH (dalteparin at 150 U/kg SC twice daily during hospitalization) with placebo. Thrombolytic therapy (streptokinase) and aspirin were administered to 91.5% and 97.6% of patients, respectively. The mean time to the start of treatment was \approx 12 hours in both the dalteparin and placebo groups. The primary end point was the composite of left ventricular mural thrombus formation diagnosed by echocardiography and systemic arterial embolism by day 92. Of the 517 patients with echocardiograms available for analysis, thrombus formation, embolism, or both developed in 59 (21.9%) of 270 patients in the placebo group and 35 (14.2%) of 247 patients receiving dalteparin ($P=0.03$). Benefit was predominantly a consequence of decreased left ventricular thrombus formation. The relative risk of thrombus formation with LMWH treatment was 0.63 (95% CI 0.43 to 0.92, $P=0.02$). Analyses of all randomized patients revealed no significant difference between treatments with respect to arterial embolism (6 versus 5 patients, respectively), reinfarction (8 versus 6 patients), or death (23 patients in each group). LMWH therapy was associated with an increased risk of both major (2.9% versus 0.3%, $P=0.006$) and minor (14.8% versus 1.8%, $P<0.001$) hemorrhage. One nonfatal and 2 fatal cerebral hemorrhages (verified by CT scan) occurred in the LMWH group. Thus, although LMWH reduced left ventricular thrombus formation in patients with acute anterior MI, its use was associated with a significantly increased risk of major hemorrhage, possibly a consequence of concomitant thrombolytic therapy and a higher dose of dalteparin than used in either the FRISC or FRIC studies.

In a small study²⁷⁸ of 103 streptokinase-treated patients randomly assigned to enoxaparin (40 mg/d for 25 days) or placebo within 5 days of acute MI, 2 (4.3%) of 43 patients in the enoxaparin group developed recurrent MI within 30 days compared with 12 (20%) of 60 patients receiving placebo ($P=0.02$). The BIOMACS II study²⁷⁹ (Biochemical Markers in Acute Coronary Syndromes), a phase III clinical trial, is currently in progress in Scandinavia to address this issue.

Coronary Angioplasty

Studies in laboratory animals indicating that LMWH suppresses neointimal proliferation after arterial balloon injury^{280,281} prompted clinical trials to evaluate the effect of LMWH on the rate of restenosis after angioplasty. In the Enoxaparin Restenosis after Angioplasty (ERA) trial,²⁸² patients were randomly assigned to receive either 40 mg of enoxaparin or placebo SC once daily for 1 month after successful coronary angioplasty. Angiographic or clinical

restenosis occurred in 51% of the 231 patients receiving placebo and 52% of the 227 patients receiving enoxaparin ($P=0.625$). Although major bleeding was more common in the enoxaparin group, the rate of major bleeding did not differ significantly. The Enoxaparin and MaxEPA for the Prevention of Angioplasty Restenosis (EMPAR) study²⁸³ randomly allocated 653 patients to either enoxaparin (30 mg SC twice daily) or placebo for 6 weeks after successful angioplasty, with randomization to either fish oil or control a median of 6 days earlier. Quantitative coronary angiography revealed no significant difference in the rate of restenosis either per patient or per lesion. The results of these 2 negative studies leave little doubt as to the lack of efficacy of enoxaparin in preventing restenosis when used in doses of up to 60 mg/d (6000 anti-factor Xa U/d) for 6 weeks.

Atrial Fibrillation

The multicenter, randomized, double-blind Heparin in Acute Embolic Stroke Trial (HAEST)²⁸⁴ found no evidence that LMWH is superior to aspirin for treatment of acute ischemic stroke in patients with AF. In that study, either the LMWH, dalteparin (100 U/kg SC twice daily), or aspirin (160 mg/d) was started within 30 hours of stroke onset in 449 patients with AF and acute ischemic stroke. The frequency of recurrent ischemic stroke during the first 14 days was 8.5% in dalteparin-allocated patients versus 7.5% in aspirin-allocated patients (OR 1.13, 95% CI 0.57 to 2.24). There was no benefit of dalteparin compared with aspirin in reducing cerebral hemorrhage (12% versus 14%), progression of symptoms within the first 48 hours (11% versus 8%), or death (9% versus 7%, all $P=NS$) or functional outcome at 14 days or 3 months.

LMWH has also been used in patients with AF as an adjunct to the strategy of transesophageal echocardiography-guided cardioversion but has not been specifically evaluated in a controlled trial. In one observational series,²⁸⁵ 242 patients referred for cardioversion of AF or flutter without prior anticoagulation were examined by transesophageal echocardiography. Those subjected to prompt cardioversion ($n=162$; mean age 62 years) were younger than others treated conventionally with warfarin before cardioversion ($n=80$; mean age 67 years; $P<0.05$) and more often had "lone" AF or flutter without associated heart disease (53% versus 34%, $P<0.05$). Dalteparin was administered together with warfarin before early cardioversion of these low-risk patients and continued until the international normalized ratio reached the therapeutic range. Although no ischemic events were observed, more systematic experience must be gained in AF patients across a broader range of intrinsic thromboembolic risk before LMWH can be routinely advocated before cardioversion.

Conclusions

LMWH preparations are at least as effective and safe as UFH and more convenient, although they have the disadvantage of expense. The higher cost of the drug itself cannot be considered in isolation, however, because savings from SC administration and reduced hospital stay offset this. One appealing feature of LMWH is a more predictable dose response

relative to UFH, which translates clinically into weight-adjusted dosing without laboratory monitoring. The only study that compared the predictability of the dose response of LMWH with that of UFH¹⁷³ demonstrated less variability, but this was not abolished entirely. The efficacy and safety of LMWH might be improved by monitoring anti-factor Xa levels, but the anticipated improvement in clinical outcome would likely be marginal and balanced by inconvenience and added expense. Weight-adjusted dosing could be misleading in patients with renal insufficiency and in obese patients. Further studies are required to determine whether monitoring is necessary in such patients. Based on current information, however, LMWH preparations should be administered with weight-adjusted dosing in the majority of patients.

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KEY WORDS: AHA Scientific Statement ■ anticoagulants ■ heparin