Prevention of Recurrent Idiopathic Venous Thromboembolism

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Abstract—Idiopathic venous thromboembolism (VTE), unassociated with surgery or trauma, is a chronic illness that warrants the implementation of strategies to prevent recurrence over a lifetime. Clinical trials show that the benefit associated with extended anticoagulation therapy ≤ 1 year in patients with idiopathic VTE is not maintained over the long term once treatment is discontinued. Controlled trials have established the efficacy of indefinite-duration anticoagulation, even if the therapy used is a novel agent that is not a coumarin derivative. The PREVENT, ELATE, and THRIVE III trials demonstrate that a strategy of long-term anticoagulation in patients with idiopathic VTE, including those with isolated calf deep vein thrombosis, is safe and effective. This successful strategy appears beneficial across all subgroups, regardless of the presence of an identified thrombophilic state. These include both young and old patients of both sexes, those with factor V Leiden or the prothrombin gene mutation, and those with first-time or recurrent VTE. Thus, the default strategy for idiopathic VTE should be universal anticoagulation unless contraindicated. Implementing this proven approach on a population basis would enable prevention of VTE recurrence with minimal individualization of treatment. Because lifelong therapy can exact a psychological and medical cost on the patient as well as the health care provider, future research should be directed to risk stratification of those most susceptible to recurrence. Avenues of investigation currently being evaluated include measurement of D-dimer levels, examination of residual venous thrombosis on ultrasound, and application of risk nomograms. (Circulation. 2004;110[suppl IV]:IV-20–IV-24.)

Key Words: idiopathic venous thromboembolism  ■  deep vein thrombosis  ■  pulmonary embolism
■ warfarin  ■ ximelagatran

During the past decade, the concept of venous thromboembolism (VTE) has undergone a radical change. VTE was once conceived of as an acute illness that would respond successfully to a finite duration of anticoagulation, ranging from 6 weeks to 1 year. The short 6-week course of treatment was reserved for patients with anatomically small clots, such as isolated popliteal or calf deep vein thrombosis (DVT). In contrast, the 1-year treatment protocol was directed to patients with massive iliofemoral DVT, large pulmonary embolism (PE), or recurrent VTE. It was unimaginable that the first occurrence of VTE would mandate a course of anticoagulation therapy of indefinite duration.

It is now known that this paradigm is flawed. Anticoagulation therapy does not, in fact, “treat” established DVT or PE; rather, its goal is secondary prevention. (Primary prevention, the subject of the rest of this monograph, is defined as preventing the occurrence of an initial VTE episode.) Treatment of acute VTE, in contrast to secondary prevention, requires strategies that dissolve or remove the clot, such as thrombolysis or embolecotomy.

Follow-up of patients for prolonged periods after an initial DVT or PE has revealed a startling fact: VTE often is a chronic illness requiring lifelong prevention strategies. This is especially true for idiopathic VTE, defined broadly as DVT or PE that is not associated with surgery or trauma. Patients who develop VTE in the setting of surgery or trauma usually do not require anticoagulation of an indefinite duration. Identifying patients with specific thrombophilias is much less helpful in determining who is likely to experience a recurrent VTE than previously supposed, with the exception of antiphospholipid antibody syndrome.

Cardiovascular specialists should change their perspective about patients who have had VTE. Everything possible must be done to prevent recurrent VTE as long as the benefits of the strategy used, usually indefinite-duration anticoagulation, outweigh the risks. The transition to this new way of thinking should not be difficult, as such specialists are used to prescribing medication for indefinite periods of time; examples include the long-term use of concomitant aspirin, statins, ACE inhibitors, and beta blockers in patients with prior myocardial infarction.

This review outlines the rationale for updating the approach for patients with established VTE to one in which the default strategy for idiopathic VTE is universal anticoagulation unless contraindicated. Data from registries and clinical trials supporting this new concept are presented.

In contrast, some vascular specialists propose that, rather than population-based use of indefinite-duration anticoagula-
tion, the ideal protocol for managing idiopathic VTE is individualized assessment of a patient’s risk for recurrence. Controversy also exists over the optimal anticoagulant to be used as well as the appropriate dose intensity for warfarin in the idiopathic DVT setting.

The “proof of concept” for anticoagulant therapy of indefinite duration requires the implementation of prospective cohort studies lasting decades. Thus, currently, support for this new approach must be gleaned from studies evaluating the natural history of idiopathic VTE after anticoagulation therapy has been discontinued.

