Antithrombotic Therapy for Venous Thromboembolic Disease

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It has been recognized for more than a century that stasis of blood, abnormalities of the vessel wall, and changes in the soluble and formed elements of the blood are the major contributors to thrombosis.

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For venous thrombosis, stasis and local alterations in blood elements are most important, since major pathologic changes are not seen routinely in the vessel wall at the nidus of a venous thrombus.

Antithrombotic regimens are available that modify one or more of these abnormalities. These modalities

Table 1—Antithrombotic Agents and Procedures in Venous Thromboembolism

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Onset of Action</th>
<th>Application</th>
<th>Route of Administration</th>
<th>Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin 25-35,000 U/d</td>
<td>Prevents extension of active, established venous thromboembolism by inhibiting thrombin activity via the cofactor (ATIII)*</td>
<td>Immediate</td>
<td>Treatment of established pulmonary embolism and deep venous thrombosis</td>
<td>IV or subcutaneous</td>
<td>Severe active bleeding, documented hypersensitivity, heparin-induced thrombocytopenia and thrombosis</td>
</tr>
<tr>
<td>Heparin 10-15,000 U/d</td>
<td>Prevents formation of venous thrombi by thrombin via the cofactor (ATIII)</td>
<td>Immediate</td>
<td>Prevention of venous thromboembolic disease in selected surgical patients</td>
<td>Subcutaneous</td>
<td>Established venous thromboembolic disease, documented hypersensitivity, heparin-induced thrombocytopenia and thrombosis</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Inhibits proper synthesis of vitamin K-dependent coagulation factors (II, VII, IX, X)</td>
<td>4-5 days</td>
<td>Long-term treatment of established disease; prevention of disease</td>
<td>Oral</td>
<td>Severe active bleeding, pregnancy, documented hypersensitivity</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>Activates plasminogen, dissolves fibrin, degrades fibrinogen and several other plasma proteins</td>
<td>Immediate</td>
<td>Treatment of severe or life-threatening pulmonary embolism or deep venous thrombosis</td>
<td>IV</td>
<td>Active bleeding, recent surgery, stroke, or severe trauma, any hemorrhagic disease, recent streptococcal infection or treatment with streptokinase, documented hypersensitivity</td>
</tr>
<tr>
<td>Urokinase</td>
<td>Activates plasminogen, dissolves fibrin, degrades fibrinogen and several other plasma proteins</td>
<td>Immediate</td>
<td>Treatment of severe or life-threatening pulmonary embolism or deep venous thrombosis</td>
<td>IV</td>
<td>Active bleeding, recent surgery, stroke, or severe trauma, any hemorrhagic disease</td>
</tr>
<tr>
<td>Tissue plasminogen activator</td>
<td>Activates plasminogen bound to fibrin; dissolves fibrin</td>
<td>Immediate</td>
<td>Treatment of severe or life-threatening pulmonary embolism or deep venous thrombosis</td>
<td>IV</td>
<td>Active bleeding, recent surgery, stroke, or severe trauma, any hemorrhagic disease</td>
</tr>
<tr>
<td>Dextran</td>
<td>Inhibits platelet function and fibrin polymerization</td>
<td>Immediate</td>
<td>Prevention of venous thromboembolic disease in selected high-risk patients</td>
<td>IV</td>
<td>Established venous thromboembolism, congestive heart failure; dextran hypersensitivity</td>
</tr>
<tr>
<td>External pneumatic leg compression</td>
<td>Prevents venous stasis, activates fibrinolytic system</td>
<td>Immediate</td>
<td>Prevention in high-risk patients</td>
<td>Local application</td>
<td>Established venous thromboembolism, severe peripheral arterial disease, trauma with compromised tissue viability, skin ulcers</td>
</tr>
</tbody>
</table>

*ATIII = antithrombin III.
include drugs that inhibit blood coagulation, such as heparin and warfarin; drugs that inhibit platelet function, such as aspirin and dextran; and techniques that counteract venous stasis, such as pneumatic compression of the lower extremity. In this broad sense, thrombolytic agents and vena caval filters are also antithrombotic (Table 1).

The effectiveness of antithrombotic agents in the treatment of established venous thromboembolic disease will be described. Several of these agents are also useful for the primary prevention of venous thromboembolic disease, and this application of antithrombotic therapy is reviewed in another chapter of this monograph. Judgment of efficacy is based on the results of controlled clinical trials that either showed a statistically significant benefit or, if negative, were sufficiently large to exclude a clinically important (level I study). Studies of lower quality will be designated level II or III.

It must be emphasized that all antithrombotic therapy with either anticoagulants or platelet-active drugs is prophylactic, since these agents interrupt the progression of the thrombotic process; unlike thrombolytic agents, however, they do not as a rule actively resolve it.

Of the agents currently available in this country, only heparin, thrombolytic agents, and warfarin in appropriate doses are used to treat established thromboembolic disease. Dextran and lower doses of heparin and warfarin are useful for prevention of disease, but these regimens are not appropriate for treatment of acute disease.

**INDIVIDUALS AT INCREASED RISK FOR VENOUS THROMBOEMBOLISM**

Several risk factors have been identified for venous thromboembolism. 1-3 The two major risk factors are venous stasis, which is caused by bed rest, immobility, congestive heart failure, venous obstruction from any cause (including previous venous thrombosis), and trauma, which includes surgery and childbirth. Increased age is a risk factor; estrogen in pharmacologic doses and a history of venous thromboembolism are also associated with increased risk. Carcinoma is a risk factor, particularly adenocarcinomas of the lung, breast, and viscera. 4 Patients with hip fractures or those undergoing major orthopedic procedures on the lower extremity are among the groups at highest risk. Individuals undergoing total hip or knee replacement suffer a 40 percent incidence of deep venous thrombosis; 5,6 about half of the thrombi are solely in the calf and the other half are thigh thrombi, with or without calf vein involvement.

Patients at lower but still substantial risk include those older than 40 years who undergo major surgery with general anesthesia that exceeds 30 minutes' duration; those undergoing urologic or neurosurgical procedures; and those with carcinoma, stroke, myocardial infarction, or congestive heart failure, or those confined to bed for other reasons. Thrombosis typically begins in the calf veins. 7,8

