Guide to Anticoagulant Therapy
Part 1: Heparin

Jack Hirsh, MD; Valentin Fuster, MD, PhD

The Thrombotic Process and Its Complications

Thrombi are composed of fibrin and blood cells and may form in any part of the cardiovascular system, including the veins, arteries, heart, and microcirculation. Because the relative proportions of cells and fibrin depend on hemodynamic factors, they differ in arterial and venous thrombi. Arterial thrombi form under conditions of high flow and are composed mainly of platelet aggregates bound together by thin fibrin strands. In contrast, venous thrombi form in areas of stasis and are composed mainly 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. 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. Leukocytes are attracted by chemoattractant factors released from aggregated platelets 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 or becomes organized by connective tissue.

The complications of thrombosis are caused by the effects of local obstruction of the vessel, distant embolization of thrombotic material, or, less commonly, consumption of hemostatic elements by their participation in the thrombotic process.

Arterial thrombi usually form either in regions of disturbed flow or at sites of rupture of atherosclerotic plaques. Plaque rupture exposes the thrombogenic sub-endothelium to platelets and coagulation proteins; it may also cause further narrowing due to hemorrhage into the plaque. Arterial thrombi may remain partially occlusive or they may embolize. Nonocclusive thrombi may become incorporated into the vessel wall and can accelerate the growth of atherosclerotic plaques. When flow is slow, the degree of stenosis severe, or the thrombogenic stimulus intense, the thrombus may become totally occlusive. Arterial thrombus usually occur in association with preexisting vascular disease, the most common of which is atherosclerosis; they produce clinical manifestations by inducing tissue ischemia, either by obstructing flow or by embolizing into the distal microcirculation. Activation of blood coagulation as well as platelet activation are important in the pathogenesis of arterial thrombosis. These two 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 their benefit has been demonstrated by the results of clinical trials.

Venous thrombi usually occur in the lower limbs and are often asymptomatic; however, they can produce acute symptoms if they cause inflammation of the vessel wall, obstruct flow, or embolize into the pulmonary circulation. They can produce long-term complications due to venous hypertension if they damage the venous valves. Activation of blood coagulation is the critical mechanism in pathogenesis of venous thromboembolism, while the role of platelet activation is less important. Therefore, as might be anticipated, anticoagulants are very effective for the prevention and treatment of venous thromboembolism, while 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, in a dilated or dyskinetic cardiac chamber, or on prosthetic valves. They are usually asymptomatic when confined to the heart but may produce serious complications if they embolize to the brain or the systemic circulation. Activation of blood coagulation appears to be more important in the pathogenesis of intracardiac thrombi than platelet activation, although the latter process also plays a contributory role. Anticoagulants are effective for prevention and treatment of intracardiac thrombi, and there is evidence that for 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 aggregation. By blocking blood flow to the tissues, microthrombi can produce ischemic damage. In addition, red cell fragmentation can occur as the cells traverse the clot-filled vessels, leading to a hemolytic anemia. Finally, activation of the coagulation sys-

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tem can lead to a hemorrhagic disorder because of consumption of platelets and clotting factors. Anticoagulants are effective in selected cases of disseminated intravascular coagulation.

Clinical Consequences of Thrombosis and Need for Anticoagulants

It has been estimated that venous thromboembolism is responsible for more than 300,000 hospital admissions per year in the United States. Pulmonary embolism causes or contributes to death in approximately 12% of patients who are in hospitals and has been estimated to be responsible for 50,000 to 250,000 deaths per year in the United States.

The burden of venous thromboembolism is due to death from pulmonary embolism, the long-term consequences of the postthrombotic syndrome, the need for hospitalization, the complications of anticoagulant therapy, and the psychological effects of having a potentially recurrent and chronic illness.

Thrombosis is responsible for many of the acute manifestations of atherosclerosis and contributes to its progression. The effect of atherosclerosis is enormous. As a generalized pathological process, atherosclerosis affects the arteries to the heart, brain, abdomen, and legs, causing acute and chronic myocardial ischemia, sudden death, myocardial infarction, unstable or stable angina, ischemic cardiomyopathy, chronic arrhythmia, ischemic cerebrovascular disease (including stroke and multi-infarct dementia), renal hypertension, and peripheral vascular disease, which causes intermittent claudication and gangrene. Atherosclerosis and its thrombotic complications can also cause bowel ischemia and contribute to the complications of diabetes and hypertension. Thromboembolism originating in the heart can cause embolic stroke and peripheral embolism in patients with atrial fibrillation, acute myocardial infarction, valvular heart disease, and cardiomyopathies.

Great strides have been made in the clinical use of anticoagulants since the publication in 1984 of the first "Guide to Anticoagulant Therapy." Because of the results of well-designed randomized trials, clinicians can now make rational decisions about whether anticoagulants are indicated, the intensity of dosage regimens, the most appropriate method of laboratory monitoring, and duration of therapy.

In 1984 heparin and oral anticoagulants had established roles in the prevention and treatment of venous thromboembolism, but their roles in arterial thromboembolism were controversial. It is now clear that heparin is effective in the early treatment of unstable angina and acute myocardial infarction. The initial study in which less intense coumarin therapy was used for the treatment of venous thrombosis has now been extended to venous thrombosis prophylaxis to the prevention of systemic embolism in patients with tissue heart valves and nonvalvular atrial fibrillation (particularly embolic stroke). Coumarins have also been shown to be effective in the long-term management of acute myocardial infarction, but their role in this situation compared with the role of aspirin remains an open question.

In this review of anticoagulant therapy, recommendations will be based on results of randomized trials whenever possible. However, for some indications and for some clinical subgroups, our recommendations will of necessity be based on less solid evidence and will be subject to revision in the light of information from future studies.

Heparin

Historical Highlights

Heparin was discovered by McLean in 1916. More than 20 years later, Brinkhous and associates demonstrated that heparin requires a plasma heparin cofactor for its anticoagulant activity; this factor was renamed antithrombin III (ATIII) by Abildgaard in 1968. In the 1970s, Rosenberg et al and Lindahl et al elucidated the mechanisms for interactions between heparin and ATIII, demonstrating that the active center serine of thrombin and other coagulation enzymes is inhibited by an arginine reactive center on the ATIII molecule and that heparin complexes to lysine binding sites on ATIII, producing a conformational change at the arginine reactive center that converts ATIII from a slow, progressive inhibitor to a very rapid inhibitor. ATIII covalently binds to the active serine center of coagulation enzymes and heparin, then dissociates from the ternary complex and can be reutilized (Fig 1). It was subsequently demonstrated that heparin binds to ATIII and potentiates its activity through a unique glucosamine unit contained within a pentasaccharide sequence, the structure of which has been confirmed by chemical synthesis.

Mode of Action of Heparin

Only about one third of heparin binds to ATIII, and this fraction is responsible for most of its anticoagulant effect. The remaining two thirds of the heparin has minimal anticoagulant activity at therapeutic concentrations, but at high concentrations (greater than those usually produced clinically) both high- and low-affinity heparin catalyze the antithrombin effect of a second plasma protein cofactor named heparin cofactor II (HCII) (Table 1).

The heparin/ATIII complex inactivates a number of coagulation enzymes, including thrombin (IIa) and factors Xa, XIIa, Xla, and IXa; of these, thrombin and factor Xa are most responsive to inhibition, and human thrombin is more responsive to inhibition by the hepa-
Hirsh and Fuster  Guide to Anticoagulant Therapy: Part 1  1451

Table 1. Antihemostatic Effects of Heparin

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

ATIII indicates antithrombin III.

Heparin binds to platelets in vitro and can either induce or inhibit platelet aggregation, depending on experimental conditions. High molecular weight heparin fractions with low affinity for ATIII have a greater effect on platelet function than low molecular weight heparin fractions with high affinity for ATIII (Table 1). Heparin prolongs bleeding time in humans and increases blood loss from the microvascularity in rabbits. The interaction of heparin with platelets and endothelial cells may contribute to heparin-induced bleeding by a mechanism independent of heparin's anticoagulant effect. Heparin also increases vessel wall permeability and suppresses the proliferation of vascular smooth muscle cells, more effects that appear to be independent of its anticoagulant activity.

