Antithrombotic Therapy for Venous Thromboembolic Disease

Thomas M. Hyers, M.D., F.C.C.P., Chairman;
Russell D. Hull, M.B., B.S., M.Sc., F.C.C.P.;
John G. Weg, M.D., F.C.C.P.

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

Several treatment regimens that modify one or more of these abnormalities may be antithrombotic. These modalities include drugs that inhibit blood coagulation, such as heparin and the coumarins; drugs that inhibit platelet function, such as aspirin and dextran; and techniques that counteract venous stasis, such as a pneumatic compression of the lower extremity. In this broad sense, thrombolytic agents are also antithrombotic, because they mediate the rapid dissolution of a formed thrombus (Table 1).

The risk factors for venous thromboembolism and the effectiveness of antithrombotic agents in the treatment of established venous thrombotic 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 will also be reviewed. 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 rule out a clinically important benefit (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; but unlike thrombolytic agents, they do not as a rule actively resolve it.

Of the agents currently available in this country, only heparin, thrombolytic agents, and the coumarins in appropriate doses are used to treat established venous 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. 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, and estrogen use and a previous history of venous thromboembolism are also associated with increased risk. Carcinoma is a risk factor, particularly adenocarcinomas of the lung, breast, and viscera. Patients with hip fractures or those undergoing major orthopedic procedures on the lower extremity are among the groups at highest risk (Table 2). Individuals undergoing total hip or knee replacement suffer a 40% incidence of deep venous thrombosis, about half of the thrombi are calf vein thrombi and the other half are thigh thrombi, with or without calf vein involvement. Prophylactic regimens usually reduce the incidence of thrombosis in these patients by 50-60%. A risk reduction in this range is useful but not satisfactory, and better prophylaxis is constantly being sought.

Patients at lower but still substantial risk include those over age 40 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. Low-dose subcutaneous heparin in a daily dose of 10-15,000 units constitutes adequate prophylaxis in many of these patients.

There has been disagreement for many years about the potential for embolization and the need to treat deep calf vein thrombosis. One study utilizing clinical findings and 185I-labeled fibrinogen testing for up to 6 days postoperatively with venographic confirmation of deep venous thrombosis concluded that the risk was low. However, 23% of patients with distal thrombi had proximal extension, and 10% had clinical evidence of pulmonary embolism. In another study of patients who had calf vein thrombosis diagnosed without venography, 10% had evidence of pulmonary embolism. 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 5-7 days and a clinical evaluation at 3 months, 21 asymptomatic patients with calf vein thrombosis had no extension. The outcome in asymptomatic patients may not be applicable to patients who have been treated with therapeutic anticoagulation.
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 units/day</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 units/day</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>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.

Presenting with symptoms. Recently Lagerstadt et al.18 conducted a controlled prospective study of symptomatic patients utilizing 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 IV heparin for only 5 days, 6 (29%) had recurrences within 90 days. There was proximal