There has been disagreement for many years about the potential for embolization and the need to treat deep calf vein thrombosis. One study using clinical findings and 125I-labeled fibrinogen testing for up to six days postoperatively with venographic confirmation of deep venous thrombosis concluded that the risk was low. 9 However, 23 percent of patients with distal thrombi had proximal extension, and a 10 percent had clinical evidence of pulmonary embolism. In another study of patients who had calf vein thrombosis diagnosed without venography, 10 percent had evidence of pulmonary embolism. 10 In both studies, approximately one half of the patients had no clinical evidence of deep venous thrombosis. In a third study with objective testing limited to 5 to 7 days and a clinical evaluation at 3 months, 21 asymptomatic patients with calf vein thrombosis had no extension. 11 The outcome in asymptomatic patients may not be applicable to patients presenting with symptoms. Lagerstedt et al. 12 conducted a controlled prospective study of symptomatic patients using physical examination and 99mTc plasmin at 5, 14, 30, and 90 days with venographic confirmation and a perfusion lung scan at 90 days. In 28 patients with deep calf vein thrombosis who received intermittent intravenous (IV) heparin therapy for only 5 days, 8 (29 percent) had recurrences within 90 days. There was proximal extension in 5 and a pulmonary embolus in 1; 1 additional patient had a recurrence at 90 days. In contrast, none of the 21 patients in the group who received anticoagulant therapy for approximately 3 months had recurrences. In the study by Huisman et al. 13 using serial impedance plethysmography (IPG) in patients with suspected deep venous thrombosis, 6 percent developed a proximal deep vein thrombosis within ten days following an initially negative study. Hull et al. 14 in a study comparing IPG with combined IPG and radioactive fibrinogen leg scanning venographically proved deep venous thrombosis, found that 5.7 percent of symptomatic patients developed deep venous thrombosis within 14 days after the initial IPG was negative. Further, these workers showed that after the first 14 days, the subsequent incidence of venous thromboembolism was only 2 percent and was usually associated with ongoing risk factors. 15 Havig 16 conducted a gross and microscopic examination of the deep venous tree from the foot to the right side of the heart in 261 autopsies and concluded that 25 percent of the 40 pulmonary emboli considered to be the cause of death and 33 percent of 32 pulmonary emboli considered serious (contributing to the cause of death) originated
in distal or calf vessels. The current evidence indicates that patients with deep calf vein thrombosis must either be anticoagulated for three months or followed up with serial noninvasive tests for 10 to 14 days to identify extension.

Heparin

This drug, an acidic glycosaminoglycan (sulfated mucopolysaccharide), is a highly effective antithrombotic agent. Clinical preparations vary over a molecular weight range of 5,000 to 30,000 daltons. The drug acts by catalyzing the effect of a plasma inhibitor, antithrombin III, so that the inhibitor more efficiently combines with and inactivates a number of serine proteinases, notably thrombin (factor IIa) factor Xa and factor IXa. Recent evidence also indicates that heparin acts to inhibit the activation of factors V and VIII by thrombin. Heparin works only when given parenterally and only in the presence of antithrombin III. Neither hepatic nor renal disease seems to interfere notably with the clearance of the drug at therapeutic concentrations. Heparin is currently obtained from either the lung or gut mucosa of animals and is available as either a sodium or calcium salt.

The unit of heparin is measured in animals using a biologic assay. Unitage may vary by as much as 50 percent on a weight basis, and consequently heparin is properly prescribed by units, not weight.

Heparin has been proved effective in the treatment of pulmonary embolism. This trial, by Barritt and Jordan, which satisfies the criteria for a level I study, was completed before the advent of perfusion lung scanning and pulmonary angiography and has several other flaws, but the much higher mortality (25 percent) in the placebo-treated patients, combined with a demonstration of autopsy-verified pulmonary embolism as the cause of death, is persuasive. Subsequent studies have attested to the reduced mortality rate when heparin was used to treat venous thromboembolic disease and to the high mortality when patients with pulmonary embolism did not receive anticoagulant therapy. A recent randomized clinical trial has confirmed the efficacy of continuous intravenous heparin in the treatment of venous thromboembolism. Another recent trial indicates that subcutaneous heparin is adequate initial therapy for deep venous thrombosis, provided the activated partial thromboplastin time (aPTT) is prolonged beyond 1.5 times the control value. A third trial has shown the efficacy of heparin and warfarin in treating symptomatic calf vein thrombosis. Deep venous thrombosis that remains confined to the deep calf veins appears to be associated with a low risk of clinically important pulmonary embolism. Serial testing with IPG or duplex ultrasound for 10 to 14 days appears to be effective for identifying patients with extending calf vein thrombosis; negative findings by serial IPG are associated with a low risk of clinically important pulmonary embolism (<1 percent) or recurrent venous thrombosis (2 percent). In patients with documented calf vein thrombosis, serial IPG may be useful to separate the 20 percent of patients who develop proximal extension (and require treatment) from the remaining 80 percent of patients who do not, in whom the risks of anticoagulant therapy may outweigh the benefits (eg, in patients at high risk of bleeding). If IPG or duplex ultrasonography is not available to monitor for extension, patients with documented calf vein thrombosis should be treated with initial heparin therapy followed by adequate long-term anticoagulant therapy. In contrast, superficial thrombophlebitis in the absence of deep venous thrombosis is generally treated effectively with nonsteroidal anti-inflammatory agents. However, it is often necessary to use IPG or duplex ultrasonography to identify and distinguish deep vein thrombi from superficial thrombophlebitis.

How Intensely To Administer Heparin: In the past 25 years, a great deal of effort has been spent to maximize heparin's safety and efficacy. Blood levels during administration of heparin are not easily predictable and more specific plasma assays for the drug have not been widely applied. The lack of a clear relationship between heparin dose and bleeding probability results from heparin's variable interference with platelet and endothelial cell function in patients. Under most circumstances, a 5 to 20 percent rate of hemorrhagic complications or an unexplained fall in hematocrit reading can be expected during heparin therapy. Since no hemostatic studies address the independent effect on bleeding or dose and response measured by in vitro coagulation tests, it is impossible to separate the influence of these two variables on bleeding risk. There is, however, some support from published studies for the commonly held clinical view that the risk of bleeding increases with increasing doses of heparin and with the hemorrhagic response reflected by in vitro coagulation tests that are used to monitor heparin. Hirsh et al described the hemorrhagic risk of heparin therapy in 100 consecutive patients treated with continuous IV heparin that was adjusted according to the results of the whole blood clotting time. Four patients had major hemorrhagic episodes, and in three, the results of whole blood clotting time were prolonged considerably above the upper limit of the targeted therapeutic range (three times control). The level of the anticoagulant effect, however, was not described in patients who did not bleed. Other studies have provided stronger evidence for a relationship between hemorrhage and the intensity of the anticoagulant effect. In the Urokinase Pulmonary Embolism Trial, bleeding occurred in
nine (20 percent) of 44 patients whose blood clotting time was greater than 60 min but in only one (4 percent) of the 25 patients whose blood clotting time was less than 60 min (relative risk, 4). Wilson and Lampman described 18 nonsurgical patients receiving heparin monitored by the whole blood clotting time. Ten (56 percent) of 18 patients who received excessive heparin (defined by a greatly prolonged whole blood clotting time) bled, whereas bleeding occurred in only 16 percent of patients who did not receive excessive heparin (relative risk, 3.5). In a recent study, predictors of major bleeding in hospitalized, anticoagulated patients were identified retrospectively and validated in an independent group. The comorbid factors identified were as follows: (1) "cardiac," defined as acute myocardial infarction (AMI), systolic blood pressure less than 90 mm Hg, or the need for an intra-aortic balloon pump; (2) "liver," bilirubin level greater than 1 mg/dl, or macrocytosis (enzyme increases were excluded); (3) "renal failure," an increase in creatinine of greater than 50 percent to greater than 1.5 mg/dl; and (4) "poor condition," cancer or a hematocrit of less than 30 without recent bleeding. The risk of bleeding increased as the number of comorbid conditions increased. Bleeding complications were also associated with intensity of anticoagulation. If the aPTT or PT prolongation was 2.0 to 2.9 times the control value, complications increased three times (relative risk, 3); if either test was 3.0 times or longer than the control, bleeding complications increased eight times (relative risk, 8).

Although none of these studies was designed to compare the effects on bleeding of either different doses of heparin or different levels of hemostatic response (level IV studies), there is strong suggestion that bleeding is more likely to occur when an in vitro test of coagulation is excessively prolonged.

