

## CLINICAL PRACTICE

## Treatment of Deep-Vein Thrombosis

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*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

**A 52-year-old-woman with no history of venous thromboembolism presents with a four-day history of discomfort in her left calf. Proximal deep-vein thrombosis is diagnosed by compression ultrasonography. How should her case be managed?**

## THE CLINICAL PROBLEM

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The annual incidence of venous thromboembolism is approximately 0.1 percent; the rate increases from 0.01 percent among persons in early adulthood to nearly 1 percent among those who are at least 60 years old.<sup>1,2</sup> More than half of these events involve deep-vein thrombosis. To minimize the risk of fatal pulmonary embolism, accurate diagnosis and prompt therapy are crucial.<sup>3</sup> Long-term complications include the post-thrombotic syndrome<sup>4-6</sup> and recurrent thromboembolism.<sup>4,7-13</sup>

The pathogenesis of venous thrombosis involves three factors, which are referred to as Virchow's triad. Those factors are damage to the vessel wall, venous stasis, and hypercoagulability. Damage to the vessel wall prevents the endothelium from inhibiting coagulation and initiating local fibrinolysis. Venous stasis due to immobilization or venous obstruction inhibits the clearance and dilution of activated coagulation factors. Finally, congenital or acquired thrombophilia promotes coagulation. Venous thromboembolism is multifactorial and often results from a combination of risk factors (Table 1).<sup>14,15</sup>

Deep-vein thrombosis typically originates in the venous sinuses of the calf muscles<sup>16</sup> but occasionally originates in the proximal veins, usually in response to trauma or surgery.<sup>17</sup> Signs and symptoms result from venous outflow obstruction and from inflammation of the vessel wall and perivascular tissue. Calf-vein thrombi often spontaneously lyse and rarely lead to symptomatic pulmonary embolism.<sup>16,18</sup> Approximately 25 percent of untreated calf thrombi extend into the proximal veins, usually within a week after presentation.<sup>19</sup> The risk of pulmonary embolism (either symptomatic or asymptomatic) with proximal-vein thrombosis is approximately 50 percent,<sup>20</sup> and most fatal emboli probably arise from proximal thrombi.<sup>21</sup> Rarely, thrombosis is massive, causing vascular compromise of the leg (i.e., phlegmasia cerulea dolens).

## STRATEGIES AND EVIDENCE

## DIAGNOSIS

Because clinical diagnosis is unreliable, accurate diagnostic tests are required when deep-vein thrombosis is suspected. The failure of a proximal deep vein to flatten when compressed with an ultrasound probe or the finding of a persistent intraluminal filling defect in any deep vein on venography provides a definitive diagnosis.<sup>22</sup> Venography is often not used clinically because of its invasive nature, its technical demands, its costs, and its potential risks, such as allergic reactions and renal dysfunction. Therefore, compression ultrasonography is the diagnostic test of choice when deep-vein thrombosis is

suspected. The sensitivity and specificity of compression ultrasonography for proximal deep-vein thrombosis are more than 95 percent.<sup>23</sup> However, for isolated deep-vein thrombosis in the calf, the sensitivity of ultrasonography is lower (approximately 70 percent), and its positive predictive value is only 80 percent.<sup>23</sup> Therefore, imaging of the calf veins is not routinely performed. Consequently, follow-up ultrasonography one week after a normal test result has been obtained is recommended to detect the possible extension of a deep-vein thrombosis from the calf into the proximal veins; if the test is negative at this time, subsequent extension is unlikely. Venography may be useful to confirm the diagnosis when ultrasonography suggests isolated distal thrombosis<sup>23</sup> and when patients are unable to return for serial ultrasonography or have highly suggestive clinical signs or symptoms but negative results on ultrasonography.

