Case Presentation: A 68-year-old woman with a history of hypertension, hyperlipidemia, and diverticulitis presents to your office for follow-up care. Three months ago, she developed 3 days of pain and swelling in her right calf and thigh. Lower-extremity venous ultrasonography demonstrated a deep vein thrombosis in the right femoral vein. No identifiable cause was noted. She was started on therapeutic enoxaparin as a bridge to warfarin anticoagulation for idiopathic venous thromboembolism (VTE). Since discharge, her international normalized ratio (INR) has been maintained between 2 and 3. She has no history of previous bleeding or thromboembolic events. She wants to know how long to continue anticoagulation and what she can do to minimize her risk of recurrent VTE.

The Clinical Problem
VTE, including deep vein thrombosis and pulmonary embolism, is a major public health concern in the United States, with an annual incidence of 117 cases per 100,000 and ≈ 300,000 to 600,000 new cases diagnosed each year.1 Therapeutic anticoagulation is indicated as initial therapy for VTE. Patients who develop VTE are susceptible to recurrent events, with a risk that can exceed 20% to 25% at 5 years. Among patients receiving long-term anticoagulation, the risk of major bleeding can approach 3%/y in clinical trials and may be higher in clinical practice. Over time, risks of bleeding can attenuate the benefit of extended anticoagulation to prevent recurrent thrombosis. Therefore, the selection and duration of anticoagulation for secondary prevention of VTE must be carefully considered.

Anticoagulant Selection and Duration of Therapy: What Is the Evidence?
Traditional therapy for a VTE typically includes heparin or a low-molecular-weight heparin as a bridge to oral therapy with a vitamin K antagonist (VKA). Novel oral anticoagulants are effective alternatives. Recent data suggest that rivaroxaban and apixaban, both factor Xa inhibitors, and dabigatran, a direct thrombin inhibitor, as initial anticoagulation agents are non-inferior to warfarin in preventing recurrent VTE.2

The optimal duration of anticoagulation for the initial treatment of first VTE remains uncertain. In the Duration of Anticoagulation trial, 6 months of therapeutic anticoagulation with a VKA substantially reduced VTE recurrence rates compared with 6 weeks of treatment.3 A randomized trial comparing 3- and 6-month courses of...
VKA anticoagulation for first proximal deep vein thrombosis or pulmonary embolism and 6- and 12-week courses for isolated calf deep vein thrombosis demonstrated that shorter durations of anticoagulation yield equivalent rates of recurrence, with no differences in bleeding. Based on these data, guidelines recommend a minimum of 3 months of therapeutic anticoagulation after a first episode of VTE.5-7

**Vitamin K Antagonist**

Longer durations of VKA anticoagulation have been evaluated to reduce rates of VTE recurrence (Table 1).6-15 Kearon et al4 randomized 162 patients who completed 3 months of anticoagulation for first VTE to continued warfarin therapy (target INR, 2–3) or placebo for an additional 24 months. Although rates of recurrent VTE were significantly lower in the warfarin arm (1.3%/y versus 27.4%/y; P<0.001), with a number needed to treat of 4, there were trends toward increased major bleeding (3.8%/y versus 0.0%/y; P=0.09) and significant increases in total bleeding events (11.5%/y versus 1.4%/y; P=0.03), with a number needed to harm of 10. The Warfarin Optimal Duration Italian Trial9 randomized patients with a proximal deep vein thrombosis who completed 3 months of warfarin to discontinue anticoagulation or to continue therapy for 9 additional months. Although there were significantly fewer recurrent VTE events in the warfarin arm at 9 months (0.7% versus 8.3%; P=0.003), clinical benefits achieved during extended anticoagulation were not maintained after discontinuation of therapy, and rates of recurrent VTE were similar in both arms by the end of the 24-month trial.16

In a study of patients with pulmonary emboli, no reduction in rates of recurrent VTE was observed with 6 or 12 months of extended anticoagulation at the 34-month follow-up, with nearly all recurrences occurring after the cessation of VKA therapy.17