**Relationship Between Risk of Bleeding and Method of Administering Heparin:** Six randomized studies compared the bleeding and thromboembolic recurrence rates when heparin was administered by intermittent injection or by continuous infusion. Two of the studies reported that continuous heparin infusion was associated with a lower frequency of bleeding (1 percent and 0 percent compared with 9 percent and 33 percent), and the third reported the trend toward reduced bleeding with continuous heparin (level II study), 5 percent compared with 10 percent. In the fourth study, there was a trend in the other direction (level II study). The other two studies were too small to draw clear conclusions about recurrence rates.

Patients receiving continuous infusion heparin, however, also received a lower dose of heparin. Therefore, it is uncertain whether the difference noted in the rates of bleeding between patients randomized into continuous IV infusion and intermittent IV injection is related to the method of heparin administered or to the difference in the total dose of heparin given to the two groups.

Only one randomized trial evaluated the benefit of monitoring heparin therapy. In this study, patients received intermittent heparin injections, either with or without laboratory control using the aPTT. There was no significant difference detected in the frequency of bleeding between the two groups (8 vs 10 percent), suggesting that when heparin is administered by intermittent injection, monitoring the response may not reduce the risk of bleeding.

It is generally accepted that a minimum level of heparin anticoagulation must be maintained to achieve an effective antithrombotic state and that inadequate anticoagulant therapy results in unacceptably higher rates of recurrent thromboembolism (Table 2). Animal experiments support the concept that a minimum level of heparin is necessary to interrupt an ongoing thrombotic process. The most widely used test for monitoring heparin therapy is the aPTT, a global coagulation test. A retrospective analysis of a prospective cohort study suggested that recurrent venous thromboembolism is infrequent if continuous IV heparin is administered in doses adjusted to prolong the aPTT more than 1.5 times the control value. More recently, a retrospective analysis of a randomized, prospective trial comparing IV and subcutaneous heparin administration in patients with proximal vein thrombosis demonstrated that failure to achieve an adequate anticoagulant response (aPTT > 1.5 times control) is associated with a high risk (20 to 25 percent) of recurrent venous thromboembolism. In that study, the control aPTT value was defined as the mean aPTT obtained from pooled plasma of normal volunteers. Sufficient heparin should be administered to maintain the aPTT above 1.5 times the control value. To date and to our knowledge, there have been no randomized

<table>
<thead>
<tr>
<th>Disease</th>
<th>Guideline</th>
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<tbody>
<tr>
<td>Suspected Confirmed</td>
<td>Give heparin 5000 U IV and order imaging study Bebolus with heparin 5-10,000 U IV and start maintenance infusion at 1300 U/h (heparin 20,000 U in 500-ml D, W, infused at 33 ml/h) Check aPTT at 6 h to keep aPTT between 1.5-2.5 times control Check platelet count daily Start warfarin therapy on day 1 at 10 mg daily for first 2 d, then administer warfarin daily at estimated daily maintenance dose Stop heparin therapy after 5 to 7 d of joint therapy when INR is 2.0-3.0 off heparin Anticoagulate with warfarin for 3 mo at an INR of 2.0-3.0</td>
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</table>
clinical trials comparing the aPTT with more direct heparin assays for the management of heparin therapy. However, it should be recognized that different assay conditions can give different results in the aPTT when heparin is present. Consequently, it is currently recommended that the therapeutic range with heparin (aPTT of approximately 1.5 to 2.5 times control) correspond to a plasma heparin level of 0.2 to 0.4 μ/ml by protamine titration or to 0.35 to 0.70 μ/ml by inhibition of factor Xa.47

Heparin is cleared rapidly from the plasma with an average half-life of 60 min when given in therapeutic doses.48 Audits of heparin therapy indicate that the current clinical practice of intuitive ordering of heparin results in inadequate therapy because of fear of bleeding.49 Recently, the importance of exceeding the lower limit of the therapeutic range has been strongly supported by findings of prospective clinical trials. Indeed, firm evidence indicates that failure to exceed the lower limit is associated with unacceptably high rates of recurrent venous thromboembolism.47 In contrast, evidence supporting the bleeding risk of exceeding the upper limit of the therapeutic range in the first few days of therapy is weaker.

The objectives of a study by Hull and associates50 were to validate prospectively an approach designed to minimize the proportion of patients receiving subtherapeutic doses of heparin and to determine the effectiveness and safety of decreasing the heparin dosage when the aPTT prolongation reflected both heparin and warfarin sodium effects. The study was a randomized double-blind trial evaluating a prescribed approach to heparin administration in patients receiving heparin or heparin with warfarin sodium. Thromboembolic and bleeding complications were objectively documented. Only 1 percent and 2 percent of patients were subtherapeutic for 24 h or more in the heparin and combined groups, respectively. Recurrent venous thromboembolism occurred infrequently in both groups (7 percent). Sixty-nine (69 percent) of 99 patients receiving combined heparin and warfarin therapy had supratherapeutic values compared with 24 (24 percent) of 100 receiving heparin alone (p<0.001); bleeding complications occurred in 9 percent and 12 percent, respectively.

These findings demonstrate that in the first few days of heparin therapy, a weak association exists between supratherapeutic aPTT responses and bleeding, which is in direct contrast to the observed association between supratherapeutic aPTT responses and recurrent venous thromboembolism. In recent years, a number of nomograms have been published to aid the clinician in reaching and maintaining the therapeutic range with heparin anticoagulation. All of these approaches are based on frequent monitoring of the aPTT in the first few days of therapy and rapid response to subtherapeutic or supratherapeutic values for the aPTT.51 In this regard, when the aPTT is less than 1.5 times control, one can raise the blood level of heparin quicker by giving another bolus and increasing the constant infusion rate simultaneously. Conversely, when the aPTT is too prolonged, the heparin infusion can be discontinued for a short time not to exceed an hour. Table 3 gives an algorithm based on the study by Hull and associates50 for heparin monitoring and dosage adjustment. Perhaps the most common mistake with heparin dosing is choice of an inadequate maintenance dose. Recent studies indicate that the average daily maintenance dose should be greater than 31,000 U (>1,300 U/h).22,32,52 When heparin is given subcutaneously as an initial anticoagulating dose, therapy should begin with 17,500 U subcutaneously every 12 h.54 The dose should then be adjusted to give an aPTT greater than 1.5 times control within 1 h of the next scheduled subcutaneous dose.

The major problem with constant IV therapy is the equipment and skilled care necessary to deliver it properly.54 More trials are needed comparing constant IV infusion to a similar dose administered subcutaneously every 8 to 12 h.22,23,55,56 It appears that heparin continues to be underdosed in clinical use56 despite the compelling human and controlled animal data that indicate that a minimum prolongation of the aPTT beyond 1.5 times control is necessary.