#### INITIAL THERAPY

Once deep-vein thrombosis is diagnosed, the goals of treatment are relief of symptoms and prevention of embolization and recurrence. The cornerstone of initial therapy is either unfractionated or low-molecular-weight heparin, followed by an oral anticoagulant drug.<sup>3,19,22,24</sup> Table 2 lists the contraindications to anticoagulant therapy.<sup>25</sup>

#### Unfractionated Heparin

Unfractionated heparin is usually given intravenously by continuous infusion after a loading dose has been administered.<sup>26</sup> The anticoagulant response varies among patients, because this drug binds nonspecifically to plasma and cellular proteins. Laboratory monitoring, with assessment of the activated partial-thromboplastin time, is required, with adjustment of the dose to achieve the target therapeutic range. This range depends on which reagent and coagulometer are used to measure the activated partial-thromboplastin time. Although the use of a fixed ratio of 1.5 to 2.5 between the patient's value and the control value is commonly suggested, this strategy results in variable (and usually subtherapeutic) degrees of anticoagulation, because of the differing degrees of responsiveness among the available reagents. Ideally, the therapeutic range of activated partial-thromboplastin times for each reagent should correspond to ex vivo plasma levels of activity against activated factor X (anti-factor Xa) of 0.3 to 0.7 U per milliliter.<sup>26</sup> Weight-based heparin nomograms facilitate the achievement of a therapeutic anticoagulant effect.

**Table 1. Risk Factors for Venous Thromboembolism.\***

Risk Factor	Estimated Relative Risk
<b>Inherited conditions†</b>	
Antithrombin deficiency	25
Protein C deficiency	10
Protein S deficiency	10
Factor V Leiden mutation	
Heterozygous	5
Homozygous	50
G20210A prothrombin-gene mutation (heterozygous)	2.5
Dysfibrinogenemia	18
<b>Acquired conditions</b>	
Major surgery or major trauma	5–200‡
History of venous thromboembolism	50
Antiphospholipid antibodies	
Elevated anticardiolipin antibody level	2
Nonspecific inhibitor (e.g., lupus anticoagulant)	10
Cancer	5
Major medical illness with hospitalization	5
Age	
>50 years	5
>70 years	10
Pregnancy	7
Estrogen therapy	
Oral contraceptives	5
Hormone-replacement therapy	2
Selective estrogen-receptor modulators	
Tamoxifen	5
Raloxifene	3
Obesity	1–3
<b>Hereditary, environmental, or idiopathic conditions</b>	
Hyperhomocysteinemia§	3
Elevated levels of factor VIII (>90th percentile)	3
Elevated levels of factor IX (>90th percentile)	2.3
Elevated levels of factor XI (>90th percentile)	2.2

\* Data are from Rosendaal<sup>14</sup> and Kearon.<sup>15</sup> Relative risks are for patients with the specified risk factor, as compared with those without the risk factor.

† The definition of deficiency of antithrombin, protein C, or protein S varies among studies; it is usually defined as a functional or immunologic value that is less than the 5th percentile of values in the control population.

‡ The risk varies greatly, depending on the type of surgery, the use and type of prophylaxis, and the method of diagnosis.

§ The definition of hyperhomocysteinemia varies among studies; it is usually defined as a persistent elevation of fasting plasma homocysteine levels or plasma homocysteine levels after methionine loading that are greater than the 95th percentile of the control population or more than 2 SD above the mean for the control population.

Hemorrhage occurs in up to 7 percent of patients during initial treatment; the risk is affected by the heparin dose, the patient's age, and concomitant use or nonuse of thrombolytic and antiplatelet agents. Long-term use of heparin (i.e., longer than one month) can cause osteoporosis.<sup>26–28</sup> Heparin-

**Table 2. Contraindications to Anticoagulant Therapy.\*****Absolute contraindications**

Active bleeding  
 Severe bleeding diathesis or platelet count  $\leq 20,000/\text{mm}^3$   
 Neurosurgery, ocular surgery, or intracranial bleeding within the past 10 days

**Relative contraindications**

Mild-to-moderate bleeding diathesis or thrombocytopenia†  
 Brain metastases  
 Recent major trauma  
 Major abdominal surgery within the past 2 days  
 Gastrointestinal or genitourinary bleeding within the past 14 days  
 Endocarditis  
 Severe hypertension (i.e., systolic blood pressure  $>200$  mm Hg, diastolic blood pressure  $>120$  mm Hg, or both) at presentation

\* Data are from Abrams et al.<sup>25</sup>

† Mild-to-moderate thrombocytopenia is defined as a platelet count that is less than normal but greater than 20,000 per cubic millimeter.

