Long-Term Management of Patients After Venous Thromboembolism

Clive Kearon, MB, MRCPI, FRCPC, PhD

Abstract—Long-term treatment of venous thromboembolism (VTE) focuses mainly on the duration of anticoagulant therapy, usually with vitamin K (VK) antagonists. The duration of therapy should be individualized based on the risk of recurrent VTE if treatment were stopped and the risk of bleeding if treatment were continued. The risk of recurrence is low if thrombosis was provoked by a major reversible risk factor such as surgery; 3 months of treatment is usually adequate for such patients. The risk of recurrence is high if thrombosis was unprovoked (“idiopathic”) or associated with an irreversible risk factor such as cancer; anticoagulant treatment for at least 6 months, and often indefinitely, is indicated for such patients. Risk of recurrence is intermediate if thrombosis was associated with a minor transient risk factor; such patients can be treated for 3 to 6 months. Within each of these categories, presentation as pulmonary embolism, >1 previous VTE, an underlying malignancy, an antiphospholipid antibody, or selected hereditary thrombophilic states favor more prolonged therapy, whereas isolated distal deep vein thrombosis, high risk of bleeding, and patient preference favor shorter treatment. The optimal intensity of anticoagulant therapy with VK antagonists corresponds to a target international normalized ratio of 2.5 (range, 2.0 to 3.0). Long-term treatment with low-molecular-weight heparin is an alternative to VK-antagonist therapy and is usually preferable in patients with active cancer. Oral direct thrombin inhibitors also appear suitable for long-term prevention of recurrent VTE but await regulatory approval and comparison with VK antagonists. (Circulation. 2004;110[suppl I]:I-10–I-18.)

Key Words: deep vein thrombosis ■ pulmonary embolism ■ anticoagulant therapy ■ warfarin

After an episode of venous thromboembolism (VTE), treatment should be continued until the benefits of anticoagulation therapy no longer clearly outweigh the risks. For some patients, the benefit of continuing therapy never decreases to the point that anticoagulation should be stopped. The optimal duration of anticoagulation, therefore, should be individualized. Foremost, this assessment weighs the risk of recurrent VTE if anticoagulation is stopped against the risk of bleeding if treatment is continued. If it is concluded that the net benefit of continuing anticoagulant therapy is small or uncertain, then patient preference and cost of therapy become important factors, particularly if indefinite therapy is considered.

This review focuses principally on the optimal duration and intensity of vitamin K (VK) antagonist therapy for VTE. Secondarily, treatment of VTE with low-molecular-weight heparin (LMWH) as an alternative to VK antagonists and the role of graduated compression stockings to prevent the postthrombotic syndrome are addressed.

Risk of Recurrent VTE After Stopping Anticoagulant Therapy

Reversibility of Risk Factors for VTE

Perhaps the most important factor in assessing risk of recurrent VTE is the relationship of the initial episode of thrombosis to risk factors. When a major reversible risk factor such as surgery can be identified as the sole explanation for VTE, then the risk of recurrence is relatively low (ie, ∼3% in the first year).1,2,4–7

In contrast, the risk is high (∼10% in the first year) in patients with unprovoked (“idiopathic”) VTE and in those with persistent, irreversible, or other risk factors (Table 1).1–7,37,38 Patients in whom thrombosis was provoked by a reversible risk factor, such as leg trauma, estrogen therapy, or prolonged air travel (eg, a flight >10 hours long), have an intermediate risk for recurrent VTE after stopping anticoagulant therapy (∼5% in the first year).7,25,39

Thrombophilia

Hereditary and acquired biochemical states associated with VTE (“thrombophilia”) are heterogeneous, both in terms of the frequency with which they occur in the normal population and the strength of their association with thrombosis (Table 1).40–43

Antiphospholipid Antibodies

Antiphospholipid antibodies (anticardiolipin antibody8,22 or lupus anticoagulant8) are associated with a 2-fold or greater risk of recurrent thrombosis after stopping anticoagulant therapy.8,22 One study also found that after a first episode of
VTE, an antithrombin antibody was associated with a higher mortality during long-term follow-up because of an excess of venous and arterial thrombotic events. Continuing anticoagulant therapy appeared to reduce this risk.22

**Factor V Leiden and the G20210A Prothrombin Gene Mutation**

Individuals with heterozygous forms of either the factor V Leiden or the G20210A prothrombin gene mutation do not appear to harbor a clinically important risk for recurrent VTE.7,8,17,38,39

Patients heterozygous for both of these mutations9,15,18,19 or homozygous for the factor V Leiden mutation14 appear to be at increased risk of recurrent VTE (Table 1).