Heparin requirements are usually greatest in the first few days after the acute thromboembolic event,17,25 and consequently therapy should be monitored most closely then. After the first few days, the monitoring test can usually be obtained daily. It is recommended that a platelet count be monitored daily when heparin is being used for short-term treatment, since the drug can induce thrombocytopenia.57-60 This syndrome recently has been reviewed.61 It appears that bovine-derived heparin is more likely than porcine-derived heparin to induce thrombocytopenia. When the platelet count falls precipitously or in a sustained fashion, serious consideration should be given to stopping heparin therapy. When the platelet count falls below 100,000/μL, heparin therapy should be stopped. A marked fall in platelet count can signal antibody-mediated injury to platelets and endothelium. This syndrome may be associated with arterial thromboembolism and extension or recurrence of existing venous thromboembolism.62 If heparin therapy is discontinued when the risk for recurrent embolism is great, an inferior vena caval filter should be inserted. Alternatively, ancrod (ancrod is not currently available in the United States for clinical use) or the organon heparinoid (Org 10172) may be used for...
temporary anticoagulation until warfarin therapy becomes fully effective. If heparin therapy is discontinued after several days of overlapping warfarin therapy and the prothrombin time has been in or near the therapeutic range for 24 to 48 h, one might consider continuing the warfarin therapy without additional interventions. Heparin use commonly leads to mild reductions in the level of circulating antithrombin III, and rarely, it has been reported to induce disseminated intravascular coagulation and rarely, it has been reported to induce disseminated intravascular coagulation. Heparin causes asymptomatic elevation of liver enzyme levels in a majority of patients between days 5 and 10 of treatment. These elevations either return to normal during treatment or following treatment without obvious untoward effect.

If full-dose heparin therapy is contraindicated for a patient with acute venous thromboembolism, as it would be for someone with an actively bleeding central nervous system (CNS) lesion, the acceptable alternative is insertion of a vena caval filter. Substitution of low-dose, prophylactic heparin or aspirin therapy for full-dose heparin in this setting is inappropriate.

**How Long to Anticoagulate with Heparin:** Heparin can be conveniently administered IV for five to ten days in recovering patients. Unfortunately, such a short period of anticoagulation does not seem to interrupt completely the thrombotic process in many patients with proximal deep venous thrombosis of the leg. Specifically, 10 to 14 days of conventional IV heparin therapy, followed by low-dose subcutaneous heparin therapy, did not prevent recurrent venous thromboembolism. Consequently, most clinicians follow the initial course of heparin with coumarin derivatives for longer-term oral anticoagulation. The alternative is to give heparin in a larger subcutaneous dose that maintains the anticoagulated state.

The optimal duration of initial IV heparin therapy in patients with venous thromboembolism has not been resolved completely (Table 2). Multiple randomized clinical trials in patients with proximal vein thrombosis indicate that when IV heparin is administered for seven to ten days and followed by adequate long-term anticoagulant therapy, the frequency of recurrent venous thromboembolism is low (<5 percent). The currently accepted approach is to begin heparin and oral anticoagulant therapy together at the time of diagnosis and to discontinue the heparin therapy on the fourth or fifth day. If this latter approach is effective, it would avoid four to five days of unnecessary hospitalization in many patients and would greatly reduce the cost of initial therapy. A randomized trial in patients with submassive venous thrombosis or pulmonary embolism suggests that four to five days of initial heparin therapy, followed by adequate long-term therapy with warfarin, is effective and safe. More recently, a second trial has been published comparing patients with venous thromboembolism with heparin and warfarin therapy started together on day 1 to a second group in whom warfarin therapy was started between days 5 and 7. This trial also showed no significant differences in rates of recurrent thromboembolism, bleeding, or death. However, another study using a five-day course of heparin therapy in patients with proximal deep venous thrombosis reported an unacceptably high subsequent rate of thrombosis. This approach must be further evaluated in persons with more extensive disease before it can be recommended for patients with massive iliofemoral thrombosis. It seems reasonable at this point to recommend that heparin be given for five to ten days and that warfarin be administered jointly with heparin for four to five days. Heparin therapy may then be discontinued when the prothrombin time is shown to be in the therapeutic range (Table 2).

**Table 3— Intravenous Heparin: Monitoring and Adjusting Dosage**

<table>
<thead>
<tr>
<th>Rate Change, mU/h</th>
<th>Dose Additional Action Next aPTT</th>
<th>Rate Change, U/24 h</th>
<th>Action</th>
<th>Next aPTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤45</td>
<td>+6</td>
<td>+5,760</td>
<td>Rebolus with 5,000 U</td>
<td>4-6 h</td>
</tr>
<tr>
<td>46-54</td>
<td>+3</td>
<td>+2,880</td>
<td>None</td>
<td>4-6 h</td>
</tr>
<tr>
<td>55-85</td>
<td>0</td>
<td>0</td>
<td>None</td>
<td>Next morning$</td>
</tr>
<tr>
<td>86-110</td>
<td>-3</td>
<td>-2,880</td>
<td>Stop infusion 1 h</td>
<td>after restart</td>
</tr>
<tr>
<td>&gt;110</td>
<td>-6</td>
<td>-5,760</td>
<td>Stop infusion 1 h</td>
<td>after restart</td>
</tr>
</tbody>
</table>

*A starting bolus of 5-10,000 U is given IV followed by IV infusion of 1,300 U/h (heparin 20,000 U in 500 ml D,W at approximately 33 ml/h). The concentration of heparin is 40 U/ml. When aPTT is checked at 6 h or longer, steady-state kinetics can be assumed. Dosage adjustments are made according to the protocol.

|$\text{Normal aPTT range with Dade-Actin FS reagent of 27 to 35 s.}$

*$\text{The therapeutic range of 55-85 s is roughly equivalent to a plasma heparin concentration range of 0.2-0.4 U/ml by protamine titration.}$

*$\text{If during the first 24 h, repeat aPTT in 4-6 h. Thereafter, monitor aPTT daily unless it is subtherapeutic.}$

**Coumarin Derivatives**

These drugs are chemical derivatives of 4-hydroxy-coumarin. They are well absorbed in the gut and transported in plasma bound to albumin. The drugs are metabolized by the liver and excreted in a hydroxylated form in the urine. In North America the predominant coumarin derivative in clinical use is racemic warfarin sodium.

Coumarins act in the liver by inhibiting the synthesis...
of four vitamin K-dependent coagulant proteins, factors II, VII, IX, and X, and at least two vitamin K-dependent anticoagulant factors, proteins C and S. The synthesis of several other vitamin K-dependent proteins is also impaired, although the significance of this inhibition is uncertain since the function of other vitamin K-dependent proteins is largely unknown. The major mechanism of action is inhibition of a specific posttranslational event in protein synthesis: the gamma-carboxylation of multiple glutamic acid residues near the aminoterminus of the polypeptide chain. The failure of gamma-carboxylation of glutamic acid residues markedly interferes with the function of the proteins by preventing calcium binding and proper alignment of the activated factors on a phospholipid surface. In the presence of coumarins, a number of analogous proteins are synthesized and released that not only are hypofunctional but also can interfere with normal coagulation reactions. For this reason, plasma from patients receiving coumarin cannot be compared directly with dilutions of normal plasma or with plasma from individuals who congenitally lack vitamin K-dependent coagulation factors.