Registry Data
Prandoni and colleagues conducted a prospective cohort study at the University of Padua, Italy, to determine the clinical course in patients during the 8 years after their first episode of symptomatic DVT. An astoundingly high rate of recurrence was found in 355 consecutively followed patients: 18% after 2 years, 25% after 5 years, and 30% after 8 years. Recurrence rates were highest in patients who had not undergone surgery or experienced trauma.

A registry of patients in Olmsted County, Minnesota, the catchment area of the Mayo Clinic, followed 1719 patients with an initial DVT or PE episode during the 25-year period from 1966 through 1990, with 10 198 person-years of follow-up. The recurrence rate after 1 year of follow-up was 13%; by 10 years of follow-up, the cumulative recurrence rate was 30%, remarkably similar to the recurrence rate found in Padua.

In Göteborg, Sweden, 738 symptomatic DVT patients were followed for 4 to 9 years. The 5-year cumulative incidence of recurrent VTE was 22% after a first episode of DVT and 28% after a second episode. The subgroup of patients with postoperative DVT had the lowest risk of recurrent VTE.

The main limitation of these registries is that the initial treatment, the duration of anticoagulation, and the intensity of anticoagulation were not randomized. Their chief strength is that patient follow-up rates were high.

Randomized Trials: Extending Anticoagulation to 1 Year
Because of the outcome of a randomized Swedish trial conducted more than a decade ago, 6 months became the standard duration of anticoagulation for most patients with VTE. In that trial, which compared 6 weeks with 6 months of warfarin therapy in 897 patients who had had a first episode of DVT, the 6-month course of anticoagulation halved the recurrence rate; after 2 years of follow-up, the recurrence rate was 18% in the 6-week group and 9.5% in the 6-month group.

This same investigative approach was used in trials of idiopathic DVT and PE. In an Italian trial, 3 months of anticoagulation with warfarin was compared with 12 months of the same agent in 267 patients with idiopathic DVT. At the time of 1-year follow-up, there was a marked difference between recurrence rates in the 2 groups: 8.3% in the 3-month group compared with 0.7% in the 12-month group. However, after 3 years of follow-up, 15.8% in the 3-month group had recurrent DVT compared with 15.7% in the 12-month group.

Thus, the clinical benefit associated with extending the duration of anticoagulant therapy to 1 year was not maintained after anticoagulation was discontinued. In this trial, 3% of the 12-month group had nonfatal major bleeding during the last 9 months of treatment.

In another Italian trial, 3 to 6 months of anticoagulation therapy was compared with 12 months of therapy in 326 patients who had had a first episode of PE. Only 1 patient had a recurrent VTE while receiving anticoagulation. However, recurrence rates soared after discontinuation of anticoagulation. After 3 years of follow-up, the recurrence rates were similar in both groups of patients who received time-limited anticoagulation: 11.2% in the group receiving 3 to 6 months of anticoagulation compared with 9.1% in the 12-month group. Among the 181 patients in the trial with idiopathic PE, the recurrence rates also were virtually identical after the 3-year follow-up: 11 of 91 who received 6 months of anticoagulation therapy experienced recurrence compared with 11 of 90 who received 12 months of treatment.

These trials showed that extending anticoagulation for 1 year did not eliminate long-term recurrence in patients with idiopathic VTE. Furthermore, the strategy of indefinite-duration anticoagulation appeared hazardous because of increased bleeding complications. For example, in a Swedish trial of patients with recurrent VTE, anticoagulation therapy of indefinite duration averted 0.43 episodes of recurrent thromboembolism per month per 100 patients, at a cost of 0.20 major hemorrhages per month.

A Canadian trial planned to randomize patients with idiopathic VTE to 3 versus 24 months of anticoagulation therapy with warfarin. After 162 patients had been enrolled and followed for an average of 10 months, the trial was terminated because of extreme beneficial results obtained in the patients assigned to 24 months of treatment. The recurrence rate was 27% in patients receiving 3 months of therapy compared with 1.3% in those assigned to long-term treatment. However, bleeding complications in the long-term group clouded the assessment of benefit. Of those patients assigned to long-term warfarin treatment, 3 of the 79 experienced major bleeding complications during the 10-month follow-up period. Thus, the optimal management of patients with idiopathic VTE had not yet been resolved because of the uncertain balance between decreased clotting and increased major bleeding in patients receiving extended-duration anticoagulation.