Heparin is heterogeneous with respect to molecular size, anticoagulant activity, and pharmacokinetic properties (Table 2). The molecular weight of heparin ranges from 3000 to 30,000, with a mean of 15,000 (approximately 50 monosaccharide chains) (Fig 4). The anticoagulant activity of heparin is heterogeneous because only one third of the heparin molecules administered to patients have an anticoagulant function and because the anticoagulant profile and the clearance of heparin are influenced by the chain length of the molecules, with the higher molecular weight species being cleared from the circulation more rapidly than the lower molecular weight species. This differential clearance results in an accumulation, in vivo, of the lower molecular weight species, which have a reduced ratio of antithrombin to anti-factor Xa activity. This effect is responsible for the differences observed when the relation between the heparin level and the activated partial thromboplastin time (APTT) is assessed in vivo and in vitro: the lower molecular weight species retained in vivo are measured in the anti-factor Xa heparin assay but have minimal effects on the APTT.

Administration, Pharmacokinetics, and Pharmacodynamics of Heparin

The two preferred routes of administration of heparin are continuous intravenous infusion and subcutaneous injection. If the subcutaneous route is selected, the initial dose must be sufficiently high to compensate for the reduced bioavailability of heparin administered this way. If an immediate anticoagulant effect is required, the initial dose should be accompanied by an intravenous bolus injection because an anticoagulant effect from subcutaneous heparin is delayed for 1 to 2 hours (Table 3).

After its passage into the bloodstream, heparin binds to a number of plasma proteins (Fig 5), a phenomenon that contributes to its reduced bioavailability at low concentrations, the variability of the anticoagulant response to fixed doses of heparin in patients with thromboembolic disorders, and the laboratory phenomenon of heparin resistance. Binding of heparin to von Willebrand factor also results in the inhibition of von Willebrand factor-dependent platelet function. Heparin also binds to endothelial cells and macrophages, a property that contributes to its complicated pharmacokinetics. Heparin is cleared through a combination of a rapid saturable mechanism and a much slower first-order mechanism of clearance (Fig 6). The mechanism of the saturable phase of heparin clearance is thought to be binding of heparin to receptors on endothelial cells and macrophages, where it is internalized and depolymerized (Fig 5). The slower nonsaturable mechanism of heparin clearance is largely renal. At therapeutic doses a considerable proportion of the administered heparin is cleared through the rapid,
saturable, dose-dependent mechanism of clearance (Fig 6). Because of these kinetics, the anticoagulant effect of heparin at therapeutic doses is not linear, although both intensity and duration increase with increasing dose. Therefore the apparent biological half-life of heparin increases from approximately 30 minutes with an intravenous bolus of 25 U/kg to 60 minutes with an intravenous bolus of 100 U/kg to 150 minutes with a bolus of 400 U/kg.52-54

The bioavailability of heparin is reduced60 when the drug is administered by subcutaneous injection in low doses (eg, 5000 units every 12 hours) or moderate doses of 12 50061 or even 15 000 units62 every 12 hours. However, at high therapeutic doses of heparin (>35 000 U per 24 hours) the plasma recovery is almost complete.52 The difference between the bioavailability of heparin when administered by subcutaneous or intravenous injection was strikingly demonstrated in a study of patients with venous thrombosis. Patients were randomly assigned to receive either 15 000 units of heparin every 12 hours by subcutaneous injection or 30 000 units of heparin by continuous intravenous infusion; both regimens were preceded by an intravenous bolus dose of 5000 units. Therapeutic heparin levels and APTT ratios were achieved at 24 hours in only 37% of patients who received subcutaneous heparin but in 71% of patients given an identical dose of heparin by continuous intravenous infusion.47 These observations are relevant to the interpretation of the results of the GISSI-263,64 and ISIS-365 studies. In these studies heparin was given in a fixed dose of 12 500 units subcutaneously twice daily beginning either 12 or 4 hours after thrombolytic therapy so that an adequate anticoagulant effect would not have been achieved in a timely manner in either study.

Laboratory Monitoring and Dose-Response Relations of Heparin

The anticoagulant effects of heparin are usually monitored by following the results of the APTT, a test sensitive to the inhibitory effects of heparin on thrombin, factor Xa, and factor IXa. When heparin is administered in fixed doses, the anticoagulant response to it varies in patients with acute venous thrombembolism66 or myocardial ischemia.67-70 Differences in the plasma concentrations of heparin-neutralizing proteins contribute to this variability. There is evidence from subgroup analysis of cohort studies for a relation between the ex vivo effect of heparin on the APTT and its clinical effectiveness in the prevention of recurrent thrombosis in patients with proximal vein thrombosis67,68; of mural thrombosis in patients with acute myocardial infarction69; of recurrent ischemia in patients after streptokinase therapy for acute myocardial infarction67,69; and of coronary artery reocclusion after thrombolytic therapy with tissue plasminogen activator (TPA)70 (Table 4). Thus, in all six studies, the relative risk of an event was increased if the APTT was below the therapeutic range. For this reason the dose of heparin administered to patients should be monitored and adjusted to achieve a therapeutic level; this anticoagulant effect is referred to as the therapeutic range.

Unfortunately, the different commercial APTT reagents vary considerably in their responsiveness to heparin.72 For many reagents, a therapeutic effect is achieved with an APTT ratio of 1.5 to 2.5 (measured by dividing the observed APTT by the mean of the laboratory control APTT). With very sensitive APTT reagents the therapeutic range is higher than a ratio of 1.5 to 2.5; for insensitive reagents the therapeutic range is lower. APTT reagents can be standardized by calibrating them against the heparin level (therapeutic range is 0.2 to 0.4 U/mL by protamine titration or 0.3 to 0.7 U/mL when measured using an anti-factor Xa chromogenic assay) in a plasma system.

The risk of heparin-associated bleeding increases with heparin dose73,74 (which in turn is related to the anticoagulant response), the concomitant use of thrombolytic therapy, recent surgery, trauma, invasive procedures, or a generalized hemostatic abnormality.73 A rapid therapeutic heparin effect is achieved by beginning with a loading dose of 5000 units as an intravenous bolus followed by 32 000 U per 24 hours by continuous infusion.46 A lower dose of 24 000 U per 24 hours is often used immediately after thrombolytic therapy because the plasminolytic state produces a variable anticoagulant effect that prolongs the APTT in its own right. The APTT should be performed approximately 6 hours and 12 hours after the bolus and the heparin dose adjusted according to the result obtained. A heparin dose adjustment nomogram has been developed for APTT reagents for which the therapeutic range is 1.9 to 2.7 times control (based on a heparin level of 0.2 to
0.4 U/mL (Table 5). This nomogram is not applicable to all APTT reagents and should be adapted to the responsiveness of the local partial thromboplastin reagent to heparin.

It is also possible to achieve therapeutic heparin levels with subcutaneous injection in a dose of 35 000 U per 24 hours in two divided doses (Table 3). The anticoagulant effects of subcutaneous heparin are delayed for approximately 1 hour and peak levels occur at approximately 3 hours.

**Limitations of Heparin Use**

The limitations of heparin use are based on its pharmacokinetic, biophysical, and nonanticoagulant, antithrombotic properties (Table 6). The pharmacokinetic limitations are due to its binding to plasma proteins and endothelial cells, which results in a complicated mechanism of clearance, as well as to heparin resistance and the variability in the anticoagulant response to fixed doses. The biophysical limitations occur because the heparin/ATIII complex is unable to access and inactivate either factor Xa in the prothrombinase complex or thrombin bound to fibrin or to subendothelial surfaces. The limitations attributable to its other (nonanticoagulant) antithrombotic properties are due to a poorly defined inhibitory effect of heparin on platelet function (Table 6).

The limitations related to the pharmacokinetic and antithrombotic properties of heparin are not shared by the low molecular weight heparins and some heparinoids, and those due to the lack of accessibility of the heparin/ATIII complex to fibrin-bound thrombin and factor Xa are overcome by several new classes of ATIII-independent thrombin and factor Xa inhibitors.