Table 2—Risk Groups for Venous Thromboembolism

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Incidence of Venous Thrombosis, %</th>
<th>Site of Thrombosis</th>
<th>Incidence of Fatal PE, %</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip fracture</td>
<td>40-70</td>
<td>Thigh and calf</td>
<td>1-5</td>
<td>Any of the following:</td>
</tr>
<tr>
<td>Total hip replacement</td>
<td>40-70</td>
<td>Thigh and calf</td>
<td>1-2</td>
<td>Dextran, adjusted-dose heparin, low-dose warfarin, low-dose heparin</td>
</tr>
<tr>
<td>Total knee replacement</td>
<td>40-70</td>
<td>Thigh and calf</td>
<td>5</td>
<td>Pneumatic compression</td>
</tr>
<tr>
<td>Urologic surgery</td>
<td>15-20</td>
<td>Calf</td>
<td>5</td>
<td>Pneumatic compression</td>
</tr>
<tr>
<td>General and gynecologic surgery</td>
<td>15-20</td>
<td>Calf</td>
<td>1</td>
<td>Low-dose heparin</td>
</tr>
<tr>
<td>Neurologic surgery</td>
<td>15-20</td>
<td>Calf</td>
<td>1</td>
<td>Pneumatic compression</td>
</tr>
<tr>
<td>Medical patients</td>
<td>15</td>
<td>Calf</td>
<td>1</td>
<td>Low-dose heparin</td>
</tr>
</tbody>
</table>
extension in 5 and a pulmonary embolus in 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 using serial impedance plethysmography (IPG) in patients with suspected deep venous thrombosis, 6% developed a proximal deep vein thrombosis within 10 days following an initially negative study. Hull et al, in a study comparing IPG with combined IPG and radioactive fibrinogen leg scanning venographically proved deep venous thrombosis, found that 5.7% of symptomatic patients developed deep venous thrombosis within 14 days after the initial IPG was negative. Most of these thrombi were in the deep calf veins. Further, these workers showed that after the first 14 days, the subsequent incidence of venous thromboembolism was only 2% and was usually associated with ongoing risk factors. Having conducted a gross and microscopic examination of the deep venous tree from the foot to the right heart in 261 autopsied patients and concluded that 25% of 40 pulmonary emboli considered to be the cause of death and 33% 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 3 months or followed up with a serial noninvasive test for 10-14 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 5,000-25,000 daltons, but the native molecule is probably much larger. The drug acts by enhancing the effect of a naturally occurring inhibitor, antithrombin III, so that the inhibitor more efficiently combines with and inactivates a number of serine proteinases, notably thrombin (factor IIa), factor IXa, and factor Xa. 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. 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% on a weight basis, and consequently heparin is properly prescribed by units, not weight.

Heparin has been proven effective in the treatment of pulmonary embolism. This trial, by Barratt 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%) in the placebo-treated patients, combined with the 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 that activated partial thromboplastin time (APTT) is prolonged 1.5 times the control value. 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 for 10-14 days is 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%) or recurrent venous thrombosis (2%). In patients with documented calf vein thrombosis, serial IPG can be used to separate the 20% of patients who develop proximal extension (and require treatment) from the remaining 80% 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.

**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 specific plasma assays for the drug have not been widely applied. The lack of a clear relationship between heparin dose and bleeding probably results from heparin's variable interference with platelet function in patients. Under most circumstances, a 5-20% 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 of 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 hemostatic response reflected by in vitro coagulation tests, which are used to monitor heparin. Hirsh et al described the hemorrhagic risk of heparin therapy in 100 consecutive patients treated with continuous IV heparin, which was adjusted according to the results of the whole blood clotting time. Four patients had major hemorrhagic episodes, and in 3 the results of whole blood clotting time was prolonged considerably above the upper limit of the targeted therapeutic range (3 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 9 of 44 (20%) of the 30 patients whose blood clotting time was greater than 60 min but in only 1 of the 28 (4%) 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 of 18 patients (56%) who received excessive heparin (defined by a greatly prolonged whole blood clotting time) bled, whereas bleeding occurred in only 16% 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 on an independent group. The comorbid factors identified were: (1) "cardiac," defined as AMI, systolic blood pressure less than 90 mm Hg, or the need for an intraaortic 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% 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 2.0-2.9 times the control value, complications increased 3 times (relative risk, 3); if either test was 3.0 times or longer than the control, bleeding complications increased 8 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 V studies), there is a 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: Four randomized studies compared the bleeding rate when heparin was administered by intermittent injection and by continuous infusion. Two of the studies (level I) reported that continuous heparin infusion was associated with a lower frequency of bleeding (1% and 0% compared with 9% and 33%), and the third reported the trend toward reduced bleeding with continuous heparin (level II study), 9% compared with 10%. In the fourth study, there was a trend in the other direction (level II study). 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 2 groups.

Only 1 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%), suggesting that when heparin is administered by intermittent injection, monitoring the response may not reduce the risk of bleeding.