**Deficiency of Protein C, Protein S, or Antithrombin**

There is little prospective information on the risk of recurrent VTE in patients with antithrombin, protein C, or protein S deficiency. In patients with 1 of these abnormalities or a lupus anticoagulant, a prospective study identified a hazard ratio of 1.4 for recurrent VTE.10 In another study, relative risks for recurrent VTE were 1.0 for protein S, 1.8 for protein C, and 2.6 for antithrombin deficiency.7 A third study found no increase in recurrence among 15 patients with any of these deficiencies.9 In a retrospective family cohort study, the presence of 1 of these abnormalities was associated with a 10% cumulative frequency of recurrent VTE in the first year after diagnosis and a 23% frequency by 5 years.44 Therefore, although there is uncertainty, these abnormalities do not appear to be clinically important risk factors for recurrent VTE.

**Elevated Factor VIII Levels**

Although a markedly elevated plasma level of factor VIII appears related to recurrent thrombosis, prospective validation is lacking (Table 1).20,21

**Hyperhomocysteinemia**

Hyperhomocysteinemia, which can be hereditary or acquired,45 was associated with a 2.7-fold increased risk of recurrent VTE in a study of patients with unprovoked VTE.23 Lowering plasma homocysteine levels with vitamin therapy did not convincingly reduce the frequency of recurrent VTE.46

**Cancer**

Cancer is associated with ≈3-fold increased risk of recurrent VTE both during56,29,47–49 and after6,10,25,29 anticoagulant therapy. Among patients with cancer, the risk of recurrence is ≈3-fold higher in those with metastatic disease than in those with localized tumors (Table 1).26 In patients with cancer, the risk of recurrent VTE after stopping anticoagulant therapy is as high as 10% to 20% in the first year, particularly in cases of progressive or metastatic disease, in those with poor mobility, or those receiving ongoing chemotherapy.4,6,25 The risk of recurrence is uncertain but probably lower when the cancer is responsive to therapy, or if the initial VTE was provoked by other reversible risk factors such as surgery or chemotherapy.

**Pulmonary Embolism Versus Deep Vein Thrombosis**

Patients with pulmonary embolism (PE) appear to have the same risk of recurrent VTE as those with proximal deep vein thrombosis (DVT).3,23,32,50 However, after an initial PE, ≈60% of recurrent episodes of VTE are also PE, whereas only ≈20% of recent episodes of VTE are PE after an initial DVT.30,32,50–52 This pattern of recurrence—with ≈3-fold higher risk of PE after an initial PE than after an initial DVT—appears persistent.32,51 Approximately 10% of symptomatic PEs are rapidly fatal33–35 and another 5% of those in whom PE is diagnosed and treated also die of it.32,51,56–59 Thus, after ≥3 months of treatment for DVT or PE, recurrent VTE presenting as PE has a case fatality rate of ≈15%. The risk of dying from acute DVT, because of early subsequent PE or other complications (eg, bleeding, precipitation of myocardial infarction), is closer to 2% or less.10,32,51,57,60 Based on these estimates, the case fatality rate associated with late recurrent VTE preceded by PE is ≈10%, whereas it is ≈5% after a preceding DVT. An overview of randomized trials involving patients with DVT who had completed 3 months of treatment noted a 5.1% case-fatality rate for recurrent VTE, consistent with the foregoing estimate.50 Hence, although the risk of recurrence is approximately the same after PE and proximal DVT, the