Randomized Trials: Extending Anticoagulation More Than 1 Year
The PREVENT (Prevention of REcurrent VENous Thromboembolism) trial used a double-blind design to test low-intensity warfarin—target international normalized ratio (INR) of 1.5 to 2.0—against placebo in 508 patients with idiopathic PE or DVT who had previously completed an average of 6 months of standard anticoagulation. As in the earlier study, the trial was terminated after 2 years of therapy because of an extreme beneficial effect in the warfarin group (Figure 1). Warfarin reduced the frequency of recurrent VTE events by two thirds: 7.2 per 100 patient-years in the control
group compared with 2.6 per 100 patient-years in the warfarin group. All subgroups benefited, including both sexes, patients with factor V Leiden or the prothrombin gene mutation, first-time and recurrent VTE enrollees, and both young and old patients, with ages ranging from 30 to 89 years. Patients randomized into the trial despite a period of ≤2 years without warfarin (after completion of standard 6 months of anticoagulation for VTE) benefited, as well as patients who were randomized as soon as they completed an initial standard 6-month course of anticoagulation.

PREVENT provided a strategy that maximized the safety of anticoagulation. With low-intensity warfarin, 5 of 255 patients had major bleeding during the 2-year study, including gastrointestinal (n=3), genitourinary (n=1), and hematoma (n=1) episodes. Only 1 patient assigned to warfarin required transfusion; this patient was actually receiving full-intensity anticoagulation rather than low-intensity anticoagulation, in violation of the protocol. In the placebo group, 2 of 253 patients had major hemorrhage, including 1 patient who experienced a fatal stroke.9 In the Canadian ELATE (Extended Low-intensity Anticoagulation for Thrombo-Embolism) study of patients with idiopathic VTE, low-intensity warfarin, target INR of 1.5 to 1.9, was compared with standard-intensity warfarin, target INR of 2.0 to 3.0.10 Overall, 738 patients were enrolled: 369 to low-intensity and 369 to standard-intensity warfarin. Patients were followed for an average of 2.4 years. The recurrence rate was 1.9 per 100 patient-years in the low-intensity group compared with 0.7 per 100 patient-years in the standard-intensity group (Figure 2). The likelihood of recurrence was 2.8 times higher with low-intensity warfarin compared with standard-intensity warfarin.

The most remarkable finding of ELATE was the low rate of bleeding complications in patients receiving standard-intensity anticoagulation: 0.9 per 100 person-years, much lower than the same group’s major bleeding episode rate of 3.8 per 100 person-years in their prior trial of idiopathic VTE.8 In ELATE, there was no significant difference in major hemorrhage between patients assigned to low-intensity versus standard-intensity warfarin.

An international trial, THRIVE (THRombin Inhibitor in VEnous thromboembolism) III, randomized 1233 patients with idiopathic VTE who had received 6 months of standard warfarin therapy to an oral direct thrombin inhibitor (ximelagatran 24 mg twice daily) versus placebo for 18 months.11 The ximelagatran group exhibited an 84% decrease in recurrent events compared with placebo, from 12.6% to 2.8%, with no increase in major bleeding (Figure 3). This trial provided "proof of principle" that idiopathic VTE is a chronic illness that can be controlled with extended-duration anticoagulation, even if the anticoagulant is a novel agent that is not a coumarin derivative.

**Predictors of Recurrence**

The PREVENT, ELATE, and THRIVE III trials demonstrate that a strategy of long-term anticoagulation in patients with idiopathic VTE, including patients with isolated calf DVT, is safe and effective. This successful strategy appears beneficial.
across all subgroups, regardless of the presence of an identified thrombophilic state. Implementing this proven approach on a population basis would enable prevention of VTE recurrence with minimal individualization of treatment.

An important caveat is that anticoagulation treatment of indefinite duration, possibly for a lifetime, is a major undertaking for both the patient and the healthcare provider, which can exert a profound emotional, social, and medical toll on quality of life. Such treatment necessitates restrictions on physical activity as well as blood test monitoring. There also is the psychological burden of living with a chronic illness requiring daily medication. For these reasons, research persists to unravel predictors of recurrence, so that patients at the highest risk of recurrence can be targeted for lifelong therapy while low-risk patients may be spared this burden.

No precise method for predicting which individuals will have recurrence in the absence of anticoagulation has yet emerged. Nevertheless, several avenues of investigation show promise.