There is increasing evidence 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. Animal experiments support the concept that a minimum level of heparin is necessary to interrupt an ongoing thrombotic process. Clinically, the currently most widely used test for monitoring heparin therapy is the APTT, a global coagulation test. An uncontrolled prospective 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 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 (20-25%) 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, there have been no randomized clinical trials comparing the APTT with more direct heparin assays for the management of heparin therapy.

The major problem with constant IV therapy is the equipment and skilled care necessary to deliver it properly. More trials are needed comparing constant IV infusion to a similar dose administered subcutaneously every 8-12 h.

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continues to be underdosed in clinical use despite the compelling human and controlled animal data, which indicate that a minimum prolongation of the APTT to 1.5 times control is necessary. 43

Heparin requirements are usually greatest in the first few days after the acute thromboembolic event, 10,22 and consequently therapy should be monitored most closely then. After the first few days, the monitoring test can usually be obtained daily. It is wise to check a platelet count every 3-4 days when administering heparin, since the drug can induce thrombocytopenia. 44-46 This problem usually presents as a mild thrombocytopenia, with a platelet count in the range of 100,000/L, that may return to normal levels even with continuation of heparin therapy. Rarely, thrombocytopenia is a serious presentation with platelet counts in the range of 20,000/L. The latter presentation appears to be a result of antibody-mediated injury to platelets and endothelium. This syndrome may be associated with arterial thromboembolism and extension or recurrence of existing venous thromboembolism. 46 If the more severe presentation occurs, heparin must be stopped immediately. If the risk of recurrent embolism is great, an inferior vena caval filter should be inserted. Alternatively, if the risk for recurrent disease appears low and the PT has been in or near the therapeutic range for 24-48 h, one might consider discontinuing the heparin and continuing with the warfarin therapy. Heparin use commonly leads to mild reductions in the level of circulating antithrombin III, and, rarely, has been reported to induce disseminated thrombosis. 50 Long-term high-dose (4 months at 15,000 units or more) heparin administration can lead to severe osteopenia. 51-55 In the rare patient with hypoadosteronism, heparin may induce hyperkalemia. 56

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

How long to anticoagulate with heparin: Heparin can be conveniently administered IV for 5-10 days in recovering patients. Unfortunately, such a short period of anticoagulation does not seem to interrupt completely the thrombotic process in many patients with acute venous thromboembolic disease. 33,57 Specifically, 10-14 days of conventional IV heparin, followed by low-dose subcutaneous heparin, did not prevent recurrent venous thromboembolism. 57 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. 31,39,40,58,59

The optimal duration of initial IV heparin therapy in patients with venous thromboembolism has not been completely resolved (Table 3). Multiple randomized clinical trials in patients with proximal vein thrombosis indicate that when IV heparin is administered for 7-10 days, and followed by adequate long-term anticoagulant therapy, the frequency of recurrent venous thromboembolism is low (<5%). An alternative 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 4-5 days of unnecessary hospitalization in many patients, and would greatly reduce the cost of initial therapy. A recent randomized trial in patients with submassive venous thrombosis or pulmonary embolism suggests that 4-5 days of initial heparin, followed by adequate long-term therapy with warfarin, is effective and safe. 60 However, another study using a 5-day course of heparin in patients with proximal deep venous thrombosis reported an acceptably high subsequent rate of thrombosis. 61 This approach must be further evaluated in persons with more extensive disease before it can be recommended for all patients with venous thromboembolism. It seems reasonable

<table>
<thead>
<tr>
<th>Disease suspected</th>
<th>Obtain baseline APTT,* PT,† and platelet count and give heparin bolus (5-10,000 units) IV; order diagnostic test, eg, ventilation-perfusion lung scan, pulmonary angiogram, contrast venogram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease confirmed</td>
<td>Give loading dose of heparin (5,000 units) and start constant IV infusion at approximately 1,000 units/h; Monitor APTT at 6 h and thereafter until the APTT is stabilized at 1.5-2 times control value; Monitor platelet count every 3-4 days while administering heparin; Start warfarin on day 1 or 2 by instituting the estimated daily maintenance dose (usually 4-10 mg); After at least 5 days of heparin and 4-5 days of joint therapy, stop heparin therapy and check PT 4 h later; Maintain PT off heparin therapy at 1.3-1.5 times control or pretreatment value; Full-dose anticoagulation for at least 3 mo in patients without continuing risk factors, longer in other patients</td>
</tr>
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</table>