induced thrombocytopenia is immune-mediated and in 30 to 50 percent of cases is associated with venous or arterial thrombosis.<sup>26</sup> Patients with previous heparin-induced thrombocytopenia should receive alternative anticoagulant agents, such as danaparoid, lepirudin, or argatroban.<sup>26</sup>

*Low-Molecular-Weight Heparins*

Meta-analyses suggest that low-molecular-weight heparins are as effective as unfractionated heparin in preventing recurrent venous thromboembolism, and they cause less bleeding (Table 3).<sup>30</sup> These heparin products — which show less nonspecific binding, have improved bioavailability, and elicit more predictable dose responses than unfractionated heparin — are administered subcutaneously once or twice daily in weight-adjusted doses,<sup>26</sup> generally without monitoring.

Although heparin-induced thrombocytopenia develops less frequently with low-molecular-weight heparins than it does with unfractionated heparin,<sup>26,29</sup> these agents often cross-react with the antibody that causes heparin-induced thrombocytopenia and are therefore contraindicated in patients with a history of this condition. Low-molecular-weight heparins also cause less osteoporosis than does unfractionated heparin.<sup>27,28</sup> In a randomized study comparing prophylactic regimens during pregnancy and the puerperium, 2 of 23 women who received unfractionated heparin were given a diagnosis of osteoporosis on the basis of postpar-

tum studies of bone mineral density, whereas none of the 21 women who received low-molecular-weight heparin (dalteparin) had osteoporosis.<sup>27</sup> In another study, symptomatic vertebral fractures occurred in 6 of 40 patients with contraindications to warfarin therapy who received three to six months of unfractionated heparin (10,000 U subcutaneously twice daily), as compared with 1 of 40 patients who received dalteparin (5000 U subcutaneously twice daily) for the same length of time.<sup>28</sup>

Outpatient therapy with low-molecular-weight heparins is safe and effective.<sup>32,33</sup> If there is a system in place for administering the medication (or for teaching patients or caregivers to administer it) and for monitoring, more than 80 percent of patients can be treated without hospitalization.<sup>26</sup> However, outpatient treatment is unsuitable for patients with massive thrombosis, serious coexisting illnesses, or a high risk of hemorrhage (e.g., patients who are very old, have recently undergone surgery, or have a history of bleeding or renal or liver disease). Low-molecular-weight heparins are more expensive than is unfractionated heparin, but they cut costs by reducing the frequency of hospital admissions and the need for laboratory monitoring.<sup>34</sup> Reductions in nursing time also make low-molecular-weight heparins cost effective for inpatients.

*Thrombolytic Therapy*

Thrombolytic agents dissolve fresh clots and restore venous patency more rapidly than do anticoagulants.<sup>35</sup> They are given systemically or by regional catheter-directed infusion, which results in a higher local concentration of the drug than does systemic administration. Theoretically, catheter-directed infusion should result in improved efficacy, but this hypothesis remains untested. Both routes of administration cause substantially more bleeding than does heparin,<sup>35</sup> and it is unclear whether either agent reduces the incidence of the post-thrombotic syndrome. Consequently, thrombolytic therapy is generally reserved for patients who have limb-threatening thrombosis, who have had symptoms for less than one week, and who have a low risk of bleeding.<sup>36</sup>

**LONG-TERM THERAPY**

Warfarin (or another coumarin) at a dose that is titrated to achieve an international normalized ratio (INR) of 2.0 to 3.0 is used for secondary prophylaxis and, as compared with placebo, reduces the risk of recurrence by 90 percent among patients

**Table 3. Options for the Initial Treatment of Deep-Vein Thrombosis with Anticoagulant Agents.**

Drug	Method of Administration	Dose*	Reported Risks	
			Risk of Heparin-Induced Thrombocytopenia†	Risk of Major Bleeding‡
			no./total no. (%)	
Unfractionated heparin	Intravenous	Loading dose, 5000 U or 80 U/kg of body weight with infusion adjusted to maintain activated partial-thromboplastin time within the therapeutic range§	9/332 (2.7)	35/1853 (1.9)
Low-molecular-weight heparin			0/333 (0)	20/1821 (1.1)
Dalteparin	Subcutaneous	100 U/kg every 12 hr or 200 U/kg daily; maximum, 18,000 U/day		
Enoxaparin	Subcutaneous	1 mg/kg every 12 hr or 1.5 mg/kg daily; maximum, 180 mg/day		
Tinzaparin	Subcutaneous	175 U/kg daily; maximum, 18,000 U/day		
Nadroparin	Subcutaneous	86 U/kg every 12 hr or 171 U/kg daily; maximum, 17,100 U/day		