<table>
<thead>
<tr>
<th>Variable and References</th>
<th>Relative Risk</th>
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<tbody>
<tr>
<td>Transient risk factors</td>
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<tr>
<td>Persistent risk factors</td>
<td>≥2</td>
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<tr>
<td>Unprovoked VTE</td>
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<tr>
<td>Protein C, protein S, and antithrombin deficiencies</td>
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<tr>
<td>Heterozygous for factor V Leiden</td>
<td>1–2</td>
</tr>
<tr>
<td>Homozygous for factor V Leiden</td>
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</tr>
<tr>
<td>Heterozygous for G20210A mutation in the prothrombin gene</td>
<td>1–2</td>
</tr>
<tr>
<td>Heterozygous for both factor V Leiden and G20210A prothrombin gene</td>
<td>2–5</td>
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<tr>
<td>Factor VIII level &gt;200 IU/dL</td>
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<td>Antiphospholipid antibodies</td>
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<td>Mild hyperhomocysteinemia</td>
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<tr>
<td>D-dimer elevation after stopping therapy</td>
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<td>Family history of VTE</td>
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<td>Discontinuation of estrogen</td>
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<td>Proximal DVT vs PE</td>
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<td>Distal DVT vs proximal DVT or PE</td>
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<tr>
<td>Residual thrombosis</td>
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<td>Vena caval filter</td>
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<td>Second vs first episode of VTE</td>
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<tr>
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<tr>
<td>Asian</td>
<td>≈0.8</td>
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case fatality rate associated with recurrence is \(\approx 2\)-fold higher after PE than DVT.

Patients with VTE and chronic thromboembolic pulmonary hypertension should generally be treated indefinitely because they may have a history of recurrent PE and cannot tolerate additional episodes.\(^{61}\)

**Residual Deep Vein Thrombosis**

It is uncertain whether residual DVT is an independent predictor of recurrent VTE. Piovella et al found that residual proximal DVT on ultrasound after 3 months of treatment was associated with a \(>3\)-fold increase in recurrent thrombosis, with three-quarters of DVT occurring in the same leg.\(^{29}\) Prandoni et al reported a \(>2\)-fold increase in the frequency of recurrent VTE when DVT persisted on ultrasound imaging.\(^{62}\) However, it is unclear whether this association persists after adjustment for the time elapsed after initial DVT. Agnelli et al reported a statistically significant \(1.4\)-fold increase in recurrent VTE among patients with PE who had concomitant DVT 3 months after initial treatment.\(^{30}\) In contrast, 2 other studies of patients with unprovoked VTE found that residual proximal DVT after \(\geq 3\) months of treatment did not predict recurrent VTE during anticoagulant therapy (hazard ratio 0.9; target international normalized ratio [INR] 1.5 to 1.9 for half of the patients)\(^{63}\) or after treatment was stopped (hazard ratio 1.3).\(^{62}\) Similarly, abnormal impedance plethysmography after 1 month of treatment (suggesting persistent proximal vein obstruction) was not predictive of recurrence when treatment was stopped at 3 months (relative risk 1.3).\(^{3}\) Furthermore, with the exception of early recurrence associated with inadequate initial treatment (eg, 6 weeks),\(^{31}\) recurrent DVT is equally distributed between the initially affected and unaffected legs.\(^{9,31,62}\) Current evidence therefore suggests that residual DVT may be weakly associated with recurrent VTE \(<2\)-fold increase), but venous obstruction is not the underlying mechanism.

**Multiple Previous Episodes of VTE**

Intuitively, one would expect that patients with \(>1\) VTE might have a higher risk of recurrence than those with a single VTE, particularly if the interval between episodes is short (<5 years). Schulman et al, however, found a similar risk of recurrence after 6 months of treatment for a first or a second episode of VTE during 2 years of follow-up.\(^{3,35}\) Even so, a large epidemiologic study of linked hospital discharge records from California\(^{33}\) and follow-up of patients who, in a recent trial stopped anticoagulant therapy after 6 months\(^{66}\) found statistically significant 50%\(^{31}\) and 75%\(^{36}\) higher ratios of recurrent VTE after a second or subsequent episode of VTE than after an initial episode.

**Vena Caval Filters**

In a randomized trial of routine placement of vena caval filters as an adjunct to anticoagulant therapy in patients with proximal DVT, filters reduced the frequency of PE during the first 12 days, but almost doubled the risk of recurrent DVT over 2 years.\(^{34}\) Despite this increase of recurrent DVT, PE did not appear to be more frequent. Epidemiologic data support this observation and suggest that caval filters act as an independent risk factor for recurrent DVT (odds ratio 1.8), but are not a risk factor for PE (odds ratio 1.0).\(^{32}\) The increase in DVT associated with filter placement was largely confined to patients initially presenting with PE.\(^{33}\) These findings support starting anticoagulant therapy in patients with filters when safe (eg, once the bleeding risk resolves), and then favor more prolonged, but not necessarily indefinite, treatment (Table 1).