*APTT, activated partial thromboplastin time.
†PT, 1-stage prothrombin time (1.3 times control performed with rabbit brain thromboplastin is roughly equal to 2.0 times control with human brain thromboplastin).
at this point to recommend that heparin be given for 5-10 days and that warfarin be administered jointly with heparin for 4-5 days. Heparin may then be discontinued when the prothrombin time is shown to be in the therapeutic range.

**Coumarin Derivatives**

These drugs are chemical derivatives of 4-hydroxycoumarin. 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 sodium warfarin.

Coumarins act in the liver by inhibiting the synthesis of 4 vitamin K-dependent coagulant proteins, factors II, VII, IX, and X, and at least 2 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. 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 chains. The failure of gamma-carboxylation of glutamic acid residues markedly interferes with the function of the proteins by preventing calcium binding\(^2\) and proper alignment of the activated factors on a phospholipid surface.\(^4\) 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.\(^6\) 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 survival times of the K-dependent factors, being shortest for factor VII and longest for factor II. Accordingly, the 1-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 3 factors would still be high.\(^6\) Moreover, protein C, a newly described vitamin K-dependent protein with anticoagulant and fibrinolytic effects, has a half-life comparable to that of factor VII.\(^6\) 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 24-48 h of therapy. Animal studies support the need for a period of overlap of heparin and warfarin therapy.\(^6\) Early introduction of warfarin on day 1 or 2 regardless of whether a loading dose is used will usually keep the total duration of heparin therapy at no more than 7 days.\(^1\) However, further studies comparing longer heparin regimens to the newer, shorter regimens are needed.

**Monitoring coumarin therapy:** Therapy is most commonly monitored with the 1-stage prothrombin time described by Quick.\(^7\) When monitoring coumarin therapy, it is important to recognize that the heparin can be easily removed from blood samples before performing the prothrombin time.\(^7\) 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,\(^7\) 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 article, but they can generally be divided into those that interfere with albumin binding of warfarin and those that increase or decrease the clearance of warfarin. Other interactions can occur with changes in clotting factor concentration, variable vitamin K absorption, and the introduction of separate hemostatic defects (Table 4). 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 con-

<table>
<thead>
<tr>
<th>Table 4—Some Warfarin Interactions*</th>
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<tbody>
<tr>
<td><strong>Enhancers (Prolonged Prothrombin Time)</strong></td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>Allopurinol</td>
</tr>
<tr>
<td>Amiodarone</td>
</tr>
<tr>
<td>Anabolic steroids</td>
</tr>
<tr>
<td>Cimetidine</td>
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<tr>
<td>Disulfiram</td>
</tr>
<tr>
<td>Erythromycin</td>
</tr>
<tr>
<td>Hepatic disease</td>
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<tr>
<td>Hypermetabolic states</td>
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<tr>
<td>Low vitamin K diet</td>
</tr>
<tr>
<td>Metronidazole</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory agents</td>
</tr>
<tr>
<td>Phenylbutazone</td>
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<tr>
<td>Quinidine</td>
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*The use of any other drug with warfarin requires careful monitoring until the stability of the prothrombin time is ensured.*
stant amount of vitamin K.74