The anticoagulant effect of heparin is modified by platelets, fibrin, vascular surfaces, and plasma proteins. Platelets limit the anticoagulant effect of heparin in two ways. First, factor Xa generated on the platelet surface is protected from inhibition by heparin/ATIII. Second, platelets release the heparin-neutralizing protein platelet factor IV. Fibrin binds thrombin and protects it from inactivation by heparin/ATIII. Therefore, much higher concentrations of heparin are needed to inhibit thrombin bound to fibrin than are required to inactivate the free enzyme. Thrombin also binds to subendothelial matrix proteins, where it is again protected from inhibition by heparin. These observations explain why in experimental animals heparin is less effective than the ATIII-independent thrombin and factor Xa inhibitors at preventing thrombosis; they also raise the possibility that ATIII-independent inhibitors may be more effective than heparin in certain clinical situations.

At clinically effective doses the low molecular weight heparins and heparinoids do not have the limitations of heparin that are due to inhibition of platelet function and the associated increase in experimental microvascular bleeding; they may therefore be administered in higher doses than heparin.

**Clinical Use of Heparin**

Heparin is effective in the prevention and treatment of venous thrombosis and pulmonary embolism, the prevention of mural thrombosis after myocardial infarction and of coronary artery rethrombosis after thrombolysis, and the treatment of patients with unstable angina and acute myocardial infarction.

As noted previously, the anticoagulant response to heparin varies widely between patients with thromboembolic disease, and the clinical efficacy of heparin is optimized if the anticoagulant effect is maintained in a therapeutic range. For these reasons, heparin treatment is usually monitored to maintain the APTT at a level equivalent to a heparin level of 0.2 to 0.4 U/mL by protamine titration or an anti-factor Xa level of 0.35 to

**Table 3. Methods of Administration and Dosages of Heparin**

<table>
<thead>
<tr>
<th>Method of Administration</th>
<th>Dose Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous intravenous</td>
<td>Start with bolus (5000 U) for immediate effect</td>
</tr>
<tr>
<td>Subcutaneous (high dose)</td>
<td>Start with bolus (5000 U) if immediate effect required</td>
</tr>
</tbody>
</table>

**Fig 4.** Molecular weight distributions of low molecular weight heparins and heparin. LMWH indicates low molecular weight heparin.

**Fig 5.** As heparin enters the circulation, it binds to heparin-binding proteins (C), endothelial cells (EC), macrophages (M), and antithrombin III (O, or ATIII). Only heparin with the high-affinity pentasaccharide binds to ATIII, but binding to other proteins and to cells is nonspecific and occurs independently of the ATIII-binding site.
was effective in patients with acute proximal vein thrombosis who received oral anticoagulants without concomitant heparin than in those receiving oral anticoagulants and heparin. In addition, in two randomized studies recurrent thrombosis was very uncommon (less than 5%) during the initial course of intravenous heparin but was common (between 29% to 47%) if full-dose heparin was discontinued after 5 to 14 days. Recurrence is markedly reduced if the initial course of heparin is followed by oral anticoagulants or adjusted-dose heparin.

Heparin administered by continuous intravenous infusion has been compared in terms of effectiveness and safety with heparin administered by intermittent intravenous injection in six studies. The continuous intravenous heparin infusion route has also been compared with high-dose subcutaneous heparin in six other studies. However, it is difficult to identify the optimal route of heparin administration from the results of these studies for several reasons: different 24-hour heparin doses were used; most of the studies were small and lacked the statistical power to demonstrate clinically important differences; and different criteria were used to assess both efficacy and safety. Nevertheless, the results of these studies indicate that the risk of bleeding increases with heparin dose; both the continuous intravenous route and the subcutaneous route are safe and effective; and the frequency of recurrent venous thromboembolism is low with all three methods of administration, provided that adequate doses of heparin are given.

In all the contemporary studies in which objective tests were used to assess outcomes, the mean daily dose of heparin has been between 30,000 and 35,000 U per 24 hours. The initial dose of heparin is critical, especially if heparin is administered by subcutaneous injection, because an adequate anticoagulant response is not achieved in the first 24 hours unless a high starting dose (17,500 units subcutaneously as the initial injection) is used. The most reliable estimates of the incidence of recurrence during adequate heparin treatment and over the subsequent 3 months of less intense warfarin therapy come from three contemporary prospective studies of a total of 523 patients to whom heparin was administered by continuous infusion. The dose of heparin was adjusted to maintain the APTT in the therapeutic range, follow-up was prospective, and diagnosis of recurrence was based on reliable objective tests. The 3-month incidence of recurrent venous thromboembolism varied from 4.7% to 7.1% over the combined period of initial heparin treatment and subsequent oral anticoagulant therapy. The incidence of major bleeding during heparin treatment varied from 1.6% to 7.1% (mean, 3.8%) and the incidence of fatal pulmonary embolism was 0%47,101,102 (Table 8).

**Table 4.** Relation Between Failure to Reach Lower Limit of Therapeutic Range of Activated Partial Thromboplastin Time and Thromboembolic Events From Subgroup Analysis of Prospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Condition</th>
<th>Outcome</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hull et al47</td>
<td>Deep vein thrombosis</td>
<td>Recurrent venous thromboembolism</td>
<td>15.0</td>
</tr>
<tr>
<td>Basu et al71</td>
<td>Deep vein thrombosis</td>
<td>Recurrent venous thromboembolism</td>
<td>10.7</td>
</tr>
<tr>
<td>Turpie et al61</td>
<td>Acute myocardial infarction</td>
<td>Left ventricular mural thrombosis</td>
<td>22.2</td>
</tr>
<tr>
<td>Kaplan et al68</td>
<td>Acute myocardial infarction</td>
<td>Recurrent myocardial infarction/angina pectoris</td>
<td>6.0</td>
</tr>
<tr>
<td>Camilleri et al87</td>
<td>Acute myocardial infarction</td>
<td>Recurrent myocardial infarction/angina pectoris</td>
<td>13.3</td>
</tr>
</tbody>
</table>

Relative risk refers to the relative increase in event rates when the rates in patients with subtherapeutic activated partial thromboplastin times are compared with the rates in patients whose values are in the therapeutic range.
Audits of heparin monitoring practices indicate that the dosage adjustments are frequently inadequate. Dosing practices can be improved by using a standardized approach.\textsuperscript{56} In a prospective study, heparin was given intravenously as a continuous infusion, starting at a dose of approximately 31 000 U per 24 h after a 5000-unit intravenous bolus, and the dose was then adjusted using a heparin protocol developed empirically through an iterative process (Table 5). An APTT above the lower limit of the therapeutic range was reached in 82% of patients at 24 hours and in 91% at 48 hours. The mean heparin dose required to produce an APTT in the therapeutic range was 32 903 U per 24 hours. The proportion of APTT results in the therapeutic range was significantly higher when the heparin protocol was used than in a historical control group ($P<.05$).\textsuperscript{56} It should be noted, however, that the protocol was developed for a single APTT reagent (Dade Actin) and should be modified for other reagents.\textsuperscript{72}

The time-honored approach of using a 7- to 10-day course of heparin with a 4- to 5-day overlap period with oral anticoagulants has been challenged by the results of two randomized studies in patients with proximal vein thrombosis. In these studies the low recurrence rate and bleeding incidence with a short course of heparin therapy (4 to 5 days) were similar to those with a longer course (9 to 10 days)\textsuperscript{101,102} (Table 9). The short-course regimen has obvious appeal; it reduces hospital stay and lessens the risk of heparin-associated thrombocytopenia. Although the shorter course of treatment can be recommended for the average patient with venous thromboembolism, it may not be appropriate for patients with massive iliofemoral vein thrombosis or major pulmonary embolism, because these patients were excluded from one study\textsuperscript{102} and constituted only a small proportion of patients in the second.\textsuperscript{101}