**D-dimer Levels After Stopping Treatment**

Laboratory evidence of activation of the coagulation system after withdrawal of anticoagulants appears related to the risk of recurrent VTE. In 2 studies, a low or negative D-dimer level \(\approx 1\) month after stopping anticoagulant therapy was associated with a much lower rate of recurrent VTE during follow-up (18 and 38 months)\(^{9,24}\) and occurred in one third\(^{24}\) and more than half\(^9\) of patients. D-dimer levels predicted recurrence in patients with and without hereditary thrombophilia or provoking risk factors for VTE. Assay standardization and prospective validation are required before D-dimer testing can be recommended as a guide to duration of anticoagulant therapy.

**Other Factors**

The influence of a number of other factors on the risk of recurrent VTE is summarized in Table 1.

**Risk of Bleeding During Anticoagulant Therapy**

After the first 3 to 6 months of treatment, long-term anticoagulation targeted to an INR of 2.0 to 3.0 is associated with an average rate of major bleeding of \(\approx 2\%\) per year in patients with VTE\(^{64–66}\) (an increase of 2- to 3-fold, or an absolute increase of \(\approx 1\%\) to 1.5% per year).\(^8,35,63,67\) Approximately 10% of major bleeds occurring on long-term anticoagulant therapy for VTE are fatal,\(^68\) yielding a 0.2% annual rate of fatal bleeding in such patients.

The risk of bleeding in individual patients differs, however, according to individual characteristics, such as age, comorbid conditions (eg, previous gastrointestinal bleeding, stroke, chronic renal disease, metastatic malignancy, alcohol-related disease, or diabetes), and use of concomitant antiplatelet therapy.\(^{26,63,66,67,69–73}\) The risk of bleeding is highest soon after starting anticoagulant therapy\(^{66,67,69}\) and is higher still if anticoagulation is difficult to control.\(^{67}\) After the first 6 months of therapy, long-term anticoagulation of patients with unprovoked VTE is associated with an annual risk of major bleeding of \(\approx 1\%\) in patients younger than 65 years old without risk factors for bleeding.\(^{63}\) Randomized trials have demonstrated that computer-assisted warfarin dosing results in better control of anticoagulant therapy than traditional dosing even by experienced medical staff.\(^{74}\) Likewise, a multicomponent intervention that promotes patient education and participation in anticoagulant management provides better anticoagulation control than usual care.\(^{75}\) Importantly, the multicomponent intervention halved the frequency of major bleeding during the first 6 months of anticoagulant therapy.\(^{75}\)

Two prospectively validated prediction rules have been published for assessing individual risk of major bleeding.
during the first 3 months\textsuperscript{70,71} and subsequent anticoagulant therapy.\textsuperscript{70} Hereditary factors, such as polymorphisms of the cytochrome P450 system, may predispose patients to bleeding by increasing sensitivity to VK antagonists.\textsuperscript{76,77}

**Relative Importance of Recurrent VTE or Major Bleeding**

In addition to considering the absolute difference in risk of thrombosis and major bleeding with and without anticoagulant therapy, the consequences of each of these outcomes must be considered. Because most patients with recurrent VTE or major bleeding that is not fatal recover without residua, this discussion focuses on the case fatality rates of each condition.

As noted previously, the likelihood of dying from recurrent VTE depends on whether the recurrence is DVT or PE case fatality rates of these conditions are \(\approx 2\%\) and 15\%, respectively. Initial presentation as PE, rather than DVT, is the only factor, other than an indwelling vena caval filter (a risk factor only for DVT) that influences whether the recurrent event is a PE rather than a DVT.\textsuperscript{32} After \(\geq 3\) months of initial anticoagulant therapy, case fatality rates for recurrent VTE is \(\approx 10\%\) after PE and 5\% after DVT (see above).

The case fatality rate with major bleeding during long-term anticoagulant therapy for VTE is \(\approx 10\%.\textsuperscript{54}\) It is likely higher with major bleeding in patients with previous noncardioembolic stroke because a greater proportion of these bleeds are intracranial (50\% case fatality rate).\textsuperscript{78,79}

**Balancing Reduction in VTE Against Bleeding During Long-Term Anticoagulation**

Comparison of associated case fatality rates suggests that the consequence of a major bleed during long-term anticoagulation is similar to that of recurrent VTE after PE, and approximately twice as severe as the consequences of recurrent VTE after DVT. Therefore, given a risk reduction for recurrent VTE of \(>90\%\) during long-term anticoagulation and a 2\% annual rate of major bleeding on anticoagulant therapy,\textsuperscript{8,22} the annual risk of VTE must exceed 1.5\% after PE and 3\% after DVT to offset fatal bleeding.