Coumarins do not act immediately, because time is required for normal coagulation factors already present in the plasma to be cleared. This lag period varies according to the plasma clearance rates of the K-dependent factors, being shortest for factor VII and longest for factor II. Accordingly, the one-stage prothrombin time might appear adequately prolonged 24 h after a large loading dose of a coumarin derivative because of the relatively short half-life of factor VII, but plasma levels of the other three factors would still be high. Moreover, proteins C and S, which have anticoagulant and fibrinolytic effects, are also vitamin K dependent. Protein C has plasma clearance kinetics similar to factor VII. Therefore, by reducing effective protein C levels, a large loading dose of a coumarin derivative might tip the hemostatic balance toward coagulation rather than anticoagulation in the first 24 to 48 h of therapy. Animal studies as well as anecdotal clinical experience support the need for a period of overlap of heparin and warfarin therapy when treating acute venous thromboembolism. Early introduction of warfarin on day 1 or 2 with a small loading dose (10 mg) will usually keep the total duration of heparin therapy at no more than seven days.

Monitoring Coumarin Therapy: Therapy is most commonly monitored with the one-stage prothrombin times described by Quick. When monitoring coumarin therapy, it is important to recognize that the heparin can be easily removed from blood samples before performing the prothrombin time. The clotting time is measured after mixing citrated plasma with calcium and a well-characterized tissue thromboplastin. Commercially available tissue thromboplastins vary in potency, and, consequently, prothrombin times performed with different thromboplastins are not always directly comparable, which has resulted in much confusion over the years as to the intensity of the anticoagulant effect required.

Another major difficulty with coumarin therapy is the number of factors that influence coumarin metabolism and action. A complete review of these factors is beyond the scope of this review. These interactions have been reviewed recently. Ideally, a patient treated with warfarin should be receiving as few other drugs as possible, should use alcohol not at all or only moderately, and would be consuming a diet that contains a decreased but constant amount of vitamin K.

Intensity of Coumarin Therapy: As with heparin, a minimum level of anticoagulation with warfarin seems necessary to achieve the antithrombotic state. In the past, the suggested therapeutic range for anticoagulation (rabbit brain thromboplastin) was a PT prolongation between 1.5 and 2.5 times the baseline value (INR of 3 to 7). Evidence from multiple studies over the last decade indicates that an effective level of anticoagulation in venous thromboembolism is reflected by a PT prolongation by an INR of 2.0 to 3.0 the baseline value. A clinical trial by Turpie et al in thrombomembolism prophylaxis for tissue cardiac valves has also shown that a less intense level of warfarin anticoagulation is effective. More recently, trials of intensity of anticoagulation with warfarin in patients with mechanical heart valves and nonvalvular atrial fibrillation have yielded similar results. The findings of all of these trials showed that less intensive anticoagulation with warfarin results in fewer bleeding complications yet protects adequately against recurrent thromboembolism. In treating venous thromboembolism, the recommended therapeutic range for the PT is an INR of 2.0 to 3.0. For prevention of venous thromboembolism in selected moderate-risk groups, even less intensive therapy (INR 1.5) appears effective.

Duration of Therapy: The duration of anticoagulation for venous thromboembolism must be tailored to the individual patient. Patients with slowly resolving risk factors, eg, prolonged immobilization, should be treated for at least three months; patients with tumors, antithrombin III, protein C or S deficiency, or recurrent venous thromboembolism should be treated indefinitely. In a controlled trial that addressed this issue, two weeks of adequate anticoagulation therapy was not sufficient. In many patients whose risk factors can be interrupted, eg, estrogen use or transient immobilization, a sufficient length of treatment may be shorter than three months. Additional clinical trials testing a shorter length of anticoagulation against three months are needed in patients without conti-
Warfarin is given routinely in the post-partum period, this complication has been associated with protein C and be easy and inexpensive to administer. Cost-effective and is associated with a low frequency of bleeding. More intensive warfarin anticoagulation (INR 3.0 to 4.5) effectively prevents recurrent venous thromboembolism but is associated with a higher frequency of bleeding. Adjusted-dose subcutaneous heparin therapy (aPTT > 1.5 times control) is effective and is associated with a low incidence of bleeding, but it is somewhat more expensive than low-intensity warfarin sodium. Less intensive warfarin therapy (INR 2.0 to 3.0) should be chosen for long-term anticoagulation of most patients with venous thromboembolism, and adjusted-dose subcutaneous heparin therapy would be the treatment of choice for pregnant patients and those with hypersensitivity to warfarin or when laboratory facilities are inadequate to monitor warfarin therapy.

It has recently been shown that warfarin anticoagulation can be effectively monitored at home using a portable device to perform PTs on whole blood obtained by finger stick. Algorithms have been developed to aid self-monitoring of PT. Because of increased long-term use of warfarin, self-management of routine anticoagulation with the drug seems more cost-effective.

Thrombolytic Therapy

Thrombolytic agents dissolve thrombi by activating an inactive plasma enzyme, plasminogen, to the active agent, plasmin. Plasmin, when in proximity to a thrombus or a hemostatic plug, degrades fibrin to soluble peptides. Circulating plasmin degrades soluble fibrinogen and, to some extent, several other plasma proteins. Streptokinase (SK), urokinase (UK), and tissue plasminogen activator (tPA) are the three thrombolytic agents currently available for clinical use in venous thromboembolism disease.

Streptokinase is a highly purified protein with a molecular weight of 47 kilodaltons derived from group C, β-hemolytic streptococci. It combines with plasminogen to form a complex that activates adjacent plasminogen to plasmin. Streptokinase is antigenic and is not recommended for repeated use within six months. The purified protein is not appreciably more pyrogenic than is UK or tPA. For venous thrombolysis, SK is approved for use in pulmonary embolism, deep venous thrombosis, and for clearing acutely occluded arteriovenous (AV) cannulas or fistulas.

Urokinase is currently available as a 34-kilodalton molecular weight protein derived from human fetal kidney cells grown in culture. The protein has also been purified from human urine. Its gene has been cloned and clinical investigation of the recombinant products is proceeding. Urokinase activates plasminogen directly to plasmin. It is neither antigenic nor pyrogenic. It is also approved for local clearance of clotted catheters and cannulas. Because of greater production costs, it is appreciably more expensive than SK and UK.
expensive than SK.

Neither agent is specific for thrombi, and each is prone to lyse any fresh platelet-fibrin hemostatic plug. Moreover, each agent will induce hemostatic abnormalities in plasma, which can be measured by a number of in vitro tests. Therapy with either agent is usually monitored with either the activated thrombo- plastin time or thrombin time, and prolongation of either time to at least 1.5 times baseline is taken as evidence for activation of the fibrinolytic system (lytic state). However, since neither bleeding nor thrombolysis correlates well with in vitro tests, complicated laboratory monitoring schemes and subsequent dosage adjustment of drug are advisable following initial demonstration of activation of fibrinolysis.130

Tissue plasminogen activator is a third activator derived as a genetic recombinant product from human cells. In the body the principal source of this protein is probably vascular endothelium. The protein has a molecular weight of 56 kilodaltons. It is more fibrin-specific than SK or UK in that it activates plasminogen associated with thrombi or hemostatic plugs in preference to circulating plasminogen. Consequently, it does not cause the marked in vitro hemostatic abnormalities associated with use of SK or UK. However, tPA appears to cause as much bleeding as the other two agents. It has not been as extensively studied in pulmonary embolism or deep vein thrombosis of the lower extremity as have SK or UK, but tPA appears to have thrombolytic capacity at least equal to the other two agents in these disorders.134