\* Doses vary in patients who are obese or who have renal dysfunction. Monitoring of anti-factor Xa levels has been suggested for these patients, with dose adjustment to a target range of 0.6 to 1.0 U per milliliter four hours after injection for twice-daily administration or 1.0 to 2.0 U per milliliter for once-daily administration. Even though there are few supporting data, most manufacturers recommend capping the dose for obese patients at that for a 90-kg patient.

† Data are from Warkentin et al.<sup>29</sup> and are based on the incidence in patients who had undergone orthopedic surgery and were receiving prophylactic doses of unfractionated heparin or low-molecular-weight heparin (i.e., enoxaparin).

‡ Data are from Gould et al.<sup>30</sup>

§ The therapeutic range of activated partial-thromboplastin time corresponds to heparin levels of 0.3 to 0.7 U per milliliter, as determined by anti-factor Xa assay. High levels of heparin-binding proteins and factor VIII may result in so-called heparin resistance. In patients requiring more than 40,000 U per day to attain a therapeutic activated partial-thromboplastin time, the dosage can be adjusted on the basis of plasma heparin levels.<sup>31</sup>

who have received four weeks to three months of therapy.<sup>36,37</sup> Because the antithrombotic effect of warfarin is delayed for 72 to 96 hours, heparin therapy is overlapped with initiation of warfarin. When therapy with the two drugs is started on the same day, heparin can be discontinued after five days, provided the INR has been at a therapeutic level for two consecutive days. Patients with massive thrombosis often receive an extended course (i.e., 7 to 14 days) of heparin. The use of oral anticoagulant therapy was reviewed recently in the *Journal*.<sup>38</sup>

Patients with cancer who have venous thromboembolism have a substantial risk of a recurrent event when they are treated with warfarin. A randomized study involving such patients showed that after standard initial therapy with low-molecular-weight heparin, patients who were taking the drug on a long-term basis had half as many recurrent events as those who were taking coumarin derivatives.<sup>39</sup> Bleeding rates were similar with both medications, and daily injections were acceptable to the patients.

Therefore, this therapy should be considered for all patients with cancer who also have deep-vein thrombosis.

For other patients, the role of long-term therapy with low-molecular-weight heparin is less clear. In a systematic review of randomized, controlled trials in which low-molecular-weight heparin was compared with warfarin for secondary prophylaxis, the rates of recurrent thrombosis and major bleeding were similar with the two regimens.<sup>40</sup> Although low-molecular-weight heparin has advantages over warfarin, its cost, the need for daily injections, and the risk of osteoporosis with long-term therapy make it unsuitable for routine secondary prophylaxis.

Inferior vena cava filters are useful in patients who have a contraindication to anticoagulation or those in whom treatment has failed (Table 2).<sup>36</sup> In a randomized trial of 400 patients with proximal-vein thrombosis who received anticoagulants either alone or with a filter, the incidence of early pulmonary embolism by day 12 was significantly lower

among patients treated with filters.<sup>41</sup> However, this difference did not persist; at two years, the reduction in symptomatic pulmonary embolism in the filter-treated patients was not significant, and mortality was similar in the two groups. The approximate doubling of the risk of recurrent deep-vein thrombosis in patients treated with filters suggests that anticoagulant therapy should be started if it is safe to do so. It remains a matter of controversy whether filters can be used to prevent embolization of “free-floating” iliofemoral thrombi to avert pulmonary embolism in patients who have deep-vein thrombosis and a reduced cardiopulmonary reserve and to treat venous thromboembolism in patients with cancer.<sup>36</sup>