Intensity of coumarin therapy: As with heparin, a minimum level of anticoagulation with warfarin seems necessary to achieve the antithrombotic state.26,33,34 In the past the suggested therapeutic range for anticoagulation (rabbit brain thromboplastin) was a prothrombin time prolongation between 1.5 and 2.5 times the baseline value (INR of 3-7).86,87 Evidence from recent studies indicates that an effective level of anticoagulation in venous thromboembolism is reflected by a prothrombin time prolongation by an INR of 2.0 to 3.0 (PT = 1.3-1.5) the baseline value.75,76 A clinical trial by Turpie et al77 in thromboembolism prophylaxis for tissue cardiac valves has also shown that a less intense level of warfarin anticoagulation is effective. The findings of both trials showed that less intensive anticoagulation with warfarin results in fewer bleeding complications yet protects adequately against recurrent thromboembolism.76,77 In venous thromboembolism, the recommended therapeutic range for the prothrombin time is an INR of 2.0 to 3.0 (PT = 1.3-1.5 North American thromboplastin). This therapeutic range is the ideal, but it must be emphasized that the range can only be attained from 50-70% of the time because of variations in diet, vitamin K absorption, and patient compliance with medications.

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 3 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, 2 weeks of adequate anticoagulation was not sufficient.57 In many patients whose risk factors can be interrupted, eg, estrogen use or transient immobilization, a sufficient length of treatment may be shorter than 3 months.55,61,78 A clinical trial testing a shorter length of anticoagulation against 3 months is needed in patients without continuing risk factors.

Complications: The major complication associated with coumarin use is hemorrhage.59,70,81 The risk of bleeding is crudely related to prolongation of the prothrombin time. There is now good evidence that bleeding is reduced when the therapeutic range is reduced from an INR of 3.0-4.5 (PT 1.5-2.0) to an INR of 2.0-3.0 (PT 1.3-1.5 North American thromboplastin). In an effort to minimize bleeding, investigators have sought to find the lowest effective level of anticoagulation and current evidence strongly suggests that many patients are being slightly overtreated.75,76,80,82,83 Any vascular site in the body can bleed following induction of anticoagulant therapy. If clinically indicated, warfarin's effects can be reversed within 24 h by large doses of parenteral vitamin K. If bleeding is very serious it can be treated with fresh frozen plasma.

Much is made of the bleeding complications associated with warfarin and heparin, but it is important to remember the high mortality and morbidity rates associated with untreated and undertreated venous thromboembolic disease.17,20,37

Another complication associated with the coumarins is a vascular purpura that causes skin necrosis and occurs occasionally in the first weeks of therapy.99-101 This complication has been associated with protein C deficiency and malignancy.95-97 Coumarins cross the placenta and cause spontaneous abortion and specific embryopathies if given in the first trimester of pregnancy.95,96 There is also concern that warfarin may cause fetopathic effects during the second trimester of pregnancy and fetal bleeding during and after delivery.96 Therefore, warfarin must not be administered during pregnancy, and all women of childbearing potential taking warfarin must avoid becoming pregnant. Heparin, given subcutaneously in an adjusted dose, is the therapy of choice in pregnant women.97

Cost-effectiveness of Anticoagulant Therapy

The most cost-effective anticoagulant therapy must prevent recurrent venous thromboembolism, have a low incidence of bleeding and other complications, and be easy and inexpensive to administer. A cost-effectiveness analysis has ranked several anticoagulant regimens.95 These regimens all began with a 10-14-day course of IV heparin followed by long-term therapy of at least 3 months. Low-dose subcutaneous heparin as long-term therapy is ineffective and associated with the highest cost owing to recurrent venous thromboembolism (Table 5). Less intensive oral anticoagulant therapy with warfarin sodium is the most cost-effective and is associated with a low frequency of bleeding. More intensive warfarin anticoagulation effectively prevents recurrent venous thromboembolism but is associated with a higher frequency of bleeding. Adjusted-dose subcutaneous heparin 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 should be chosen for long-term anticoagulation of most patients with venous thromboembolism, and adjusted-dose subcutaneous heparin 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.

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.\textsuperscript{89} Circulating plasmin degrades fibrinogen and, to some extent, several other plasma proteins. Streptokinase, urokinase, and tissue plasminogen activator (tPA) are the 3 thrombolytic agents currently available for clinical use, although only streptokinase and urokinase are approved for treatment of venous thromboembolism.