### Prophylaxis of Venous Thromboembolism

Heparin in a fixed low dose of 5000 units subcutaneously every 8 or 12 hours is an effective and safe form of prophylaxis in medical and surgical patients at risk for venous thromboembolism. Overview analyses of clinical trials in patients undergoing elective general surgery and in medical patients have reported that low-dose heparin produces a 60% to 70% risk reduction in venous thrombosis and in fatal pulmonary embolism\textsuperscript{103,104} (Tables 10 and 11). In one analysis the incidence of fatal pulmonary embolism was 0.7% in the control group and 0.2% in treated general surgical patients ($P<.001$)\textsuperscript{103}; in another, in which orthopedic surgical patients were included, the results were 0.8% and 0.26% respectively ($P<.001$), and there was also a small but statistically significant difference in mortality (3.3% and 2.4% respectively [$P<.02$]).\textsuperscript{104} The use of low-dose heparin is associated with a small excess of wound hematomas\textsuperscript{103,105} and a minimal, nonsignificant increase in major bleeding but no increase in fatal bleeding. Low-dose heparin has also been shown to be effective in reducing venous thromboembolism after myocardial infarction and in patients with other serious medical disorders\textsuperscript{106} and to reduce in-hospital mortality by 31% ($P<.05$) among 1358 patients over the age of 40 who were admitted to general medical wards.\textsuperscript{107} Low-dose heparin is also effective in reducing deep-vein thrombosis after hip surgery.\textsuperscript{104} The risk of thrombosis, however, remains substantial at an incidence of 20% to 30% and can be reduced further by treatment with either adjusted low-dose heparin\textsuperscript{108} or fixed-dose low molecular weight heparin\textsuperscript{96} (Table 12). Moderate-dose warfarin is effective in patients undergoing major ortho-

### Table 5. Protocol for Heparin Dose Adjustment\textsuperscript{56}

<table>
<thead>
<tr>
<th>APTT\textsuperscript{*} (s)</th>
<th>Repeat bolus dose (U)</th>
<th>Stop Infusion (min)</th>
<th>Change rate (dose) of Infusion mL/h\textsuperscript{a} (U per 24 h)</th>
<th>Time of next APTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>5000</td>
<td>0</td>
<td>+3 (+2880)</td>
<td>6 h</td>
</tr>
<tr>
<td>50-59</td>
<td>0</td>
<td>0</td>
<td>+3 (+2880)</td>
<td>6 h</td>
</tr>
<tr>
<td>60-85\textsuperscript{a}</td>
<td>0</td>
<td>0</td>
<td>0 (0)</td>
<td>Next morning</td>
</tr>
<tr>
<td>86-95</td>
<td>0</td>
<td>0</td>
<td>-2 (-1920)</td>
<td>Next morning</td>
</tr>
<tr>
<td>96-120</td>
<td>0</td>
<td>30</td>
<td>-2 (-1920)</td>
<td>6 h</td>
</tr>
<tr>
<td>&gt;120</td>
<td>0</td>
<td>60</td>
<td>-4 (-3840)</td>
<td>6 h</td>
</tr>
</tbody>
</table>

\textsuperscript{*}APTT indicates activated partial thromboplastin time; U, unit; h, hour.

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

\textsuperscript{a}Normal range for APTT with Dade Actin FS reagent is 27 to 35 s.

\textsuperscript{b}Therapeutic range of 60 to 85 s equivalent to a heparin level of 0.2 to 0.4 U/mL by protamine titration or 0.35 to 0.7 U/mL as an anti-factor Xa heparin level. Therapeutic range will vary with responsiveness of APTT reagent to heparin.

### Table 6. Limitations of Heparin

**Pharmacokinetics**

- Binding to plasma proteins and endothelium results in variability between patients' dose response, a dose-dependent mechanism of clearance, and heparin resistance

**Biophysical**

- Inability to access factors IIa and Xa bound to surfaces results in incomplete inactivation of fibrin-bound thrombin and platelet-bound factor Xa

**Antithrombotic**

- Binding to platelets and inhibition of platelet function contributes to hemorrhagic effect
pedic surgical procedures, but direct comparisons of low-dose heparin and warfarin have not been performed in these patients.

Coronary Artery Disease

Coronary thrombosis is important in the pathogenesis of several acute complications of coronary artery disease: unstable angina and its complications, acute myocardial infarction, and many cases of sudden death; and recurrent infarction and death in patients with acute myocardial infarction who are treated with thrombolytic therapy. Heparin has the potential to prevent the acute thrombotic manifestations of coronary artery disease, but its clinical use cannot be considered in isolation; rather, it must be considered when combined with standard treatment, which is aspirin in all potentially eligible patients with myocardial ischemia and both aspirin and thrombolytic therapy in patients with evolving myocardial infarction. Unfortunately, studies using clinically important outcomes to evaluate the benefits and risks of adding heparin to aspirin alone or to aspirin and thrombolytic therapy are relatively few, and the results have been inconclusive.

Unstable Angina

Four large trials in which aspirin was given to patients with unstable angina have shown marked reductions of acute myocardial infarction and cardiac death in both the short and long term. The suggestion has been made that the addition of heparin to aspirin improves short-term outcome. Heparin when used alone is also effective in the short term and in preventing acute myocardial infarction and recurrent refractory angina in patients with unstable angina, but a rebound is seen when heparin is stopped. Aspirin appears to prevent the cluster of ischemic events that occur when heparin is discontinued.

Acute Myocardial Infarction

Heparin reduced reinfarction and death in two open randomized trials in which a heparin group was compared with an untreated control group. In one study, there was a statistically significant 61% reduction in reinfarction when 12,500 units of heparin was given subcutaneously to patients who had had a myocardial infarction 6 to 18 months before recruitment into the study. In another study there was a significant 44% reduction in mortality when 12,500 units of heparin was given subcutaneously every 12 hours to patients with acute myocardial infarction. In neither of these studies were the added benefits or risks of adding heparin to aspirin evaluated. Therefore, the results of these studies may not be relevant to the current situation in which patients with acute or previous myocardial infarction are treated with aspirin.

### Table 7. Clinical Use of Heparin

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommended heparin regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous thromboembolism</td>
<td>5000 U subcutaneously every 8 or 12 h or adjusted low-dose heparin*</td>
</tr>
<tr>
<td>Prophylaxis of DVT and PE</td>
<td>5000 U intravenous bolus followed by 32 000 U per 24 h by intravenous infusion or 35 000 to 40 000 U per 24 h subcutaneously, adjusted to maintain APTT* in the therapeutic range</td>
</tr>
<tr>
<td>Treatment of DVT</td>
<td>5000 U intravenous bolus followed by 32 000 U per 24 h intravenous infusion adjusted to maintain APTT in the therapeutic range</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>5000 U intravenous bolus followed by 24 000 U per 24 h adjusted to maintain APTT in the therapeutic range</td>
</tr>
<tr>
<td>Unstable angina or acute myocardial infarction without thrombolytic therapy</td>
<td>5000 U intravenous bolus followed by 32 000 U per 24 h intravenous infusion adjusted to maintain APTT in the therapeutic range</td>
</tr>
<tr>
<td>Acute myocardial infarction post-thrombolytic therapy†</td>
<td>5000 U intravenous bolus followed by 24 000 U per 24 h adjusted to maintain APTT in the therapeutic range</td>
</tr>
</tbody>
</table>

DVT indicates deep venous thromboembolism; PE, pulmonary embolism; U, unit; h, hour; APTT, activated partial thromboplastin time. *APTT varies in responsiveness to heparin. †Role of heparin unproven.

### Table 8. Confirmed Recurrences, Major Bleeding Events, and Fatal Pulmonary Embolism Among Patients With Venous Thromboembolism Who Receive Treatment With Heparin Administered as a Continuous Intravenous Infusion and Followed by Administration of Less Intense Oral Anticoagulants

<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence of confirmed recurrence*</th>
<th>Incidence of major bleeding†</th>
<th>Incidence of fatal pulmonary embolism*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallus et al102</td>
<td>13/266 (4.9%)</td>
<td>5/266 (1.9%)</td>
<td>...</td>
</tr>
<tr>
<td>Hull et al147</td>
<td>3/58 (5.2%)</td>
<td>2/58 (3.4%)</td>
<td>0/58 (0%)</td>
</tr>
<tr>
<td>Hull et al101</td>
<td>14/199 (7.0%)</td>
<td>13/199 (6.5%)</td>
<td>0/199 (0%)</td>
</tr>
<tr>
<td>Total</td>
<td>30/523 (5.7%)</td>
<td>20/523 (3.8%)</td>
<td>0/257</td>
</tr>
</tbody>
</table>

*During the 3-mo period of heparin and oral anticoagulant treatment. †During heparin treatment.