#### DURATION OF ANTICOAGULATION

Patients should receive anticoagulant therapy for at least three months. The optimal duration of treatment should be determined so as to balance the risks of recurrence and bleeding. When anticoagulation is adjusted to achieve an INR of 2.0 to 3.0, the annual risk of major bleeding is approximately 3 percent.<sup>42</sup> In patients whose thrombosis is associated with a major transient risk factor, the risk of recurrence after three months of anticoagulation is also approximately 3 percent per year.<sup>36</sup> Case fatality rates of 5 percent for recurrence<sup>43</sup> and 10 percent for major bleeding<sup>42</sup> have been reported. After three months, the risk of a fatal recurrence among patients who are not receiving treatment is lower than the risk of fatal hemorrhage among patients taking warfarin (i.e., approximately 0.15 percent vs. 0.3 percent per year); therefore, therapy of three months' duration is generally sufficient for patients whose thrombosis is associated with a major transient risk factor.<sup>36</sup>

The optimal duration of therapy for patients who have had idiopathic events or who have continuing risk factors remains controversial.<sup>7-13,36,44</sup> Patients with idiopathic deep-vein thrombosis who are treated for approximately three months have a 10 to 27 percent risk of recurrence during the year after they discontinue anticoagulants.<sup>8,9-12</sup> With six months of treatment, the risk of recurrence is approximately 10 percent in the year after anticoagulation is stopped<sup>12,13</sup>; patients whose initial events occur in association with a minor transient risk factor probably have a lower risk of recurrence. Extending therapy beyond six months does not substantially reduce the risk of recurrence after discontinuation of treatment.<sup>11</sup> Although continuing treatment pre-

vents recurrences, it also exposes the patient to the risk of anticoagulant-induced bleeding. On the basis of the rates of recurrent venous thromboembolism and major bleeding that are cited above, extended anticoagulant therapy should be considered for patients with idiopathic deep-vein thrombosis whose estimated risk of major bleeding is less than 5 percent per year. However, therapy for six months or less may be more appropriate for patients at higher risk of bleeding or those in whom thrombosis occurred in association with a minor transient risk factor (Table 4).

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### AREAS OF UNCERTAINTY

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#### THE ROLE OF REDUCED-INTENSITY ANTICOAGULATION

The role of reduced-intensity anticoagulation (that is, anticoagulant therapy targeted to achieve an INR of 1.5 to 1.9) after three months of conventional therapy has been examined in two randomized, controlled trials. One of the studies suggested that, as compared with placebo, low-intensity warfarin is highly effective and safe when used to prevent recurrences.<sup>45</sup> The other study suggested that low-intensity warfarin was less effective and not safer than conventional-intensity warfarin for extended treatment after idiopathic venous thromboembolism.<sup>46</sup> In both studies, the small number of major bleeding events probably precludes an accurate assessment of the true risk of major hemorrhage with either regimen.

#### NEW ANTICOAGULANTS

The limitations of traditional anticoagulants have prompted the development of new agents. Drugs that are in an advanced stage of development but have not yet received approval from the Food and Drug Administration include parenteral synthetic pentasaccharide analogues (e.g., fondaparinux and idraparinux) and oral direct thrombin inhibitors (e.g., ximelagatran). In a large randomized trial comparing fondaparinux with enoxaparin for the initial treatment of deep-vein thrombosis, rates of symptomatic, recurrent venous thromboembolism and major bleeding were not statistically different between the two groups.<sup>47</sup> Similar results were obtained in a randomized trial involving 2489 patients with acute deep-vein thrombosis (with or without pulmonary embolism) that compared six months of ximelagatran monotherapy with six months of therapy consisting of enoxaparin followed by warfarin.<sup>48</sup>

**Table 4. Recommendations for the Duration of Anticoagulant Therapy for Patients with Deep-Vein Thrombosis.\***

Characteristics of Patient†	Risk of Recurrence in the Year after Discontinuation (%)	Duration of Therapy
Major transient risk factor	3	3 mo
Minor risk factor; no thrombophilia	<10 if risk factor avoided >10 if risk factor persistent	6 mo Until factor resolves
Idiopathic event; no thrombophilia or low-risk thrombophilia	<10	6 mo‡
Idiopathic event; high-risk thrombophilia	>10	Indefinite
More than one idiopathic event	>10	Indefinite
Cancer; other ongoing risk factor	>10	Indefinite

\* Data are from Hirsh and Hoak,<sup>22</sup> Hyers et al.,<sup>36</sup> and Kearon.<sup>44</sup>

† Examples of major transient risk factors are major surgery, a major medical illness, and leg casting. Examples of minor transient risk factors are the use of an oral contraceptive and hormone-replacement therapy. Examples of low-risk thrombophilias are heterozygosity for the factor V Leiden and G20210A prothrombin-gene mutations. Examples of high-risk thrombophilia are antithrombin, protein C, and protein S deficiencies; homozygosity for the factor V Leiden or prothrombin-gene mutation or heterozygosity for both; and the presence of antiphospholipid antibodies.