In light of bleeding risks with full-dose VKA, the Prevention of Recurrent Venous Thromboembolism Trial (PREVENT) randomized patients with idiopathic VTE who completed 6.5 months of therapeutic anticoagulation to low-intensity warfarin (INR, 1.5–2.0) or placebo. There was a significantly lower rate of recurrent VTE in the low-intensity warfarin group (2.6%/y versus 7.2%/y; P<0.001) with no difference in the annual rates of major bleeding (0.9%/y versus 0.4%/y; P=0.25) or death (0.7%/y versus 1.4%/y; P=0.26) with a mean follow-up of 2.1 years.9 In the Extended Low-Intensity Anticoagulation for Thromboembolism (ELATE) trial, 738 patients who completed at least 3 months of initial anticoagulation for unprovoked VTE were randomized to either ongoing low-intensity warfarin (target INR, 1.5–1.9) or conventional warfarin therapy (target INR, 2.0–3.0). Low-intensity therapy was associated with a significantly higher rate of recurrent VTE (1.9%/y versus 0.7%/y; P=0.03) with no difference in the frequency of major bleeding (1.1%/y versus 0.9%/y; P=0.76) or death (1.9%/y versus 0.9%/y; P=0.09) between the 2 groups.10 Therefore, in ELATE, low-intensity VKA therapy provided suboptimal reduction of recurrent VTE compared with therapeutic VKA with no safety advantage.

**Novel Oral Anticoagulants**

Novel oral anticoagulants may offer efficacy comparable to that of VKA anticoagulation with superior bleeding profiles over the course of extended treatment. To date, only the direct thrombin inhibitor dabigatran has been directly compared with warfarin [Secondary Prevention of Venous Thrombo Embolism (VTE) (RE-MEDY)] and placebo [Twice-daily Oral Direct Thrombin Inhibitor Dabigatran Etxilate in the Long Term Prevention of Recurrent Symptomatic VTE (RE-SONATE)] in randomized trials of extended durations of treatment; rivaroxaban and apixaban were studied only in placebo-controlled trials.13 In RE-MEDY, patients who completed 3 to 12 months of anticoagulation for VTE were randomized to either ongoing treatment with dabigatran (at a fixed dose of 150 mg twice daily) or warfarin (with a target INR of 2.0–3.0) for up to 36 months. Dabigatran was noninferior to warfarin (hazard ratio [HR], 1.44; 95% confidence interval, 0.78–2.64) in the prevention of recurrent or fatal VTE. Although dabigatran was associated with significantly less clinically relevant bleeding (5.6% versus 10.2%; P<0.001), a higher incidence of acute coronary events was observed in the dabigatran group (0.9% versus 0.2%; P=0.02). However, a recent observational cohort study of 134410 Medicare beneficiaries identified similar rates of myocardial infarction associated with dabigatran and warfarin.18 RE-SONATE, a placebo-controlled study, randomized patients who completed initial anticoagulation for VTE to either fixed-dose dabigatran or placebo for 6 months. Extended dabigatran therapy resulted in significantly fewer recurrent VTE events, with a number needed to treat of 19 (0.4% versus 5.6%; P<0.001), and more major or clinically relevant nonmajor bleeding, with a number needed to harm of 29 (5.3% versus 1.8%; P<0.001).19

Apixaban after the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis with First-Line Therapy-Extended Treatment (AMPLIFY-EXT) randomized patients with VTE who completed 6 to 12 months of anticoagulation to either 2.5 or 5 mg apixaban twice daily or placebo for 12 additional months. Both doses of apixaban were associated with a significantly reduced rate of VTE or VTE-related death (1.7% versus 8.8% for placebo). Remarkably, clinically relevant bleeding was not significantly more common in patients randomized to either dose of apixaban compared with placebo.11

The Once-Daily Oral Direct Factor Xa Inhibitor Rivaroxaban in the Long-Term Prevention of Recurrent Symptomatic Venous Thromboembolism in Patients With Symptomatic Deep-Vein Thrombosis or Pulmonary Embolism: The EINSTEIN-Extension Study (EINSTEIN-EXT) evaluated 6 or 12 months of rivaroxaban 20 mg daily or placebo in patients who completed 3,
6, or 12 months of initial anticoagulation for VTE. Symptomatic, recurrent VTE was significantly lower in the rivaroxaban group (1.3% versus 7.1%; P<0.001); bleeding was more common (6.0% versus 1.2%; P<0.001); and there was no impact on all-cause mortality.12