### Table 9. Comparison of Long and Short Courses of Heparin in the Treatment of Proximal Vein Thrombosis

<table>
<thead>
<tr>
<th>Gallus et al102</th>
<th>Hull et al101</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
<td><strong>Short (4 d)</strong></td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>266</td>
</tr>
<tr>
<td>Recurrent VTE (%)</td>
<td></td>
</tr>
<tr>
<td>During heparin</td>
<td>3.6</td>
</tr>
<tr>
<td>During warfarin</td>
<td>3.3</td>
</tr>
<tr>
<td>Total during treatment (%)</td>
<td>6.9</td>
</tr>
</tbody>
</table>

VTE indicates venous thromboembolism.
TABLE 10. Meta-analysis of Randomized Trials Comparing Groups on Low-Dose Heparin With Untreated Control Groups to Assess Efficacy

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Trials (n)</th>
<th>Treatment group (n)</th>
<th>Incidence (%)</th>
<th>Control group (n)</th>
<th>Incidence (%)</th>
<th>Odds ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT (+FUT)</td>
<td>29</td>
<td>3265</td>
<td>8.7</td>
<td>3382</td>
<td>25.2</td>
<td>0.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Confirmed DVT (+FUT) (+FUT, phlebogram)</td>
<td>8</td>
<td>831</td>
<td>6.0</td>
<td>891</td>
<td>15.4</td>
<td>0.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DVT (+FUT) (Double-blind trials)</td>
<td>11</td>
<td>673</td>
<td>11.6</td>
<td>524</td>
<td>24.6</td>
<td>0.40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DVT (+FUT) (Malignant disease)</td>
<td>10</td>
<td>474</td>
<td>13.3</td>
<td>445</td>
<td>30.6</td>
<td>0.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>12</td>
<td>1564</td>
<td>1.4</td>
<td>1788</td>
<td>6.4</td>
<td>0.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All PE</td>
<td>10</td>
<td>4215</td>
<td>0.5</td>
<td>4228</td>
<td>1.2</td>
<td>0.42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FPE</td>
<td>24</td>
<td>4699</td>
<td>0.2</td>
<td>4772</td>
<td>0.7</td>
<td>0.30</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

DVT indicates deep venous thrombosis; FUT, radioactive fibrinogen uptake test; PE, pulmonary embolism; FPE, fatal pulmonary embolism.

From Clagett and Reisch.103

The effect of heparin on the incidence of *mural thrombosis* was evaluated in two randomized trials61,118 in which patients taking moderate-dose heparin (12 500 units subcutaneously every 12 hours) were compared with either an untreated control group118 or patients taking low-dose heparin (5000 units subcutaneously every 12 hours).61 In these two studies, the incidence of mural thrombosis detected by two-dimensional echocardiography was 72% and 58% lower, respectively (P<.05), in the patients taking moderate-dose heparin than in the comparison groups.

The effectiveness of heparin in *preventing early coronary artery reocclusion after successful thrombolysis* has been evaluated in a number of studies. In one study, a single intravenous bolus of 10 000 units did not appear to influence coronary artery patency at 90 minutes.119 In four other studies in which TPA was used, heparin was administered as an intravenous bolus of 5000 units and then as a continuous infusion of 1000 U/h either during or at the end of a TPA infusion. The dose of heparin was adjusted to maintain the APTT at 1.5 to 2.0 times control. In the Heparin-Aspirin Reperfusion Trial of 205 patients, the comparison group received 80 mg of aspirin per day.120 Coronary artery patency at 18 hours was 82% in the heparin group and 52% in the aspirin group (P<.0002). The conclusion that heparin is more effective than aspirin in maintaining patency has been criticized because the aspirin dose was too low to have a rapid and marked suppressive effect on thromboxane A2 production. In the trial reported by Bleich and associates121 of 83 patients, the control group received no treatment. Patency at 2 days was 71% in the heparin group and 44% in the control group (P<.023). In the European Coronary Study Group-6 Trial, all 687 patients received aspirin and were randomly assigned to receive either heparin or no heparin. Patency at 81 hours was 80% in the heparin group and 75% in the control group (P<.01).69 In the Australian National Heart Study Trial, all 202 patients received heparin for 24 hours.122 They were then randomly assigned to receive either continuous intravenous heparin or a combination of aspirin (300 mg) and dipyridamole (300 mg) daily. Patency at 1 week was 80% in both groups. The results of these studies suggest that heparin in a dose of 5000 units by intravenous bolus and 1000 U/h by continuous infusion increases patency during the first few days after coronary thrombolysis with TPA, probably by preventing rethrombosis.

In two other studies the effect of adding heparin to aspirin given in adequate doses has been evaluated. The OSIRIS investigators treated 128 patients with streptokinase and aspirin and randomly assigned the patients to receive either an intravenous bolus of heparin or no heparin. There was no difference in coronary patency at 24 hours (86% and 87%).123 The Duke University Clinical Cardiology Studies-1 investigators treated 250

TABLE 11. Meta-analysis of Randomized Trials Comparing Groups on Low-Dose Heparin With Untreated Control Groups to Assess Bleeding

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Trials (n)</th>
<th>Treatment group (n)</th>
<th>Incidence (%)</th>
<th>Control group (n)</th>
<th>Incidence (%)</th>
<th>Odds ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major hemorrhage</td>
<td>21</td>
<td>4251</td>
<td>0.33</td>
<td>4265</td>
<td>0.33</td>
<td>1.00</td>
<td>0.99</td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>4</td>
<td>392</td>
<td>1.8</td>
<td>243</td>
<td>0.82</td>
<td>2.19</td>
<td>0.32</td>
</tr>
<tr>
<td>(double-blind trials)</td>
<td>20</td>
<td>3379</td>
<td>6.3</td>
<td>3368</td>
<td>4.1</td>
<td>1.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wound hematomas</td>
<td>4</td>
<td>363</td>
<td>8.0</td>
<td>216</td>
<td>2.3</td>
<td>3.04</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(double-blind trials)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

From Clagett and Reisch.103
patients with anisoylated plasminogen-streptokinase activator complex and aspirin and randomly assigned the patients to receive either heparin or no heparin. There was no significant difference in coronary artery patency (80% in the heparin group and 74% in the control group).124

Subgroup analysis of the European Coronary Study Group-6 Trial16 and the Heparin-Aspirin Reperfusion Trial120 revealed some interesting and provocative results. In both studies, heparin was given intravenously in a fixed dose, and the APTT was performed but was not used to adjust the dose of heparin in a systematic manner. In the Heparin-Aspirin Reperfusion Trial, the subgroup of patients whose APTT ratio was considered optimal had a significantly higher patency rate than those whose APTT ratio was suboptimal125; patency was 45% in those whose APTT was <45 seconds; 88% in those whose APTT was >45 seconds but <60 seconds; and 95% in those whose APTT was >60 seconds. These findings suggest that the effectiveness of heparin in maintaining patency is dependent on keeping APTT in the therapeutic range, and that coronary patency achieved with TPA is improved by using high-dose intravenous heparin in therapeutic doses.