‡ Therapy may be prolonged if the patient prefers to prolong it or if the risk of bleeding is low.

A placebo-controlled trial showed that ximelagatran reduced the risk of recurrent venous thromboembolism without increasing the risk of major hemorrhage in patients who had already completed six months of standard treatment.<sup>49</sup> In contrast to warfarin, ximelagatran does not require monitoring of the degree of anticoagulation. However, ximelagatran has potential limitations, including the occurrence of elevations in liver enzyme levels (specifically, alanine aminotransferase) in 5 to 10 percent of patients receiving long-term therapy. To date, such elevations are not usually associated with symptoms and are reversible, even if the medication is continued. Further studies are required to define the appropriate role of these new agents.

#### TESTING FOR THROMBOPHILIA

At least one third of patients with idiopathic venous thromboembolism have an identifiable thrombophilia on laboratory testing.<sup>15,44</sup> Although testing for hypercoagulable states is costly, the procedure is routine in many centers for patients who have had a single episode of thrombosis. However, there is no clear evidence that modifying treatment because a hypercoagulable state has been found improves outcome or that more intensive therapy is required in patients with laboratory evidence of thrombophilia. Although it is assumed that the presence of a thrombophilic abnormality increases the risk of recurrence and, consequently, justifies prolonged therapy, the available data are inconsistent, and these

assumptions remain unproved (Table 5).<sup>15,44,50-52</sup> The effectiveness of testing asymptomatic relatives and its potential consequences — including anxiety, avoidance of effective hormonal contraception, unnecessary exposure to anticoagulants in patients with a positive test, and possibly false reassurance from a negative test — have not been formally assessed. Thus, there are no unequivocal indications for testing for the presence of thrombophilic abnormalities in either patients or their relatives.

#### PREVENTION OF THE POST-THROMBOTIC SYNDROME

In an unblinded, randomized trial, daytime use of knee-length, graduated compression stockings for at least two years starting two to three weeks after the diagnosis of proximal deep-vein thrombosis reduced the frequency of the post-thrombotic syndrome by 50 percent.<sup>5</sup> However, in a placebo-controlled trial in which the definition of the post-thrombotic syndrome focused on the quality of life (i.e., the presence of chronic pain and swelling six months or more after deep-vein thrombosis), compression stockings worn “as much as possible” during waking hours did not prevent the condition.<sup>6</sup> Although the role of compression stockings in preventing the post-thrombotic syndrome remains uncertain, they are widely used to control symptoms in patients with established disease. Thrombolytic therapy has the potential to prevent the post-thrombotic syndrome by preventing damage to venous

**Table 5. Prevalence of Thrombophilic Abnormalities and the Associated Risk of Recurrent Venous Thromboembolism after the Cessation of Anticoagulant Therapy.\***

Risk Factor†	Estimated Prevalence (%)‡	Estimated Relative Risk of Recurrence
Antithrombin deficiency	1	1.5–3
Protein C deficiency	3	1.5–3
Protein S deficiency	3	1.5–3
Factor V Leiden mutation		
Heterozygous	20	1–4
Homozygous	2	About 4
G20210A prothrombin-gene mutation (heterozygous)	5	1–5
Dysfibrinogenemia	<1	NA
Factor V Leiden and G20210A prothrombin-gene mutations	2	2–5
Antiphospholipid antibodies	5	2–4
Elevated factor VIII levels	10–50	1–7
Elevated factor IX levels	10–50	1–5
Hyperhomocysteinemia	10–25	1–3

\* Data are from Kearon,<sup>44</sup> Christiansen et al.,<sup>50</sup> Baglin et al.,<sup>51</sup> Margaglione et al.,<sup>52</sup> and Kyrle et al.<sup>53</sup> Relative risks are for patients with the risk factor in question, as compared with those without the risk factor.

† The definition of deficiency of antithrombin, protein C, or protein S varies; it is usually defined as a functional or immunologic value that is less than the 5th percentile of values in the control population.

