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 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.1,2 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.3 Long-term complications include the post-thrombotic syndrome4-6 and recurrent thromboembolism.4,7-13

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).14,15

Deep-vein thrombosis typically originates in the venous sinuses of the calf muscles16 but occasionally originates in the proximal veins, usually in response to trauma or surgery.17 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.16,18 Approximately 25 percent of untreated calf thrombi extend into the proximal veins, usually within a week after presentation.19 The risk of pulmonary embolism (either symptomatic or asymptomatic) with proximal-vein thrombosis is approximately 50 percent,20 and most fatal emboli probably arise from proximal thrombi.21 Rarely, thrombosis is massive, causing vascular compromise of the leg (i.e., phlegmasia cerulea dolens).

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.22 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. 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. 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 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. Table 2 lists the contraindications to anticoagulant therapy.

**Unfractionated Heparin**

Unfractionated heparin is usually given intravenously by continuous infusion after a loading dose has been administered. 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. Weight-based heparin nomograms facilitate the achievement of a therapeutic anticoagulant effect.

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### Table 1. Risk Factors for Venous Thromboembolism.

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

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* Data are from Rosendaal and Kearon. 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.
induced thrombocytopenia is immune-mediated and in 30 to 50 percent of cases is associated with venous or arterial thrombosis.\textsuperscript{26} Patients with previous heparin-induced thrombocytopenia should receive alternative anticoagulant agents, such as danaparoid, lepirudin, or argatroban.\textsuperscript{26}

**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).\textsuperscript{30} 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,\textsuperscript{26} generally without monitoring.

Although heparin-induced thrombocytopenia develops less frequently with low-molecular-weight heparins than it does with unfractionated heparin,\textsuperscript{26,29} 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.\textsuperscript{27,28} 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 postpartum studies of bone mineral density, whereas none of the 21 women who received low-molecular-weight heparin (dalteparin) had osteoporosis.\textsuperscript{27} 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.\textsuperscript{28}

Outpatient therapy with low-molecular-weight heparins is safe and effective.\textsuperscript{32,33} 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.\textsuperscript{26} 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.\textsuperscript{34} Reductions in nursing time also make low-molecular-weight heparins cost effective for inpatients.

**Table 2. Contraindications to Anticoagulant Therapy.\textsuperscript{25}**

<table>
<thead>
<tr>
<th>Absolute contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active bleeding</td>
</tr>
<tr>
<td>Severe bleeding diathesis or platelet count &lt;20,000/mm\textsuperscript{3}</td>
</tr>
<tr>
<td>Neurosurgery, ocular surgery, or intracranial bleeding within the past 10 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-to-moderate bleeding diathesis or thrombocytopenia†</td>
</tr>
<tr>
<td>Brain metastases</td>
</tr>
<tr>
<td>Recent major trauma</td>
</tr>
<tr>
<td>Major abdominal surgery within the past 2 days</td>
</tr>
<tr>
<td>Gastrointestinal or genitourinary bleeding within the past 14 days</td>
</tr>
<tr>
<td>Endocarditis</td>
</tr>
<tr>
<td>Severe hypertension (i.e., systolic blood pressure &gt;200 mm Hg, diastolic blood pressure &gt;120 mm Hg, or both) at presentation</td>
</tr>
</tbody>
</table>

* Data are from Abrams et al.\textsuperscript{25} † Mild-to-moderate thrombocytopenia is defined as a platelet count that is less than normal but greater than 20,000 per cubic millimeter.
who have received four weeks to three months of therapy.\textsuperscript{36,37} 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.\textsuperscript{38}

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.\textsuperscript{39} 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.\textsuperscript{40} 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).\textsuperscript{36} 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.

\begin{table}[h]
\centering
\caption{Options for the Initial Treatment of Deep-Vein Thrombosis with Anticoagulant Agents.}
\begin{tabular}{|l|c|p{10cm}|c|}
\hline
\textbf{Drug} & \textbf{Method of Administration} & \textbf{Dose}\textsuperscript{a} & \textbf{Reported Risks} \\
\hline
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\textsuperscript{b} & 9/332 (2.7) & 35/1853 (1.9) \\
\hline
Low-molecular-weight heparin & & & & \\
Dalteparin & Subcutaneous & 100 U/kg every 12 hr or 200 U/kg daily; maximum, 18,000 U/day & 0/333 (0) & 20/1821 (1.1) \\
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 & & \\
\hline
\textsuperscript{a} 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. \\
\textsuperscript{b} Data are from Warkentin et al.\textsuperscript{29} 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). \\
\textsuperscript{c} Data are from Gould et al.\textsuperscript{30} \\
\textsuperscript{d} 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.\textsuperscript{31}
\end{tabular}
\end{table}
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. 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.

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. 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.
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. 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. 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).

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. 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. 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

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

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

* Data are from Hirsh and Hoak, Hyers et al., and Kearon.
† 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.
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 and the American Heart Association 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. Temporary 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...
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., 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, more data are required before these findings can be incorporated into routine recommendations regarding the duration of treatment.

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