The effectiveness of heparin in preventing reinfarction or death after thrombolytic therapy for acute myocardial infarction has been evaluated in a number of randomized studies. In the ISIS-2 study,136 approximately half of the patients received intravenous heparin over 48 hours in a 2×2 factorial design that included streptokinase and aspirin; heparin treatment was associated with a nonsignificant decrease in recurrent infarction. In the Studio Sulla Calciparina nell’Angina e Nella Trombosi Ventricolare Nell’Infarto study,118 in which the control group received no anticoagulant treatment, mortality was reduced significantly in patients randomly assigned to receive heparin (2000 units intravenous bolus followed by 12 500 units administered subcutaneously every 12 hours) after thrombolytic therapy for acute myocardial infarction on a subgroup analysis. The same trend was seen with streptokinase but not with TPA in the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico (GISSI-2)/International Study. In the patients who received streptokinase and heparin (90% of whom also received aspirin) the mortality rate was 7.9% (408/5191); in the patients who received streptokinase alone it was 9.2% (479/5205) (P<.02). When patients who died before heparin was started were excluded from the analysis, the same trend was still apparent; the rates were 5.0% (254/5037) and 6.2% (311/5037) (P<.02). The mortality rate among the patients who received TPA and heparin was 9.2% (476/5170), and was 8.7% (453/5202) in those who received TPA not followed by heparin (P=.393). After the patients who died before heparin was started were excluded from analysis, the mortality rate, 5.9%, was almost identical for those who received heparin (298/5047) and those who did not (298/5047) (P=.984).6364

The ISIS-3 study provides additional important information on the relative safety and efficacy of adjuvant heparin and on the relative safety of streptokinase and TPA.65 The addition of heparin (1250 units subcutaneously every 12 hours, starting 4 hours after thrombolytic therapy was begun) to aspirin and thrombolytic therapy produced a small excess of major noncerebral bleeds (1.0% compared with 0.8%; P<.01) and of cerebral bleeds (0.56% compared with 0.40%; P<.05). Thus, the addition of heparin resulted in an excess of 3.6 per 1000 serious bleeding events. On the other hand, the addition of heparin resulted in a reduction of reinfarction of 3.1 events per 1000 treated (P<.09) and a reduction in 35-day mortality of 3 events per 1000 treated (difference not significant). The incidences of stroke and of stroke from presumed cerebral hemorrhage were significantly lower in patients receiving streptokinase than in those given TPA or anisoylated plasminogen-streptokinase activator complex. Thus, compared with streptokinase, TPA was associated with an excess of 3.5 strokes per 1000 and 4.2 episodes of presumed hemorrhagic strokes per 1000 (stroke rate, 1.04% for streptokinase and 1.39% for TPA; cerebral hemorrhage rate, 0.24% for streptokinase and 0.66% for TPA; P<.05 for both comparisons). Based on these findings, it seems possible that any additional benefit from higher-dose and monitored intravenous heparin will be associated with an increase in hemorrhagic stroke.

However, the results of the recently completed Global Utilization of Streptokinase and Tissue Plasminogen Activator for Ocluded Coronary Arteries study indicate otherwise. In this multinational study, 41 021 patients with evolving myocardial infarction were randomly assigned to treatment with four different strategies: streptokinase and subcutaneous heparin, streptokinase and intravenous heparin, accelerated TPA and intravenous heparin, or the combination of both thrombolytic agents with intravenous heparin. The mortality for the four treatment groups was 7.2%, 7.4%, 6.3%, and 7.0% respectively. The 14% reduction of mortality in the group receiving TPA, compared with the mortality in the groups receiving the streptokinase strategies, was highly significant (P=.001). The rates of hemorrhagic stroke were 0.49%, 0.54%, 0.72%, and 0.94%

### Table 12. Meta-analysis of Randomized Trials Comparing Groups Receiving Low Molecular Weight Heparins or Low Dose Heparin After Elective Hip Surgery

<table>
<thead>
<tr>
<th></th>
<th>Proximal DVT</th>
<th>Distal DVT</th>
<th>Major bleeding</th>
<th>Minor bleeding</th>
<th>Pulmonary embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common odds ratio*</td>
<td>0.43</td>
<td>0.92</td>
<td>0.57</td>
<td>0.89</td>
<td>0.30</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.30-0.62</td>
<td>0.69-1.23</td>
<td>0.29-1.11</td>
<td>0.59-1.33</td>
<td>0.09-1.02</td>
</tr>
</tbody>
</table>

DVT indicates deep vein thrombosis.

*Common odds ratio of less than 1 favors use of low molecular weight heparin over heparin.

The incidence of proximal vein thrombosis was reduced significantly. There was also a trend for reduced major bleeding and pulmonary embolism in patients randomly assigned to receive low molecular weight heparins.

respectively, reflecting a significant excess of events in the TPA group compared with the streptokinase group \( (P=0.03) \). The combined incidence of death or nonfatal hemorrhagic stroke was significantly reduced for the TPA group compared with the groups receiving streptokinase (6.6% and 7.5% respectively; \( P=.004 \)). There was no difference between the TPA and streptokinase groups in terms of extracranial bleeding. The incidence of severe or life-threatening bleeding was 0.3%, 0.5%, and 0.4%, respectively, in the groups receiving streptokinase and subcutaneous heparin, streptokinase and intravenous heparin, and TPA and intravenous heparin. The incidence of moderate or severe bleeding was 5.8%, 6.3%, and 5.4% respectively. Thus, the improved survival seen in the group receiving TPA and high-dose intravenous heparin was associated with a small increase in the risk of hemorrhagic stroke and no increase in major extracranial bleeding. In contrast, there was no advantage to using intravenous heparin in patients treated with streptokinase.127

Bleeding

The results of the GISSI-2 and the ISIS-3 studies show that the addition of heparin therapy to thrombolytic treatment increases the risk of bleeding\(^{43-66} \) (Table 13): minor bleeds were reported for 594 of the 6195 patients (9.6%) who received heparin and 326 of the 6206 (5.3%) who did not (relative risk, 1.88; \( P<.001 \); GISSI centers only), and major bleeds were reported for 103 of 10 361 patients (1%) in the heparin group and 57 of 10 407 (0.5%) in the group who did not receive heparin (relative risk, 1.79; \( P<.01 \)). As discussed above, in the ISIS-3 study\(^{65} \) heparin produced a small but significant excess of major bleeding episodes and cerebral hemorrhage. In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries study there was a small but significant increase in the incidence of cerebral hemorrhage in the group receiving accelerated TPA and intravenous heparin, no difference in the incidence of hemorrhagic stroke between the intravenous and subcutaneous arms of the streptokinase groups, and no difference in the incidence of major extracranial bleeding between these three groups.

Low Molecular Weight Heparins and Heparinoids

The experimental observations with low molecular weight heparins of the 1970s and early 1980s led to clinical trials that demonstrated the effectiveness and safety of these antithrombotic agents for the prevention and treatment of venous thrombosis.

Low molecular weight heparins are approximately one third the size of heparin (Fig 4). Like heparin, they are heterogeneous in size with a molecular weight range of 1000 to 10 000 and a mean molecular weight of 4000 to 5000. Depolymerization of heparin results in a change in its anticoagulant profile, bioavailability and pharmacokinetics, and effects on platelet function and experimental bleeding (Table 14). The Organon heparinoid Orgaran, a mixture of 80% heparan sulfate and smaller amounts of dermatan sulfate and chondroitin sulfates, has also been tested clinically.

Anticoagulant Effects of Low Molecular Weight Heparins

Like heparin, low molecular weight heparins produce their major anticoagulant effect by binding to ATIII through a unique pentasaccharide sequence.\(^{19,20,22-24,37-130} \) This sequence, all that is necessary for factor Xa inhibition, is present on less than one third of low—molecular weight heparin molecules. A minimum chain length of 18 saccharides (including the pentasaccharide sequence) is required for thrombin inhibition. Virtually all the heparin molecules of standard heparin contain at least 18 saccharide units, whereas only 25% to 50% of the different low—molecular weight heparins contain fragments with 18 or more.\(^{76,131-133} \) Therefore, compared with unfractionated heparin, which has a ratio of anti—factor Xa to anti—factor IIa activity of approximately 1:1, the various commercial low-molecular weight heparins have anti—factor Xa to anti—IIa ratios that vary between 4:1 and 2:1, depending on their molecular size distribution (Table 14) (Fig 7).

Pharmacokinetics of Low Molecular Weight Heparins

The bioavailability and pharmacokinetics of low molecular weight heparins differ from those of heparin because of differences in the binding properties of the two sulfated polysaccharides (Table 14).

Low molecular weight heparins bind much less avidly to heparin-binding proteins than does heparin,\(^{50,80,134-138} \) a property that contributes to their superior bioavailability at low doses and their more predictable anticoagulant response.\(^{139} \) They also do not bind to endothelial cells in culture,\(^{51,140,141} \) a property that could account for their longer plasma half-life.\(^{60,142,149} \) Low molecular weight heparins are cleared principally by the renal route, and their biological half-life is increased in patients with renal failure.\(^{148,150,151} \) Preparations of low molecular weight heparins also have a lower affinity than heparin for von Willebrand factor,\(^{50} \) in accord with the observation that they produce less experimental bleeding than heparin for equivalent antithrombotic effects.\(^{152-157} \) (Table 14).