**Comparisons of Different Durations of Anticoagulant Therapy**

**Short-Term (4 to 6 Weeks) Versus Conventional (3 to 6 Months) Therapy**

Three large trials have assessed the safety of shortening the duration of oral anticoagulant therapy from 3 to 6 months to 4 to 6 weeks in heterogeneous groups of patients (ie, those with transient or permanent risk factors or unprovoked VTE) generally with first episodes of VTE (Table 2).\textsuperscript{1,3,37} The 3 studies that enrolled patients with proximal DVT or PE found that brief anticoagulation nearly doubled the frequency of recurrent VTE (Table 2).\textsuperscript{1,3} Major bleeding was uncommon during the extended period of anticoagulation in these studies (\(\approx 7\) episodes among 1009 patients during 259 patient-years of additional treatment [2.7\% per year]).\textsuperscript{1,3} The main conclusion was that anticoagulant therapy should not be shortened to 4 to 6 weeks in patients with VTE.

Subgroup analysis in 1 study suggested that isolated calf vein thrombosis provoked by a transient risk factor can be safely treated with only 6 weeks of therapy.\textsuperscript{3} A fourth study, which compared 6 versus 12 weeks of therapy in patients with isolated calf DVT (unprovoked or secondary, diagnosed mainly by ultrasound imaging), found no evidence that abbreviated therapy increased recurrence (relative risk 0.6; 95\% CI, 0.01 to 3.4); in general, the frequency of recurrent VTE with isolated calf DVT was low (\(\approx 2\%\) in the first year).\textsuperscript{37} Based on these findings, shortening the duration of anticoagulation for proximal DVT or PE from 3 to 6 months to 4 to 6 weeks is associated with a substantial increase in the frequency of recurrent VTE without a clinically important reduction in bleeding.

**Anticoagulant Therapy: 6 to 12 Months Versus 3 Months**

Pinede et al compared 3 and 6 months of anticoagulant therapy in patients with a first episode of proximal DVT or PE (unprovoked or secondary) (Table 2).\textsuperscript{37} After 15 months of follow-up, the frequency of recurrent VTE did not differ between the 2 groups (relative risk 0.9 in favor of 3-month group; 95\% CI, 0.5 to 1.6).

Agnelli et al compared stopping anticoagulant therapy at 3 months versus an additional 9 months of treatment after a first episode of unprovoked proximal DVT (Table 2).\textsuperscript{52} By the end of the first year, recurrent VTE was less frequent in the group given extended anticoagulant therapy (3.0\% versus 8.3\%), but this benefit was lost 2 years after stopping anticoagulation (relative risk 1.0; 95\% CI, 0.6 to 1.7).

Agnelli et al also compared extending oral anticoagulation for a first PE from 3 to 6 months in patients with a transient risk factor, and from 3 to 12 months in patients with unprovoked PE (Table 2).\textsuperscript{30} Although recurrent VTE was uncommon with extended anticoagulation, there was no difference in the rate of recurrent VTE after 3 years of follow-up (rate ratio 0.8 in favor of longer therapy; 95\% CI, 0.4 to 1.6). Based on these results, reduction in recurrent VTE achieved by extending anticoagulation for 3 or 9 months after an initial 3 months of treatment is lost if therapy is then stopped.

**Long-Term Versus Conventional Durations of Anticoagulant Therapy**

Three trials compared long-term anticoagulation (target INR ranges of 2.0 to 2.85,\textsuperscript{35} 2.0 to 3.0,\textsuperscript{8} and 1.5 to 2.0\textsuperscript{38}) with stopping therapy in patients with VTE at high risk for recurrence (Table 2). Schulman et al compared 6 months with 4 years of warfarin therapy in patients with a second episode of VTE (Table 2).\textsuperscript{35} Recurrent VTE was markedly reduced by long-term anticoagulation (0.65\% versus 5.2\% per patient-year by intention-to-treat [ITT] analysis) but was associated with a higher rate of major bleeding (2.2\% versus 0.45\% per year). Overall, there was no convincing benefit of long-term anticoagulation in this population.