Streptokinase is a highly purified protein with a molecular weight of 47 kilodaltons derived from group C, \( \beta \)-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 6 months. The agent is not appreciably more pyrogenic than is urokinase or tPA. For venous thrombolysis, streptokinase is approved for use in pulmonary embolism, deep venous thrombosis, and for clearing acutely occluded AV cannulas or fistulas. It is easily administered through a peripheral vein in a loading dose of 250,000 IU followed by a maintenance dose of 100,000 IU/h. Duration of treatment is recommended to be 24 h for pulmonary embolism and 48-72 h for deep venous thrombosis.

Urokinase is currently available as a 34-kilodalton molecular weight protein derived from human fetal kidney cells grown in culture.\textsuperscript{89} 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. Urokinase is currently approved for systemic treatment of pulmonary embolism at a loading dose of 4,400/kg body weight followed by a maintenance dose of 4,400/kg/h for 12 h. It is also approved for local clearance of clotted catheters and cannulas. Because of greater production costs, it is appreciably more expensive than streptokinase.

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 \textit{in vitro} tests. Lytic therapy with either agent is usually monitored with either the activated thromboplastin 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 \textit{in vitro} tests, complicated laboratory monitoring schemes and subsequent dosage adjustment of drug are inadvisable following initial demonstration of activation of fibrinolysis.\textsuperscript{100}

tPA is a third activator derived as a genetic recombinant product from human cells. In the body the largest source of this protein is probably vascular endothelium. The protein has a molecular weight of 56 kilodaltons. tPA is more fibrin specific in that it activates plasminogen associated with thrombi or hemostatic plugs in preference to circulating plasminogen. Consequently, it does not cause the marked \textit{in vivo} hemostatic abnormalities associated with use of streptokinase or urokinase. However, tPA can also cause bleeding, especially in higher doses. tPA has not been extensively studied in pulmonary embolism or deep vein thrombosis of the lower extremity, but seems to have thrombolytic capacity at least equal to the other two agents in these disorders.\textsuperscript{101,104}

Urokinase and streptokinase have been widely studied in the treatment of venous thromboembolism. Both agents have similar thrombolytic effects as judged by large clinical trials in pulmonary embolism.\textsuperscript{105-107} Using paired angiographic comparisons in each patient, the thrombus resolution seen with 12 or 24 h of urokinase or with 24 h of streptokinase was comparable at 24 h and was approximately 3 times that seen with heparin alone.\textsuperscript{106} Pulmonary vascular resistance was also reduced at 24 h by 35\% compared with 4% in the heparin group. Whereas initial lung scan improvement was greater in the thrombolytic group at 1 and 3 days, subsequent scan improvement was similar in the 2 groups. If 12 h of urokinase 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 urokinase and 24 h of streptokinase are the recommended infusion times for pulmonary embolism.

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 streptokinase can decrease subsequent pain, swelling, loss of venous valves, and in some studies, the incidence of the postphlebitic syndrome.\textsuperscript{106-112} However, this syndrome is notoriously slow and variable in its development, and conflicting findings indicate that more controlled studies are needed.\textsuperscript{113} For pulmonary embolism, thrombolytic therapy followed by heparin clearly achieves a superior effect on early resolution of thromboembolus compared with heparin alone.\textsuperscript{103} 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. The contraindications to thrombolytic therapy are given in Table 1. 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 urokinase and streptokinase. The low mortality (less than 10%) of patients treated with heparin and warfarin 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 better carbon monoxide diffusing capacity in the lungs at 2 weeks and 1 year in patients treated with thrombolytic therapy in comparison to conventional anticoagulation.114 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 incidence of chronic pulmonary hypertension and cor pulmonale in “adequately” treated patients with acute pulmonary embolism.