One approach is to measure the D-dimer levels after completion of a standard course of anticoagulation. D-dimer elevations indicate high cross-linked fibrin turnover. One study found that the negative predictive value of a normal D-dimer was 95.6% in a cohort of 396 patients with PE or DVT. In a more extensive cohort of 599 patients with VTE, 37% of patients had elevated D-dimer levels 1 month after completing anticoagulation. The negative predictive value of the D-dimer obtained 1 month after withdrawal of oral anticoagulation was 92.9%. In patients who had elevated D-dimer levels 1 month after cessation of anticoagulation, the likelihood of recurrence of VTE was 2.0 times higher among the entire cohort and 2.4 times higher in the subgroup with idiopathic VTE.

Another approach for predicting recurrent VTE examines residual venous thrombosis on ultrasound. Prandoni and colleagues investigated a cohort of 313 consecutive symptomatic outpatients with proximal DVT, each of whom received a 3-month course of anticoagulation. They received follow-up ultrasounds every 6 months for 3 years and clinical follow-up for as long as 6 years. Residual venous thrombosis on ultrasound was a risk factor for recurrent VTE; of 58 recurrent episodes, 41 occurred among patients with residual venous thrombosis (hazard ratio 2.4 for patients with persistent residual thrombosis).

The classic predictor of recurrent VTE has been heritable thrombophilia. However, thrombophilia did not aid in predicting who would respond to or fail long-term anticoagulation in the PREVENT, ELATE, or THRIVE III trials. In a cohort of 570 first-time VTE patients from Cambridge, England, recurrence rates were not related to the presence of thrombophilia. The ultimate approach to individualized risk assessment for recurrent VTE can be formulated with a decision model. To construct this model, estimates are required for recurrence risk without anticoagulation and bleeding risk with anticoagulation. Comorbidities must be factored into the equation, including thrombophilia, age, and the presence of cancer. Other variables include whether the VTE is itself a first episode or a recurrence and whether it is idiopathic. A formula for the optimal duration of anticoagulation, expressed as time (T) in months, can then be derived:

\[
T = -\frac{1}{12} \ln \left( \frac{0.39 \times (RR_{\text{bleeding}}/RR_{\text{recurrence}})}{1/12} \right)
\]

A nomogram can simplify the calculations, but the process remains cumbersome, depends on estimates of bleeding risk and recurrent DVT risk, and has not been validated.

### Table 1. Optimal Duration and Intensity of Anticoagulation in VTE

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Regimens Tested</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Swedish VTE³ (n=897)</td>
<td>Warfarin for 6 weeks vs 6 months</td>
<td>Recurrence rate was halved in 6-month group.</td>
</tr>
<tr>
<td>Italian DVT５ (n=267)</td>
<td>Warfarin for 3 months vs 12 months</td>
<td>Initial decreased recurrence rate in 12-month group was not maintained after warfarin was discontinued; 3% of 12-month group had nonfatal major bleeding during extra 9 months of anticoagulation.</td>
</tr>
<tr>
<td>Italian PE³ (n=326)</td>
<td>Warfarin for 3–6 months vs 12 months</td>
<td>Initial decreased recurrence rate in 12-month group was not maintained after warfarin was discontinued.</td>
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<tr>
<td>Canadian VTE⁶ (n=162)</td>
<td>Warfarin, INR 2.0–3.0, vs placebo, after initial 3 months of anticoagulation; 10-month study</td>
<td>Warfarin group had 95% reduction in recurrence, but borderline statistically increased major bleeding.</td>
</tr>
<tr>
<td>PREVENT³ (n=508)</td>
<td>Warfarin, INR 1.5–2.0, vs placebo, after initial average of 6 months of anticoagulation; 2-year study</td>
<td>Warfarin reduced recurrence rate by two thirds without increased major bleeding.</td>
</tr>
<tr>
<td>ELATE¹⁰ (n=738)</td>
<td>Warfarin, INR 1.5–1.9, vs warfarin, INR 2.0–3.0</td>
<td>Warfarin, INR 2.0–3.0, had fewer recurrences and no increased bleeding compared with warfarin, INR 1.5–1.9.</td>
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<tr>
<td>THRIVE III¹¹(n=1,233)</td>
<td>Ximelagatran 24 mg twice daily for 18 months vs placebo, after initial 6 months of anticoagulation</td>
<td>Ximelagatran group had 85% fewer recurrences without increased major bleeding.</td>
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Conclusion
Patients with idiopathic DVT or PE have a high risk of experiencing a recurrent event. Rigorous clinical trials have established indefinite-duration anticoagulation therapy as an effective and safe strategy for most of these patients (Table). Future trials will follow cohorts receiving lifelong anticoagulation in an attempt to provide further risk stratification to identify those patients who are most susceptible to recurrent VTE.

References
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