We compared an additional 2 years of anticoagulant therapy versus placebo in patients with a first episode of unprovoked VTE who had completed 3 months of warfarin therapy (Table 2).\textsuperscript{8} The trial was stopped after an average of
10 months when interim analysis revealed unexpectedly high recurrence rates (27% per patient-year) in patients who discontinued treatment after 3 months. Long-term warfarin therapy resulted in a 95% reduction in risk of recurrent VTE but was associated with more major bleeding (3 episodes [3.8% per patient-year] versus none).8

Ridker et al, in the Prevention of Recurrent Venous Thromboembolism (PREVENT) trial, compared long-term anticoagulation at a lower intensity (INR 1.5 to 2.0) with placebo in patients with unprovoked VTE (distal or proximal DVT or PE) who had completed at least 3 months (median 6.5 months) of initial anticoagulant therapy (INR 2.0 to 3.0) (Table 2).38 The trial was stopped after an average of 2.1 years of follow-up because of a 64% risk reduction for recurrent VTE with extended low-intensity anticoagulation (2.6% versus 7.2% per patient-year according to ITT analysis) and a small increase in the absolute frequency of major bleeding (5 [0.9% per patient-year] versus 2 [0.4% per patient-year] episodes).38 Using a target INR of 1.5 to 2.0, the risk reduction for VTE was ~80% among those who remained on treatment.38

Findings in studies of long-term anticoagulation (INR 2.0 to 3.0) are consistent with a 95% risk reduction for recurrent VTE among patients without cancer who remain using treatment (see next section).3,35,38,63 The benefits of long-term anticoagulation appear to exceed the risks in patients with unprovoked proximal DVT or PE, even after a first episode.

Optimal Intensity of Anticoagulation With VK Antagonists

Hull et al established that acute treatment of VTE (ie, first 3 months) with a target INR of 2.0 to 3.0 was as effective as, but caused less bleeding than, treatment to a target INR of 3.0 to 4.0.80 In patients with VTE and an antiphospholipid antibody, Crowther et al showed that targeting VK antagonist therapy to an INR of 2.5 is as effective as an INR target of 3.5.81

Two trials3.35 that reported no episodes of recurrent VTE among patients using extended-duration anticoagulant therapy (INR 2.0 to 3.0) suggest that lowering the intensity of anticoagulation to a target INR of 1.5 to 2.0 after the first 3 months of treatment might reduce bleeding without loss of

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TABLE 2. Recurrent Venous Thromboembolism in Randomized Trials Comparing Durations and Intensities of Anticoagulant Therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient Population</th>
<th>Follow-Up</th>
<th>Control Treatment</th>
<th>Experimental Treatment</th>
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<tr>
<td></td>
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<td></td>
<td>Recurrent VTE, %</td>
<td>Recurrent VTE, %</td>
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<td>Duration</td>
<td>Duration</td>
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<tr>
<td>BTS 19921</td>
<td>DVT, PE Mixed RF</td>
<td>1 y*</td>
<td>12 wk</td>
<td>4 wk 7.8 (28/358)</td>
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<td>4.0 (n=14/354)</td>
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<tr>
<td>Levine 19952</td>
<td>Prox. DVT Mixed RF</td>
<td>11 mo†</td>
<td>12 wk</td>
<td>12 (12/104)</td>
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<td>6.8 (n=7/103)</td>
<td>1.7</td>
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<tr>
<td>Schulman 19953</td>
<td>First DVT, PE Mixed RF</td>
<td>2 y*</td>
<td>6 mo</td>
<td>18 (80/442)</td>
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<td>9.5 (n=43/456)</td>
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<td>Keanon 19994</td>
<td>First Prox. DVT, PE Unprovoked</td>
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<td>21 (n=17/83)</td>
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<td>5.5 (14/253)</td>
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<tr>
<td>Pinede 200137</td>
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<td>15 mo*</td>
<td>3 mo</td>
<td>6 mo 8.6 (23/269)</td>
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<td>12 wk 3.3 (3/92)</td>
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<td>Agnelli 200138</td>
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<td>16 (n=21/133)</td>
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<td>First PE Unprovoked</td>
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<td>3 mo</td>
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<tr>
<td></td>
<td>First PE Temporary RF</td>
<td>34 mo†</td>
<td>3 mo</td>
<td>6 mo 5.3 (4/75)</td>
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<td>10 (n=7/70)</td>
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<tr>
<td>Ridker 200334</td>
<td>DVT, PE Unprovoked</td>
<td>2.1 y†</td>
<td>INR 2–3 ≥3 mo, then stop</td>
<td>5.5 (14/255)</td>
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<td></td>
<td></td>
<td></td>
<td>15 (n=37/253)</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>Prox. DVT, PE Unprovoked</td>
<td>2.4 y†</td>
<td>INR 2–3 ≥3 mo, then indefinite INR 1.5–1.9</td>
<td>4.3 (16/369)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.6 (n=6/369)</td>
<td>2.7</td>
</tr>
</tbody>
</table>