Antithrombotic and Hemorrhagic Effects in Animal Models

The antithrombotic and hemorrhagic effects of heparin have been compared with those of low molecular weight heparins, the Orgaran heparinoid, and dermatan sulfate in a variety of animal models.\(^{152-162} \) In these models of thrombosis, temporary venous stasis is produced by ligating an appropriate vein, and blood coagulation is stimulated by injection of serum, factor Xa, thrombin, or tissue factor.\(^{157,161,162} \) When compared on a gravimetric basis, low molecular weight heparins are slightly less effective antithrombotic agents than heparin but produce much less bleeding in models used to measure blood loss from a standardized injury.\(^{152-157,160} \) These differences in the relative antithrombotic to hemorrhagic ratio among these sulfated polysaccharides could be due in part to their different effects on platelet function\(^{50,32,50,163} \) and vascular permeability.\(^{40} \) (Table 14).
TABLE 13. Influence of Heparin on Incidence of Bleeding in Patients With Acute Myocardial Infarction Treated With Thrombolytic Agents

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Major bleeding, noncerebral (%)</th>
<th>Intracranial bleeding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Heparin</td>
<td>Control</td>
</tr>
<tr>
<td>GISSI-263</td>
<td>12 500 U subcutaneously; every 12 h starting 12 h after thrombolytic therapy</td>
<td>0.99</td>
<td>0.55</td>
</tr>
<tr>
<td>ISIS-365</td>
<td>12 500 U subcutaneously; every 12 h starting 4 h after thrombolytic therapy</td>
<td>1.02</td>
<td>0.75</td>
</tr>
</tbody>
</table>

U indicates unit; h, hour.

Patients in GISSI-2 were randomly allocated to receive either streptokinase or rTPA treatment and those in the ISIS-3 trial to receive streptokinase, rTPA, or anistreplase treatment independently of the allocation to heparin treatment (factorial design).

Reversal of Anticoagulant and Hemorrhagic Effects With Protamine

Protamine sulfate neutralizes the anticoagulant effect of heparin, but it does not completely neutralize the anticoagulant activity of low molecular weight heparins. It is likely that protamine forms complexes with the higher molecular weight fractions of these heparins but not with the very low molecular weight fractions. Nevertheless, in an experimental model of microvascular bleeding in rabbits, protamine sulfate completely neutralized abnormal blood loss induced by both heparin and a low molecular weight heparin, even though it only partly neutralized the anti-factor Xa activity ex vivo.

Clinical Studies

Low molecular weight heparins have a longer plasma half-life and a more predictable anticoagulant response than unfractionated heparin, so they can be administered once daily and without laboratory monitoring. In animal models they produce less bleeding than heparin for an equivalent antithrombotic effect, so patients can be treated with doses of low molecular weight heparins that produce a higher anti-factor Xa level than unfractionated heparin without safety being compromised. This potential advantage of low molecular weight heparins has been demonstrated in one study of prophylaxis in which heparin produced a significant increase in bleeding when the dose was increased to match the anticoagulant effect ex vivo of a low molecular weight heparin, as well as in two studies in which high doses of a low molecular weight heparin were compared with full doses of heparin for the treatment of venous thrombosis. Low molecular weight heparins have been evaluated for the prevention and treatment of venous thromboembolism and are highly effective.

Prevention of Venous Thrombosis

General Surgery

Low molecular weight heparins were found to be effective and safe in two well-designed randomized trials in which a group treated with them was compared with an untreated control group. In one study, there was an increase in minor bleeding in the group taking them (compared with the group taking placebo) but in neither was there an increased incidence of major hemorrhage. In one study of 4498 patients there was a statistically significant reduction in thromboembolic mortality in those taking low molecular weight heparins (0.36% compared with 0.09% [risk reduction, 75%].) In the other a marked risk reduction in fibrinogen scan-detected thrombi was observed.

In two studies low molecular weight heparin was more effective than low-dose heparin, but in six other studies there was no significant difference in efficacy. In six of these eight studies there was no difference in the incidence of bleeding; in one study bleeding was significantly less in the low molecular weight heparin group and in another, bleeding was significantly greater in that group.

Orthopedic Surgery

Compared with placebo, treatment with low molecular weight heparins resulted in a risk reduction for all thrombi and for proximal vein thrombi of between 70% and 79%. This reduction occurred without an increase in clinically important bleeding in two studies and with a small increase in minor bleeding in a third (Table 15).

TABLE 14. Comparison of Properties of Unfractionated Heparin (UFH) and Low Molecular Weight Heparins (LMWHs)

<table>
<thead>
<tr>
<th>Property</th>
<th>Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td></td>
</tr>
<tr>
<td>Molecular weight (mean)</td>
<td>15 000</td>
</tr>
<tr>
<td>Saccharide units (mean)</td>
<td>45</td>
</tr>
<tr>
<td>Anticoagulant profile</td>
<td></td>
</tr>
<tr>
<td>Ratio of anti-factor Xa to anti-factor IIa activity</td>
<td>3:3</td>
</tr>
<tr>
<td>Binding characteristics</td>
<td></td>
</tr>
<tr>
<td>Plasma proteins</td>
<td>Marked</td>
</tr>
<tr>
<td>Vascular wall matrix proteins</td>
<td>Marked</td>
</tr>
<tr>
<td>Endothelial cells and macrophages</td>
<td>Moderate</td>
</tr>
<tr>
<td>Binding to platelets</td>
<td>Moderate</td>
</tr>
<tr>
<td>Experimental microvascular bleeding</td>
<td>Marked</td>
</tr>
<tr>
<td>Experimental antithrombotic effects</td>
<td>Marked</td>
</tr>
</tbody>
</table>

*Approximate
Fractions containing less than 18 saccharide units
50-75%
ATIII > Thrombin
No inhibition of thrombin

ATIII > Xa
Inhibition of Factor Xa (Xa)

Fractions containing 18 or more saccharide units
25-50%
ATIII > Thrombin
Inhibition of thrombin

ATIII > Xa
Inhibition of Factor Xa

Fig 7. Approximately 25% to 50% of the low molecular weight heparin (LMWH) molecules of the different commercial preparations contain at least 18 saccharide U; these molecules inhibit both thrombin and factor Xa. The remaining 50% to 75% of low molecular weight heparin molecules contain less than 18 saccharide U and inhibit only factor Xa. LMWH indicates low molecular weight heparin. U indicates unit.

The use of low molecular weight heparins has been compared with a variety of other methods of prophylaxis during orthopedic surgery, including low-dose heparin,171,188 low-dose heparin and dihydroergotamine,189 adjusted-dose heparin,190,191 Dextran,192,193 and warfarin.194

A pooled analysis of studies in which low molecular weight heparins are compared with low-dose heparin is presented in Table 12. Low molecular weight heparins were significantly more effective than standard low-dose heparin, and there was a trend for a decrease in major bleeding.

In the limited number of comparative trials, low molecular weight heparins were as effective and safe as adjusted-dose heparin190,191 and warfarin194 in patients having elective hip surgery and were much more effective than Dextran.195 They were also more effective than warfarin in patients having major knee surgery.194

There has only been one randomized trial evaluating a low molecular weight heparin or heparinoid in patients with hip fracture.194 Orgaran was compared to Dextran, both drug regimens beginning preoperatively. The incidence of thrombosis was 10% in the Orgaran group and 30% in the Dextran group (P<.001). However, the number of units of blood transfused was significantly higher in the group given Dextran.

Medical Patients

Low molecular weight heparins are very effective and safe prophylactic agents in medical patients and have been compared with placebo in two studies of patients with ischemic stroke195,196 and in one study of high-risk medical patients over the age of 65 years.197 Low molecular weight heparins have also been compared with low-dose heparin in two studies.198,199 In all of the reported studies, fibrinogen leg scanning was used to detect venous thrombosis. Compared with placebo, treatment with low molecular weight heparins produced a relative risk reduction in venous thrombosis of between 40% and 86% in patients with stroke and in high-risk medical patients; this effect was seen without an increase in clinically important bleeding. In both studies in which low molecular weight heparins were compared with heparin, patients randomly assigned to receive low molecular weight heparin had a statistically significant relative risk reduction for thrombosis of greater than 70%.198,199

Treatment of Established Thrombosis

Low molecular weight heparins have been compared with standard heparin in six relatively large studies.172,173,200-203 Most of the randomized trials used a change in thrombus size between the pretreatment and 5- to 10-day posttreatment venograms as the outcome measure. In all studies, low molecular weight heparins were at least as effective as unfractionated heparin in preventing extension of venous thrombosis, and in most they were associated with a greater reduction in thrombus size than heparin. In most of these studies, unfractionated heparin was administered by continuous intravenous infusion and was monitored to maintain the APTT in a defined therapeutic range, and the low molecular weight heparin was usually administered by subcutaneous injection without laboratory monitoring.