‡ Prevalence and relative risk depend on the definitions of hyperhomocysteinemia and elevations in levels of factor VIII and factor IX and on the reference group.

valves and subsequent venous hypertension, but outcome data supporting such an effect are lacking.

#### GUIDELINES

Guidelines for the treatment of deep-vein thrombosis have been published by the American College of Chest Physicians<sup>36</sup> and the American Heart Association<sup>22</sup> and are consistent with the approach outlined in this article.

#### RECOMMENDATIONS

For most patients with deep-vein thrombosis, such as the patient described in the vignette, low-molecular-weight heparin administered on an outpatient basis is appropriate as initial therapy. If patients or family members cannot administer injections, home care should be arranged. Hospital admission is still warranted for some patients (Fig. 1). Thrombolytic therapy should be considered for patients less than 60 years of age who have limb-threatening circulatory compromise. Inferior vena cava filters should be inserted in patients with contraindications to anticoagulation (Table 2) and in those who require urgent surgery that precludes anticoagulation. Tem-

porary filters should be used if anticoagulation is likely to be safe within 14 days after the bleeding event.

Oral anticoagulation should generally be started on the first day of treatment. Heparin should be given for a minimum of five days and not stopped until the patient's INR has been 2.0 or higher for two consecutive days. A platelet count should be obtained three to five days after initiating heparin administration. The INR should be measured after three to four days of warfarin treatment and the dose adjusted to maintain a target INR of 2.5. Twice-weekly monitoring of the INR is usually required for the first one to two weeks, followed by weekly monitoring until the INR is stable. Thereafter, the INR can be measured every two to four weeks, or more frequently if there are changes in medications or health status. Patients with cancer should receive long-term maintenance therapy with low-molecular-weight heparin, if that is practical.

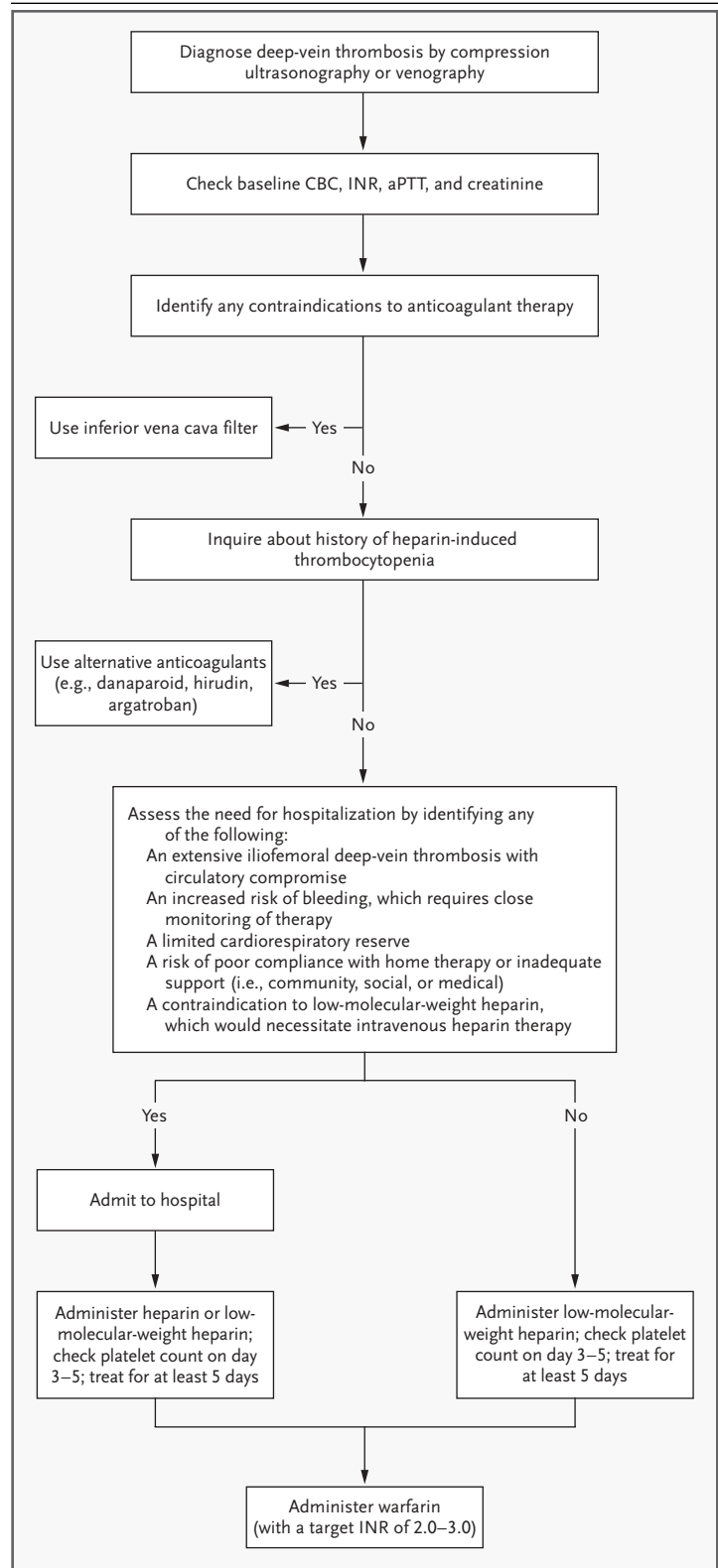
Although the indications for testing for thrombophilia remain controversial, we test for the presence of thrombophilic states — the factor V Leiden mutation, the G20210A prothrombin-gene mutation, hyperhomocysteinemia, antiphospholipid antibodies, and deficiencies of antithrombin, protein