**Antiplatelet Therapy**

Antiplatelet therapy with aspirin may reduce the risk of recurrence after unprovoked VTE. The Aspirin for the Prevention of Recurrent Venous Thromboembolism (the Warfarin and Aspirin [WARFASA]) trial randomly assigned 403 patients who completed 6 to 18 months of oral anticoagulation for unprovoked VTE to aspirin 100 mg daily or placebo for up to 4 years. Aspirin did not significantly reduce the rate of VTE (4.8%/y versus 6.5%/y; P=0.09) but reduced the composite end point of recurrent VTE, myocardial infarction, stroke, major bleeding, or death (HR, 0.67; 95% confidence interval, 0.49–0.91) with no significant increase in bleeding (1.1%/y versus 0.6%/y; P=0.22).15 A pooled analysis of WARFASA and ASPIRE demonstrated that aspirin is associated with a significant reduction in VTE (HR, 0.68; P=0.007) and major vascular events.
(HR, 0.66; P=0.002) with a numerically higher rate of clinically relevant bleeding that was not statistically significant (HR, 1.47; P=0.31). Aspirin is a compelling therapy in light of its low cost, ease of administration, safety in renal insufficiency, excellent safety profile, and arterial cardiovascular event reduction. Although not as effective as anticoagulation for the secondary prevention of VTE, prolonged aspirin therapy may be considered for patients at low risk for recurrence or those with a significant risk of bleeding on full-dose anticoagulation.

Areas of Uncertainty
Despite the benefits of long-term anticoagulation and data from recent VTE secondary prevention trials, there is no consensus on the preferred agent(s) to reduce rates of VTE recurrence and to minimize bleeding (Table 1). Additional head-to-head comparisons of aspirin and other novel oral anticoagulants with warfarin are necessary.

Alternative approaches to reducing VTE rates have also been explored. In a large randomized trial of rosuvastatin in otherwise healthy adults with an elevated C-reactive protein, statin therapy significantly decreased the risk of first symptomatic VTE. Confirmatory studies and trials of secondary prevention in patients at risk for recurrent VTE are warranted.

How Can I Identify Patients at High Risk for VTE Recurrence?
The optimal duration of anticoagulation after VTE remains uncertain, especially because patients with the greatest propensity for recurrent thromboembolic events and the strongest indications for extended anticoagulation are frequently excluded from clinical trials.
Subjects at highest risk of recurrent VTE have the greatest potential benefit (Figure), and the duration of treatment should be individualized and guided by risk of VTE recurrence. Risks of recurrent VTE are complex and multifactorial (Table 2). VTE recurrences are 2-fold higher in men, 3-fold higher after a pulmonary embolism or proximal lower-extremity thrombosis, and 2-fold higher after an idiopathic VTE in the absence of a transient risk factor (eg, surgery, hospitalization for acute medical illness, trauma, oral contraceptive use, and pregnancy). Patients with VTE and malignancy represent a particularly high-risk subgroup. No consensus has been reached on the significance of hereditary thrombophilia on recurrent VTE. Among patients who complete at least 3 months of anticoagulant therapy for first idiopathic VTE, positive D-dimers or residual thrombus on ultrasonography is associated with higher annual risks for recurrence. Strategies of extended anticoagulation for patients with residual thrombus on ultrasonography or abnormal D-dimers after initial anticoagulation yield reductions in recurrent VTE events.

Clinical prediction rules may estimate risks of VTE recurrence after an initial course of anticoagulation and help guide the duration and intensity of ongoing therapy. Nonetheless, their use has not been prospectively validated or formally incorporated into guideline recommendations.

VTE recurrence risks must be weighed against bleeding risks when deciding on the type and duration of anticoagulation. Bleeding risk models have been developed to identify patients at increased risk for long-term anticoagulation, with risk factors including advanced age, high-intensity anticoagulation, previous bleeding episodes, renal or hepatic impairment, and concomitant use of drugs affecting hemostasis. Studies incorporating both thrombotic and bleeding risk would likely be helpful in determining the duration and potency of extended antithrombotic therapy after VTE.

Case Resolution

After the patient completed 3 months of warfarin therapy, an extended duration of anticoagulation was recommended, and risks and benefits were discussed with the patient. Despite the recommendation, she expressed concerns about her long-term risks of bleeding and requested that anticoagulation be discontinued. As an alternative, low-dose aspirin was initiated for secondary VTE prevention. She has experienced no further VTE events.

Conclusions

Currently, warfarin, rivaroxaban, apixaban, and dabigatran have US Food and Drug Administration indications for extended-duration therapy to prevent recurrent VTE. All patients should receive anticoagulation for at least 3 to 6 months after a first VTE, but the subsequent duration of therapy should be individualized. Patients at high risk for recurrent VTE may derive the greatest benefit from an extended course of anticoagulation. Therapy in these patients may be continued until bleeding risks become prohibitive, although cost and patient preference should also be considered. Low-dose aspirin may be a preferred strategy in patients at a low risk of recurrence or those with a high risk of bleeding. Accurate risk stratification, careful consideration of the competing risks of bleeding and thrombosis, and an individualized approach to the selection and duration of anticoagulation are necessary to achieve optimal clinical outcomes.

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Disclosures

None.

References


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