Both SK and UK have similar thrombolytic effects as judged by large clinical trials in pulmonary embolism.135,136 Using paired angiographic comparisons in each patient, resolution of thromboembolus, seen with 12 or 24 h of UK therapy or with 24 h of SK therapy, was comparable at 24 h and was approximately three times that seen with heparin alone.135 Pulmonary vascular resistance was also reduced at 24 h by 35 percent compared with 4 percent in the heparin group. Whereas initial lung scan improvement was greater in the thrombolytic group at one and three days, subsequent scan improvement was similar in the two groups. If 12 h of UK therapy is comparable to 24 h of the same drug, an obvious need is to study even shorter infusion regimens of the drug. These studies are currently being performed. However, at this time, 12 h of UK therapy and 24 h of SK therapy are the recommended infusion times for pulmonary embolism.135-137

The optimum application of thrombolytic therapy in the treatment of deep venous thrombosis and pulmonary embolism remains relatively undefined. In the treatment of deep venous thrombosis, it appears that early use of a thrombolytic agent such as SK can decrease subsequent pain, swelling, loss of venous valves, and in some studies, the incidence of the postphlebitic syndrome.139-142 However, this syndrome is notoriously slow and variable in its development, and conflicting findings indicate that more controlled studies are needed.143 For pulmonary embolism, thrombolytic therapy followed by heparin clearly achieves a superior effect on early resolution of thromboembolus compared with heparin alone.144 Thrombolytic agents also result in superior early resolution of lung scan abnormalities and more rapid hemodynamic improvement. Further, with careful selection of patients for thrombolytic therapy, it has become evident that the incidence of hemorrhage can be greatly decreased from that seen in the early trials. However, there is as yet no proved short-term mortality effect with a thrombolytic agent in pulmonary embolism. This finding is not surprising, since previous drug trials were designed primarily to establish the thrombolytic effect of UK and SK. The low mortality (<10 percent) of patients treated with heparin and warfarin therapy precluded the identification of a mortality effect of thrombolytic therapy because of the relatively small number of patients studied. Thrombolytic therapy should be considered in the treatment of patients with acute massive embolism who are hemodynamically unstable and do not seem prone to bleeding. One study reported a small increase in carbon monoxide diffusing capacity in the lungs at two weeks and one year in patients treated with thrombolytic therapy in comparison to conventional anticoagulation.139 A great deal of confirmatory evidence is needed before one can state that thrombolytic therapy decreases the incidence of long-term disability after massive pulmonary embolism. Obviously, epidemiologic data must also be obtained to determine the occurrence of chronic pulmonary hypertension and cor pulmonale in "adequately" treated patients with acute pulmonary embolism.

More recently, work has aimed at developing agents for thrombolysis that will not induce marked systemic hemostatic aberrations in the hope that such agents will cause less bleeding. In this regard, anisoylated plasminogen-SK activator complex, single-chain UK, and single-chain tPA appear promising.145-148 Anisoylated plasminogen-streptokinase activator complex (APSAC) has been made inactive by acylation of the catalytic center of the plasmin portion. After injection, deacylation occurs spontaneously and results in sustained generation of fibrinolytic activity, with a slow turnover rate in blood.149 The complex has relatively low fibrin selectively similar to that of SK and UK.150,151 Single-chain urokinase plasminogen activator (SCUPA) has a blood turnover rate similar to that of conventional UK but has fibrin selectivity similar to that of double-chain tPA.152,153 Single-chain tPA is the most fibrin-specific of all and also has the shortest
half-life. These studies were performed for the most part in patients with AMI, but there is no reason to think the properties of these newer agents would change appreciably in patients with venous thromboembolism. One problem is that none of these agents will distinguish a thrombus from a beneficial hematic plug. This lack of distinction will always necessitate careful selection of patients for therapy. In early studies, tPA was being given with a heparin infusion in patients with pulmonary embolism. In contrast, when UK or SK is being infused, it has been recommended that heparin therapy be withheld. However, concurrent infusions of heparin and SK have also been investigated. More recently, infusion of tPA without concurrent heparin therapy has been investigated in venous thromboembolism. Currently it is recommended that all of these drugs be administered without concurrent heparin therapy.

Work is also needed on the optimum duration of thrombolytic therapy for deep venous thrombosis and pulmonary embolism. In deep venous thrombosis, it appears that 48 to 72 h of therapy is necessary for effective thrombolysis. However, in pulmonary embolism, 12 h of UK therapy appears to be as effective as 24 h of either UK or SK, and information may emerge to support the hypothesis that shorter courses of UK treatment will be as effective. This question can only be answered by controlled studies comparing standard and shorter durations of thrombolytic therapy.

All of these agents are administered by constant IV infusion (Table 4). These dosing regimens are designed to activate fibrinolysis systemically in more than 90 percent of patients. The regimens are also designed to achieve thrombolysis throughout the body. Although tPA and APSAC are somewhat more fibrin specific than SK and UK, all of the agents have the potential to lyse a fresh platelet-fibrin plug anywhere and cause bleeding at that site. For pulmonary embolism, SK is recommended to be given as a 250,000 IU loading dose followed by 100,000 IU hourly for 24 h. Urokinase is recommended to be given as a 4,400 IU/kg of body weight loading dose followed by 2,200 IU/kg hourly for 12 h. For pulmonary embolism, tPA is recommended to be given as a 100-mg infusion over 2 h. For deep venous thrombosis, SK should be given in the same manner as for pulmonary embolism, but the duration of therapy should probably be lengthened to 48 to 72 h. Heparin should not be infused concurrently with SK, UK, or tPA. Since all of these agents, even in lower doses, cause systemic activation of fibrinolysis and a body-wide thrombolytic effect, direct infusion into the pulmonary artery or into a leg vein appears to offer no local benefit in comparison to systemic infusion through a peripheral vein in the arm.

All thrombolytic agents act systemically. There is not good correlation between in vitro tests of fibrinolysis on one hand, and thrombolysis or bleeding on the other. This statement is particularly true for tPA and APSAC but applies to SK and UK as well. Consequently, when SK or UK is infused, a thrombin time or activated partial thromboplastin time may be monitored 2 to 4 h into treatment. Prolongation of either test by 10 s or more indicates activation of fibrinolysis. Further laboratory monitoring of therapy is unnecessary. No laboratory monitoring of tPA or APSAC therapy is recommended. After infusion of thrombolytic therapy is stopped, intravenous heparin therapy should be restarted once the thrombin time or activated partial thromboplastin time is shown to be less than two times normal.

Beside the lack of a proven mortality effect, thrombolytic therapy of venous thromboembolism differs from therapy of myocardial infarction in another way. In myocardial infarction, thrombolytic therapy appears to dissolve the coronary thrombus in a majority of cases, but in venous thromboembolism, particularly pulmonary embolism, complete dissolution of thrombus is the exception. Partial dissolution appears to be the rule because venous thromboemboli are older and more organized than coronary thrombi. Since no currently available agent or regimen usually dissolves the venous thromboembolus completely, interest has turned to smaller doses and shorter durations of therapy in an effort to achieve the desired thrombolytic effect with less bleeding. It is not yet clear that these regimens will cause less bleeding but some of them do appear to effect comparable thrombus resolution to that seen with the longer regimens.