**Figure 1. Management of Uncomplicated Deep-Vein Thrombosis.**

For patients with limb-threatening iliofemoral thrombosis, symptoms for less than one week, and a low risk of bleeding, thrombolysis should be considered. Absolute contraindications to thrombolysis include suspected aortic dissection, acute pericarditis, active bleeding, cerebral neoplasm, intracranial vascular lesion, and previous central nervous system hemorrhage. The following are relative contraindications to thrombolysis: head trauma, major surgery, organ biopsy, major trauma, prolonged cardiopulmonary resuscitation with resultant chest trauma, or puncture of a noncompressible vessel within the past two to four weeks; severe hypertension at presentation (i.e., systolic blood pressure above 200 mm Hg, diastolic blood pressure above 120 mm Hg, or both); nonhemorrhagic stroke within the past six months; endocarditis; pregnancy; cancer; bleeding diathesis; and hepatic dysfunction.<sup>25</sup> For patients with cancer, long-term therapy with low-molecular-weight heparin should be considered. CBC denotes complete blood count, INR international normalized ratio, and aPTT activated partial-thromboplastin time.

C, and protein S — if patients have clinical features suggestive of these abnormalities. These features include a family history of venous thromboembolism, venous thromboembolism before the age of 45 years, recurrent venous thromboembolism, thrombosis in an unusual site (e.g., in mesenteric, renal, hepatic, or cerebral veins), idiopathic venous thromboembolism or thromboembolism after minimal provocation, heparin resistance (in the case of antithrombin deficiency), warfarin-induced skin necrosis (in the case of protein C or protein S deficiency), and neonatal purpura fulminans (in the case of homozygous protein C or protein S deficiency). We also offer the test if identifying a thrombophilic mutation will alter the care of patients or their relatives or if a patient requests it. Testing for dysfibrinogenemia is often not undertaken, given its low yield. We do not routinely test for elevated levels of factor VIII or IX, given the concern about the variability of this assay, the variation in factor levels among patients, and the most appropriate cutoff values.

We treat patients with a major transient risk factor for three months and those with a first episode of idiopathic thrombosis for at least six months. We recommend indefinite therapy for patients with a high-risk thrombophilia (e.g., a deficiency of antithrombin, protein C, or protein S; persistent anti-





phospholipid antibodies; or homozygosity for factor V Leiden or the prothrombin-gene mutation or heterozygosity for both), a continuing risk factor (e.g., advanced cancer), or recurrent episodes of idiopathic venous thrombosis, provided the risk of bleeding is not high. Although it has recently been suggested that the risk of recurrent venous thromboembolism is significantly higher in men than it

is in women,<sup>53</sup> more data are required before these findings can be incorporated into routine recommendations regarding the duration of treatment.

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