DVT includes isolated calf DVT.
Mixed RF includes temporary risk factors, unprovoked, with or without cancer.
Unprovoked indicates no temporary risk factors, with or without nonmetastatic cancer.
* Randomization at diagnosis of VTE.
†Randomization after initial period of treatment (INR 2–3).
Relative risk determined by experimental vs. control, calculated from the values in the table (not based on annualized rates of recurrent VTE reported by authors).
efficacy. This hypothesis was tested in the Extended Low-intensity Anticoagulation for Unprovoked Thromboembolism (ELATE) study, a double-blind comparison of a target INR of 1.5 to 1.9 with a 2.0 to 3.0 INR for long-term treatment of unprovoked VTE (Table 2).63 Contrary to expectations, the lower-intensity anticoagulation was less effective at preventing recurrent VTE (1.9% versus 0.7% per patient-year by ITT analysis; hazard ratio 2.8 [95% CI, 1.1 to 7.0]) and associated with the same frequency of major bleeding as conventional intensity therapy (1.1% versus 0.9% per patient-year; hazard ratio 1.2 [95% CI, 0.4 to 3.0]).61 Based on these findings, a target INR of 2.0 to 3.0 appears optimal for both acute and long-term treatment of VTE.

Alternatives to VK Antagonists

**Unfractionated and LMWH**

Various subcutaneous heparin regimens have been used instead of VK antagonists to treat VTE for 3 or 6 months.5,82–96 Of these studies, the 13 most recent compared widely differing LMWH regimens with VK antagonists (INR 2.0 to 3.0)5,82–96 or, in 1 small study, unfractionated heparin.85 Three months of low-dose unfractionated heparin (5000 U twice daily) was inadequate treatment for proximal DVT.92,93 Two studies not included in this analysis suggest that prolonged treatment with LMWH is preferable to VK antagonists to treat VTE for 3 or 6 months.84,85 or LMWH,5,85–96 in doses that varied from one-third5,86,89,90 to full91–94,96 therapeutic doses were effective. A meta-analysis of 7 of these studies (total of 1379 patients)5,86,88–91,93 found 3 months of LMWH therapy associated with less recurrent VTE (odds ratio 0.7; 95% CI, 0.4 to 1.1) and less major bleeding (odds ratio 0.4; 95% CI, 0.2 to 1.1) than treatment with a VK antagonist for 3 months. Compared with VK antagonists, between-study differences in mean daily dose of LMWH had little effect on efficacy but did influence bleeding (odds ratio of ≈0.2 with ≈4000 IU/d to ≈0.7 with 12 000 IU/d for major bleeding relative to the VK antagonist groups).97

Two studies not included in this analysis suggest that prolonged treatment with LMWH is preferable to VK antagonists in patients with active cancer.92,96 In the larger of these 2 studies (700 patients), daily injections of LMWH (dalteparin 200 IU/kg for the first month and ≈150 IU/kg for 5 months) was associated with half the frequency of recurrent VTE during 6 months of treatment (9% versus 17% with VK antagonists) with no significant increase in major bleeding (6% versus 4%).96

**Oral Direct Thrombin Inhibitors**

After 6 months of initial treatment with VK antagonists, the oral direct thrombin inhibitor ximelagatran (24 mg twice daily) prevented recurrent VTE by 84% without an apparent increase in bleeding (see Weitz article in this issue).36

**Nonanticoagulant Treatment**

Wearing below-knee graduated compression stockings for 2 years after acute DVT halves the frequency of the post-thrombotic syndrome98 but does not influence the risk of recurrent thrombosis.98

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**TABLE 3. Guidelines for Duration of Anticoagulant Therapy for VTE**