Recently, a preliminary report was published of the use of tPA given as an IV bolus in the treatment of acute pulmonary embolism. Thirty-three patients with objectively determined pulmonary embolism,

<table>
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<th>Table 4 — Thrombolytic Agents in Venous Thromboembolism</th>
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<td>Stop heparin infusion: Start thrombolytic infusion when aPTT or thrombin time (TT) is ≤1.5 times control</td>
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<tr>
<td>Streptokinase (SK)*:</td>
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<td>Urokinase (UK)*:</td>
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<tr>
<td>Tissue plasminogen activator (tPA)*:</td>
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<tr>
<td>After terminating thrombolytic infusion, restart heparin infusion</td>
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*Duration of therapy. Streptokinase is recommended for 24-h infusion in pulmonary embolism, 48-72 h in deep venous thrombosis. Urokinase is recommended for 12-h infusion in pulmonary embolism, 24-48 h in deep venous thrombosis. Tissue plasminogen activator is recommended for a 2-h infusion in pulmonary embolism at a total dose of 100 mg.
some of whom also had deep venous thrombosis, received a 2-min infusion of tPA at a dose of 0.6 mg/kg followed by heparin given in the usual manner. Results were compared in a randomized fashion with 25 patients who received only heparin. In the patients receiving the bolus of tPA, lung scan improvement at 24 h was twice that in those receiving heparin (37 percent vs 18.8 percent improvement in perfusion defect). By day 7, no difference in lung scan resolution was apparent between the two groups. The investigators reported no differences between the two groups in major bleeding or blood transfusion requirements. In the tPA group, 15 of the 34 patients had what was called minor bleeding at sites of angiogram catheter insertion or venipuncture. Unfortunately, this trial was too small (level II study) to determine if this regimen would reduce the small but real incidence of intracranial bleeding seen with thrombolytic agents, which has been in the range of 0.3 to 0.7 percent in the myocardial infarction trials. However, this study does point to the need to seek safer, but clinically effective, regimens of lytic therapy in venous thromboembolism. Since lytic agents usually do not completely resolve venous thromboembolic, the acutely ill patient's clinical response is as important as angiographic or lung scan responses. Lower doses and shorter durations of therapy may give the desired clinical response with greater safety.

**Inferior Vena Caval Procedures**

The major rationale for inferior vena caval interruption is the presence of a contraindication or complication of anticoagulation in an individual with or at high risk for proximal vein thrombosis of the lower extremity. Less frequent indications include recurrent thromboembolism despite adequate anticoagulation, the presence of a large free-floating caval thrombus, chronic recurrent embolism with pulmonary hypertension, and the concurrent performance of surgical pulmonary embolectomy or pulmonary endarterectomy.

The most popular method of inferior vena caval interruption is placement of a filter developed by Greenfield. This six-legged device can be inserted through the internal jugular vein or femoral vein, and advanced into place in the inferior vena caval using fluoroscopic guidance. In a reported series of 469 patients with a mean follow-up of 43 months, the long-term filter patency rate was 98 percent. Although most authorities recommend resuming anticoagulation after filter placement, a recent report supports the use of the filter as the only treatment. A current review has summarized results and complications with various filters. In a recent report, patients were excluded from filter placement for venous anatomic abnormalities, pregnancy, and thrombus proximal to the intended point of filter deployment.

Recently, a modified hook, Titanium filter has been described that uses a smaller dilator for percutaneous insertion. The migration and penetration rates of the new filter appear to be acceptably low and the 30-day patency rate is as high as with the old filter. With the new filter, the incidence of thrombosis at the insertion site, determined by duplex ultrasound, was 8.7 percent in a subset of 46 patients. The ease of insertion of the modified hook, Titanium filter should widen the indications for use of a filter. Recently, insertion of an inferior vena caval filter has been recommended for primary prophylaxis of thromboembolism in patients at high risk to bleed, including those with extensive trauma, visceral cancer, or undergoing hip and knee surgery.

**Pulmonary Embolectomy**

The role of emergent pulmonary embolectomy remains in some dispute. If it is to be attempted, there is a general consensus that a candidate meet the following criteria: (1) massive pulmonary embolus (angiographically documented if possible); (2) hemodynamic instability ("shock") despite heparin therapy and resuscitative efforts; and (3) failure of thrombolytic therapy or a contraindication to its use. Operative mortality in the era of immediately available cardiopulmonary bypass has ranged from 10 to 75 percent in uncontrolled retrospective case series. In patients who have had cardiopulmonary arrest, mortality has been reported between 50 and 94 percent. In a recent series of 96 patients (55 percent of whom did not meet the criteria of hemodynamic instability), univariate analysis identified cardiac arrest and shock as predictors of mortality and multivariate analysis confirmed the significance of cardiac arrest and underlying cardiopulmonary disease as predictors of mortality. Reported postoperative complications include adult respiratory distress syndrome, mediastinitis, acute renal failure, and, of particular concern, severe neurologic sequelae. Pulmonary embolectomy should be considered when a patient meets the above criteria and an experienced cardiac surgical team is immediately available.

**Transvenous Catheter Extraction of Emboli**

A cap device has been developed that fits over an 8.5-French double lumen, balloon-tipped steerable catheter to permit suction extraction of pulmonary emboli under fluoroscopy with electrocardiographic monitoring. In a series of 26 patients undergoing catheter embolectomy, extraction was successful in 23 (88 percent) with a mortality rate of 27 percent. Two patients subsequently underwent open embolectomy. Over the same time in the same institution, six patients had open embolectomy for acute pulmonary embolism.
with a mortality of 33 percent. Recently, a report of catheter embolectomy in 18 patients with a 28 percent mortality rate has been published. The procedure resulted in immediate improvement in 11 (61 percent) and was unsuccessful in seven (39 percent). Good results were associated with a shorter period from first episode of pulmonary embolism (4.7 ± 54 days vs 18.3 ± 69 days, p < 0.0004) and the duration of hemodynamic impairment (13 ± 12 h vs 59 ± 38 h, p < 0.0003). Thirteen patients had absolute contraindications to thrombolytic therapy and five did not respond to lytic therapy over 2 to 3 h. Since catheter extraction appears to be technically successful with an acceptable mortality rate, continued evaluation is warranted.

NEW ANTICOAGULANTS

Low Molecular Weight Heparin

Although continuous intravenous heparin therapy is both highly effective and relatively safe, the regimen usually requires hospitalization. An initial treatment of proximal vein thrombosis, which could be given on an outpatient basis and does not require laboratory monitoring, would markedly simplify treatment and improve cost-effectiveness. A conservative estimate of the number of hospital days that would be saved by outpatient administration of initial therapy is five to six days for each patient. It has been estimated that such a decrease in the duration of hospitalization would result in savings to the health care system on the order of at least $500 million annually in the United States alone.

In recent years, low molecular weight (LMW) fractions of commercial heparin have been prepared that have a mean molecular weight of 4,000 to 5,000 daltons in contrast to unfractionated heparin, which has a mean molecular weight of 12,000 to 16,000 daltons. The excellent bioavailability of LMW-heparin, together with a longer plasmin half-life (antifactor Xa activity) than unfractionated heparin suggests that it may be possible to develop an effective regimen for initial treatment with LMW-heparin using a once daily subcutaneous injection. The anticoagulant response (factor Xa units per milliliter) observed with a given dose of LMW-heparin was highly correlated with body weight, so it is possible that LMW-heparin may be effective when given in standard doses (factor Xa units per kilogram) without laboratory monitoring.

Studies in experimental animal models of venous thrombosis have shown that some LMW fractions have equal (or greater) antithrombotic efficacy, but less hemorrhagic effects, in comparison to heparin. Whether this latter experimental observation applies clinically is currently uncertain; demonstration of this property in man has remained elusive.