Two recent large studies used the more clinically relevant end point of confirmed symptomatic recurrent thromboembolism as the outcome measure.172,173 The results of these studies indicate that in patients with proximal vein thrombosis, low molecular weight heparins administered by subcutaneous injection in a fixed dose or weight-adjusted dose are at least as safe and probably more effective than conventional standard heparin administered by continuous infusion and monitored with the APTT.

Recommendations

Firm recommendations based on solid evidence can be made for the prevention and treatment of venous thromboembolism and for the treatment of unstable angina. The evidence supporting specific dosage regi-
mens for the treatment of acute myocardial infarction is less conclusive and subject to revision. In all cases of treatment, the dose of heparin should be adjusted to maintain the APTT at a ratio of 1.5 to 2.5 times control (equivalent to a heparin level of 0.2 to 0.4 U/mL by protamine titration).

Treatment of Venous Thromboembolism

Patients with venous thromboembolism should be treated with a 5000-unit intravenous bolus of heparin followed by either 32 000 U per 24 hours by continuous infusion or 17 500 U subcutaneously every 12 hours, and the dose should be adjusted to maintain the APTT at 6 hours within the therapeutic range of 1.5 to 2.5 times control.

Prevention of Venous Thromboembolism

General surgical and medical patients should receive 5000 U of heparin subcutaneously every 12 hours. Patients having major orthopedic surgery or very high-risk patients (those with a history of recurrent venous thrombosis) should receive low molecular weight heparin,76 adjusted low-dose heparin (adjusted to the upper normal APTT range),108 or less intense warfarin.109,110 Of these regimens, low molecular weight heparin has the advantage of being more convenient because it does not require monitoring. It is also more effective than warfarin in patients undergoing major knee surgery.104 In addition, low molecular weight heparin is more effective than adjusted-dose standard heparin in reducing the incidence of proximal deep vein thrombosis after elective hip surgery.100

Treatment of Unstable Angina or Acute Myocardial Infarction

If thrombolytic therapy is not given, patients with unstable angina or acute myocardial infarction should receive 325 mg aspirin and 5000 U heparin as an intravenous bolus followed by 32 000 U per 24 hours. If thrombolytic therapy is used, the need for added heparin therapy is less clear. If a decision is made to use heparin, it should be given in a dose of 24 000 U per 24 hours. Heparin should be given concomitantly with TPA but can be delayed for 2 to 3 hours after streptokinase.

Side Effects of Heparin

The most common side effect of heparin is hemorrhage. Other complications are thrombocytopenia with or without thrombosis,204,205 osteoporosis,206,207 skin necrosis,208 alopecia,209 hypersensitivity reactions,210 and hypoaaldosteronism.211 Four variables have been reported to influence bleeding during heparin treatment: the dose of heparin, the patient’s anticoagulant response, the method of heparin administration, and patient factors. There is indirect evidence that the frequency of bleeding is increased by heparin dose and anticoagulant effect.73,74 Pooled analysis of randomized trials in which different methods of heparin administration were compared shows an average incidence of major bleeding of 6.8% in the continuous infusion group and 14.2% in the intermittent intravenous group (odds ratio, 0.42; P=.01). However, this comparison is confounded by the difference in the 24-hour heparin dose, which was greater in the intermittent intravenous group in five of the six studies; the observed increase in bleeding could have been contributed to by the higher dose of heparin. For studies in which continuous intravenous heparin was compared with subcutaneous heparin, the average incidence of bleeding was 4.4% and 4.3% respectively (odds ratio, 1.0).73 Other factors that predispose the patient to anticoagulant-induced bleeding are serious concurrent illnesses73,75 and chronic heavy alcohol consumption.212

The concomitant use of aspirin has long been identified as a risk factor for heparin-induced bleeding.73,212,213 Aspirin increases operative and postoperative bleeding in patients who receive the very high doses of heparin required during open-heart surgery.214 However, the risk of adding aspirin to a short course of regular therapeutic doses of heparin is likely to be much lower, and is acceptable in patients with ischemic heart disease.

Renal failure and patient age and gender have also been implicated as risk factors for heparin-induced bleeding.73,215 The reported association with female gender is not consistent and remains in question.

Thrombocytopenia, a well-recognized complication of heparin therapy, has been reviewed recently.204,205 In most cases, it is asymptomatic.204,205 The reported incidence of heparin-associated thrombocytopenia varies widely. Thrombocytopenia is more common with heparin derived from bovine lung than with that from porcine gut.204 Pooled analysis of studies in which patients were randomly assigned to receive heparin derived from different sources revealed an overall incidence of thrombocytopenia of 15.6% in the 173 patients receiving bovine heparin and

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**Table 15. Double-Blind Trials Comparing Low-Molecular Weight Heparins With Placebo in Orthopedic Elective Surgery**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of surgery</th>
<th>Treatment</th>
<th>Patients (n)</th>
<th>DVT (%)</th>
<th>Bleeding‡ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turpie et al185</td>
<td>Hip</td>
<td>Enoxaparin</td>
<td>37</td>
<td>10.8</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>39</td>
<td>51.3‡</td>
<td>4.0</td>
</tr>
<tr>
<td>Leclerc et al184</td>
<td>Knee</td>
<td>Enoxaparin</td>
<td>41</td>
<td>19.5</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>54</td>
<td>64.6‡</td>
<td>7.6</td>
</tr>
<tr>
<td>Hoek et al186</td>
<td>Hip</td>
<td>Orgaran</td>
<td>97</td>
<td>15.5</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>99</td>
<td>56.6‡</td>
<td>0‡</td>
</tr>
</tbody>
</table>

DVT indicates deep vein thrombosis.
*Prophylaxis begun postoperatively.
‡More patients were included in safety analysis than in efficacy analysis.
5.8% in the 223 patients receiving porcine heparin. On pooled analysis of all prospective studies with porcine heparin, the mean incidence of thrombocytopenia is 2.4% for therapeutic heparin and 0.3% for prophylactic heparin. The incidence of arterial or venous thrombosis with heparin-associated thrombocytopenia is approximately 0.4%. Arterial thrombosis occurs as a consequence of platelet aggregation in vivo, but venous thrombosis could result from heparin resistance caused by the neutralizing effect of heparin-induced release of platelet factor IV. Thrombocytopenia usually begins between 3 and 15 days (median, 10 days) after heparin therapy is started, but it has been reported within hours of the start of heparin therapy in patients previously exposed to heparin. The platelet count usually returns to baseline levels within 4 days after heparin is stopped. Heparin-associated thrombocytopenia is thought to be caused by an IgG-heparin immune complex involving both the Fab and Fc portion of the IgG molecule. Although low molecular weight heparins can exhibit immunologic cross-reactivity with heparin, the heparinoid Orgaran 10172 exhibits minimal cross-reactivity and has been used successfully to manage a small number of patients with heparin-associated thrombocytopenia.

Pregnancy

Heparin is the anticoagulant of choice in pregnancy because it does not cross the placenta and its administration to the mother during pregnancy is not associated with undesirable effects in the fetus or neonate. The drug should be given in therapeutic doses (approximately 15 000 units subcutaneously every 12 hours) when used to treat pregnant patients with prosthetic heart valves or with venous thromboembolism. The use of heparin in doses of greater than 20 000 units for more than 5 months is problematic because it can cause osteoporosis.

References


Bhatt G, Aberg W, Johansson M, Törnbohm E, Granqvist S, Lockner D. Two daily subcutaneous injections of fragmin as compared with intravenous standard heparin in the treatment of