More recently, a great deal of 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-streptokinase activator complex, single-chain urokinase, and tPA appear promising.115-118 Anisoylated plasminogen-streptokinase activator complex (APSAC) has been made inactive by acylation of the catalytic center of the plasmin portion. After injection, deacetylation occurs spontaneously and results in sustained generation of fibrinolytic activity, with a slow turnover rate in blood.119 The complex has relatively low fibrin selectively similar to that of streptokinase and urokinase.120-122 Single-chain urokinase plasminogen activator (SCUPA) has a blood turnover rate similar to that of conventional urokinase but has fibrin selectivity similar to that of double-chain tPA.120-123 Single-chain tissue plasminogen activator is the most fibrin specific of all and also has the shortest plasma half-life.124-125 These studies were performed for the most part in patients with acute myocardial infarction (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 pathologic thrombus from a beneficial hemostatic plug. This lack of distinction will always necessitate careful selection of patients for therapy. Currently, tPA is being given with a heparin infusion in pulmonary embolism.101,102 In contrast, when urokinase or streptokinase is being infused, it is recommended that heparin be withheld. However, concurrent infusions of heparin and streptokinase are also being investigated.106,107 Recently, infusion of tPA without concurrent heparin has been investigated in venous thromboembolism.104

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 48-72 h of therapy is necessary for effective thrombolysis. However, in pulmonary embolism, 12 h of urokinase appears to be as effective as 24 h of either urokinase or streptokinase, and information may emerge to support the hypothesis that shorter courses of urokinase treatment will be as effective. This question can only be answered by controlled studies comparing standard and shorter durations of thrombolytic therapy.180

**Prevention of Venous Thromboembolism**

Since venous thromboembolism is difficult and expensive to diagnose, a major effort should be directed at preventing thromboembolism in high-risk groups. The preventive treatment of choice in most patients is low-dose, subcutaneous heparin. There is evidence for efficacy in general surgical patients,7-8 following AMI;120 in patients in respiratory failure;120 in those with elective surgery of the thorax, abdomen, or extremities; and following acute paraplegia, quadriplegia, and stroke.124-128 The standard regimen of 5,000 units of heparin given subcutaneously every 8-12 h has been shown to have some prophylactic efficacy in almost every clinical trial, but this repeatedly proved prophylaxis has been underutilized. More use of the regimen could save many lives in high-risk patients.129 A promising prophylaxis for general surgery, although not yet confirmed, is very low-dose warfarin at 1 mg daily started 3 weeks before elective surgery.134

In high-risk patients undergoing hip or knee orthopedic procedures, several antithrombotic agents and procedures are available. In patients undergoing elective total hip replacement, coumarin with protrombin time prolongation 1.3-1.5 × baseline value (INR 2.0-3.0) using rabbit brain thromboplastin, dextran, adjusted doses of subcutaneous heparin, heparin combined with dihydroergotamine, or low molecular weight heparin is effective and is associated with a low risk of clinically important bleeding.95,126-140,154-160 Data reviewed in a recent overview of this field suggest that conventional low-dose subcutaneous heparin offers major prophylactic benefit (50-60% risk reduction) in these high-risk patients.125 In both hip fracture repair and elective hip surgery, spinal anesthesia has been reported to have lower incidence of deep venous thrombosis than general anesthesia.161-163 This effect may be related to increased blood flow or better fibrinolytic function.164

Dextran is a branched polysaccharide produced by bacteria that is used in a molecular range of 40,000-
70,000 daltons. It interferes with both platelet and coagulation protein function. Dextran has prophylactic effects comparable to low-dose, subcutaneous heparin to moderate risk patients (level I)\textsuperscript{78,136-137} and appears to be superior to heparin in prophylaxis of very high-risk patients such as those undergoing hip replacement or urologic surgery.\textsuperscript{138-140} Since the agent must be given by IV infusion, it can contribute to fluid overload in patients with poor cardiac reserve, and it rarely causes severe allergic reactions.\textsuperscript{137,141,142} Dextran is also comparable in expense and incidence of bleeding to low-dose subcutaneous heparin.\textsuperscript{137,142} It is probably best used for prophylaxis of the high-risk patient\textsuperscript{142} when subcutaneous heparin is contraindicated. As with low-dose heparin, dextran should not be used to treat established venous thromboembolic disease.