Multiple randomized clinical trials have compared LMW-heparin with unfractionated heparin for the initial treatment of patients with venous thrombosis. Five studies compared continuous IV LMW-heparin with continuous IV unfractionated heparin; one trial compared subcutaneous LMW-heparin with subcutaneous unfractionated heparin; and four studies compared subcutaneous LMW-heparin with continuous intravenous unfractionated heparin. These data suggest that LMW-heparin administered subcutaneously twice a day is as effective and safe as continuous IV heparin. The conclusions of efficacy are largely based on venographic observations rather than clinical outcome.

Two studies evaluated long-term outcome using LMW-heparin. One study by Prandoni et al. studied 170 consecutive symptomatic patients with venographically proven proximal deep vein thrombosis. Eighty-five patients received standard heparin (to achieve an aPTT of 1.5 to 2.0 times the pretreatment value) and 85 patients received LMW-heparin (adjusted only for body weight) for ten days. Oral coumarin therapy was started on day 7 and continued for at least three months. The frequency of recurrent venous thromboembolism diagnosed objectively did not differ significantly between the standard heparin and LMW-heparin groups (12 [14 percent] vs 6 [7 percent]; difference 7 percent [95 percent confidence interval -0.3 percent to 15 percent]; p = 0.13). Clinically important bleeding was infrequent in both groups (3.5 percent for standard heparin vs 1.1 percent for LMW-heparin; p > 0.2).

The other study reported by Hull and associates compared fixed-dose subcutaneous LMW-heparin once daily with adjusted-dose IV heparin by continuous infusion for the initial treatment of patients with proximal vein thrombosis. These therapeutic approaches were evaluated by a multicenter double-blind clinical trial using objective documentation of clinical outcomes. Six (2.8 percent) of 213 patients who received LMW-heparin and 15 (6.9 percent) of 219 patients who received IV heparin suffered new episodes of objectively documented venous thromboembolic complications. The observed frequency of objectively documented thromboembolic events (2.8 percent) favors the LMW-heparin group. It is unlikely (p < 0.05) that the observed difference would be less than 0.02 percent and could be as much as 8.1 percent in favor of LMW-heparin. Major bleeding associated with initial therapy occurred in one patient receiving LMW-heparin (0.5 percent) and in 11 patients receiving intravenous heparin (5.0 percent) (p = 0.006), a risk reduction of 91 percent. This protective effect against major bleeding was lost during long-term therapy. Minor hemorrhagic complications occurred infrequent.
sequently. Ten patients receiving LMW-heparin (4.7 percent) died compared with 21 patients receiving intravenous heparin (9.6 percent), a risk reduction of 51 percent \( (p = 0.049) \).

These findings indicate that at least the LMW-heparin used in these studies is equivalent to classic IV heparin therapy. The simplified therapy provided by this LMW-heparin offers the potential for treating patients with uncomplicated proximal deep vein thrombosis in an outpatient setting. The accumulating evidence indicates that certain LMW-heparins administered subcutaneously may replace classic IV heparin therapy. Certain of these subcutaneously administered LMW-heparins do not require monitoring. The simplified regimens offered by LMW-heparin therapy offer the possibility of initial outpatient care in otherwise uncomplicated patients with deep vein thrombosis. It is uncertain at present whether the findings associated with LMW-heparin preparation can be extrapolated to a different LMW-heparin. For this reason, the findings of clinical trials apply only to the particular LMW-heparin evaluated and cannot be generalized to the LMW-heparins at large.

**Hirudin**

Hirudin is the progenitor of a family of peptides that directly inhibit thrombin function independent of any interaction with antithrombin III. Because of this property, these peptides, particularly the lower molecular weight analogues, more effectively inhibit thrombus action in the interstices of a developing thrombus than does the larger heparin-antithrombin complex.\(^ {296} \) In experimental models of arterial and venous thrombosis, hirudin was more effective than heparin as an antithrombin.\(^ {296,297} \) Clinical availability of hirudin is probably some years away, however, since it has only recently entered clinical efficacy trials in patients.

**Chronic Pulmonary Thromboembolism and Pulmonary Hypertension**

A small minority of individuals with massive pulmonary embolism or recurrent disease do not resolve the process and subsequently develop pulmonary hypertension. In contrast to the more concentric, distal lesion of primary pulmonary hypertension, the vessels involved in thromboembolic pulmonary hypertension are proximal and amenable to thromboendarterectomy. The syndrome should be considered in anyone with unexplained dyspnea on exercise. The most important diagnostic test is the pulmonary perfusion scan, which always shows segmental or larger perfusion defects. This finding again contrasts with perfusion scan findings in primary pulmonary hypertension in which perfusion defects, if present, are minimal. With an experienced surgical and medical team, surgical endarterectomy has been shown to result in significant relief of pulmonary hypertension and disability.\(^ {298} \)

**Primary Pulmonary Hypertension**

There has been some interest in treating primary pulmonary hypertension with antithrombotic or fibrinolytic agents.\(^ {299,301} \) There is as yet no convincing evidence that antithrombotic agents benefit patients with this rare disease. However, the role of thrombosis in primary pulmonary hypertension remains under investigation and retrospective studies point to the need for a controlled, prospective trial of anticoagulants in this disorder.\(^ {298} \)

**Recommendations**

**Treatment of Venous Thromboembolism**

1. Patients with deep vein thrombosis or pulmonary embolism should be treated with IV heparin or adjusted-dose subcutaneous heparin sufficient to prolong the aPTT between 1.5 and 2.5 times control. This grade A recommendation is based on level I studies in patients with pulmonary embolism\(^ {19} \) and deep venous thrombosis\(^ {20} \) and level II studies on the relationship between the aPTT and effectiveness.\(^ {20,24-30} \)

2. It is recommended that treatment with heparin should be continued for five to ten days and that oral anticoagulation should be overlapped with heparin for four to five days. For many patients, heparin and warfarin therapy can be started together and heparin therapy discontinued on day 5 or 6 if the PT is therapeutic. For massive pulmonary embolism or ileofemoral thrombosis, a longer period of heparin therapy may be considered. This grade A recommendation is based on four level I studies.\(^ {12,25,32,50} \)

3. Long-term anticoagulant therapy should be continued for at least three months using oral anticoagulants to prolong the PT to an INR of 2.0 to 3.0 or adjusted-dose heparin to prolong the aPTT beyond 1.5 times the control for most of the dosing interval, when oral anticoagulants are either contraindicated or inconvenient. This grade A recommendation is based on two level I studies.\(^ {74,78} \)

4. It is recommended that patients with recurrent venous thrombosis or a continuing risk factor, such as antithrombin III deficiency, protein C or S deficiency, or malignant neoplasm, should be treated indeﬁnitely. This grade C recommendation is not based on published data.

5. Accumulated level I, II, and level IV evidence indicates that symptomatic isolated calf vein thrombosis should be treated with anticoagulation for three months.\(^ {13-14} \) If for any reason anticoagulation cannot be given, serial noninvasive studies of the lower extremity should be performed to assess for proximal extension of thrombus.
6. The use of thrombolytic agents in the treatment of venous thromboembolism continues to be highly individualized. Further clinical investigation is needed before more definitive recommendations can be made.

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