<table>
<thead>
<tr>
<th>Risk Factor for VTE</th>
<th>Duration of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major transient risk factor†</td>
<td>3 mo</td>
</tr>
<tr>
<td>Minor risk factor‡</td>
<td>6 mo‡</td>
</tr>
<tr>
<td>Unprovoked</td>
<td>Indefinite‡</td>
</tr>
<tr>
<td>Isolated calf DVT; anticoagulant therapy a burden; or moderate to high risk of bleeding§</td>
<td>6 mo</td>
</tr>
<tr>
<td>Uncontrolled malignancy</td>
<td>Indefinite (preferably with LMWH)‡</td>
</tr>
</tbody>
</table>

Uncontrolled malignancy and also:

- A very high risk of bleeding§; or an additional reversible provoking risk factor
- Consider 6 mo rather than indefinite therapy

* Major transient risk factors include within 3 months of surgery with general anesthesia; plaster cast immobilization of a leg; hospitalization.
†Minor transient risk factors include within 6 weeks of estrogen therapy; prolonged air travel (ie, >10 hours); pregnancy; less marked leg injuries; or immobilization. Six months of treatment reflects the author’s preference but 3 months is also reasonable.
‡Decision should be reviewed annually to consider new developments in antithrombotic therapy or change in the patient’s risk of bleeding. Additional factors favoring indefinite therapy include PE vs proximal DVT at presentation; >1 episode of unprovoked VTE; antiphospholipid antibodies; protein C, protein S, or antithrombin deficiency; homozygous factor V Leiden or G20210A prothrombin mutation; combined thrombophilic abnormalities; inferior vena caval filter; and patient preference.
§Risk factors for bleeding include age 65 years or older; previous stroke; previous bleeding (eg, gastrointestinal); active peptic ulcer disease; renal impairment; anemia; thrombocytopenia; liver disease; diabetes mellitus; use of antiplatelet therapy; poor patient compliance; poor control of anticoagulation; and structural lesion (including tumor) expected to be associated with bleeding. One or 2 risk factors suggests moderate risk and 3 or more risk factors suggest high risk of bleeding.

**Recommended Durations of Anticoagulation in Individual Patients**

Based largely on the preceding analysis of risk factors for recurrent thrombosis and bleeding, and on studies comparing different durations and intensities of anticoagulation, Table 3 outlines an approach to anticoagulation of individual patients with VTE. Because the presence of a reversible risk factor for VTE, lack of a provoking factor, or cancer at the time of thrombosis has the greatest prognostic influence on recurrence, this assessment carries the most weight.

For patients with VTE associated with a major transient risk factor such as recent surgery, stopping anticoagulant therapy after 3 months of treatment is associated with a subsequent risk of recurrent VTE of ≈3% in the first year and ≈10% over 5 years.1,2,5,6,10,30,36–38 This rate is not high enough to justify treatment for longer than 3 months.

For patients with unprovoked VTE, stopping anticoagulant therapy after 6 or more months of treatment is associated with a subsequent risk of recurrent VTE of ≈10% in the first year and ≈30% over 5 years.3,6,37,52 justifying long-term anticoagulation for the majority of such patients. The argument
favoring long-term therapy is stronger if the unprovoked episode was PE; if a second or subsequent episode of unprovoked VTE occurs; or if an antiphospholipid antibody, homozygous factor V Leiden mutation, deficiency of antithrombin, protein C or S, or combined heterozygous state for factor V Leiden and the prothrombin gene mutation is present. Because there was a very high rate of recurrence when treatment was interrupted after 3 months in patients with a first unprovoked VTE in our own study,5 we avoid stopping treatment before 6 months in this situation. Patients with active cancer should generally maintain long-term anticoagulant therapy (LMWH or VK antagonists) because the risk of recurrent VTE is >10% within 1 year of stopping treatment.

Patients who do not clearly fall into one or another of these 3 categories have a risk of recurrence higher than that of patients with a major reversible risk factor but lower than those in patients with unprovoked VTE after anticoagulant therapy. I favor treating such patients for 6 months, although 3 months may be adequate.

When oral anticoagulant therapy is relatively contraindicated by a high risk of bleeding because of risk factors or lack of access to appropriate anticoagulant monitoring, the duration of anticoagulation for unprovoked VTE may be shortened to 3 to 6 months. This does not apply to extended treatment with LMWH in patients with malignancy. Annual review is recommended for patients using long-term therapy to ensure that the benefits continue to outweigh the risks.

References
Long-Term Management of Patients After Venous Thromboembolism

Clive Kearon

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