Aspirin has failed in multiple trials to decrease the incidence of venous thromboembolism (level II).\textsuperscript{143-150} In other studies it partly reduced the incidence of venous thromboembolism in high-risk hip surgery patients (level I).\textsuperscript{151-153} Aspirin is not recommended for prophylaxis or treatment of deep venous thrombosis. Adjusted-dose heparin\textsuperscript{154} and low-dose warfarin\textsuperscript{155} appear to reduce the incidence of postoperative venous thrombosis in patients undergoing hip surgery. Hydroxychloroquine may decrease the incidence of venous thrombosis in postoperative patients, but this agent has not found general use.\textsuperscript{165}

Recently, large trials have shown that a combination of low-dose subcutaneous heparin and dihydroergotamine had prophylactic efficacy comparable to dextran with greater safety for certain patients undergoing emergency or elective abdominal or thoracic surgery.\textsuperscript{141,158-160} Dihydroergotamine may cause vasopressor responses and aggravate coronary artery disease or cause microvascular thrombosis in patients with sepsis and is currently not available for use in this country.

Ancrod is a protein purified from the venom of the Malayan pit viper (\textit{Agkistrodon rhodostoma}). The agent acts by bringing about the cleavage of fibrinopeptide A but not B from fibrinogen. Further proteolysis occurs on the A chain of fibrinogen, and the resultant abnormal fibrin monomer is cleared from the circulation rapidly with a subsequent marked fall in circulating fibrinogen levels, which brings about a hypocoagulable state. Rapid infusion of ancrod can result in microthrombi throughout the circulation.\textsuperscript{166} Similar but not identical proteins have been isolated from the venoms of other snakes. These agents have been useful for research but are not currently available for clinical use in the United States. In countries where ancrod is available to clinicians, it has been used as an alternative agent in patients with severe heparin-induced thrombocytopenia.

Mechanical means of preventing venous thrombosis appear most promising in very high-risk patients and in neurosurgical patients in whom even a minimal amount of bleeding can be serious. Electrical stimulation of calf muscles can be used only intraoperatively, because it is not tolerated by awake patients,\textsuperscript{167} and is of only historical interest. Intermittent external pneumatic compression of the calf muscles has relatively few contraindications and complications and has proved to be extremely useful in patients undergoing orthopedic (total knee replacement), urologic, and neurosurgical procedures (level I).\textsuperscript{168-171} Its major drawback during the introductory phase was the cumbersome equipment required, but the more recent devices have been simplified, and patient acceptance is good.\textsuperscript{166}

**Primary Pulmonary Hypertension**

Over the years there has been some interest in treating primary pulmonary hypertension with anti-thrombotic or fibrinolytic agents. There is as yet no convincing evidence that antithrombotic agents benefit patients with this rare disease.\textsuperscript{172-179} 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.\textsuperscript{177-179}

**Summary and Recommendations**

**Prevention**

1. It is recommended that moderate-risk patients should be treated prophylactically with low-dose heparin (5,000 units subcutaneously every 12 h) or intermittent pneumatic compression. This grade A recommendation is based on multiple level I studies for heparin and dextran,\textsuperscript{7,8,136,139,155-157} and intermittent pneumatic compression.\textsuperscript{168-171}

2. It is recommended that patients undergoing neurosurgical procedures, major knee surgery, and urologic surgery should be treated with intermittent pneumatic compression. This grade A recommendation is based on level I studies in all three conditions.\textsuperscript{168-171}

3. It is recommended that patients undergoing elective hip surgery should be pretreated prophylactically with adjusted-dose heparin (to prolong the APTT in the upper half of the normal range) or moderate-dose warfarin sodium (to prolong the prothrombin time to an INR of 2.0-3.0 (1.3-1.5 times control using rabbit brain thromboplastin). This grade A recommendation is based on level I studies for both prophylactic agents.\textsuperscript{58,140,154-157}

4. It is recommended that patients undergoing surgery for fractured hips should be treated prophylactically with moderate-dose warfarin to prolong the prothrombin time to an INR of 2.0-3.0 (1.3-1.5 times control using North American thromboplastin). This
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