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Optimal Duration of Anticoagulation After Venous Thromboembolism

Samuel Z. Goldhaber, MD; Gregory Piazza, MD

Case 1: A 79-year-old woman suffered idiopathic proximal right popliteal and calf deep vein thrombosis (DVT) 6 years previously. She had a normal hypercoagulability workup. Her warfarin has been managed successfully by a centralized pharmacist-run anticoagulation service, and she has easily achieved and maintained her target international normalized ratio range between 2.0 and 3.0. She has had no bleeding or thrombotic complications. She and her referring physicians want to know whether she should continue to take warfarin. Two years after her initial DVT, a repeat venous ultrasound examination showed recanalization of the right popliteal and calf veins. She has been anticoagulated for 14 months, most recently with enoxaparin as monotherapy without warfarin because of difficulty achieving a therapeutic international normalized ratio with warfarin. Her mother and sister have protein C deficiency. We were consulted to advise whether the patient should continue anticoagulation.

Advising patients and referring physicians about the optimal duration of anticoagulation after acute venous thromboembolism (VTE) is our most common PE/DVT consultation in the outpatient setting. Evaluation is complex and requires balancing the risks of recurrent VTE in the absence of anticoagulation against the risks of bleeding complications with continued pharmacological therapy. Discussion with our patients must include their preferences, and the message that we communicate must be nuanced yet understandable.

Risk Factors for Recurrent VTE
Risk factors for VTE recurrence (Table 1) during anticoagulation include immobilization, cancer, and chronic obstructive pulmonary disease. Risk factors for recurrence after anticoagulation is discontinued include male sex, elevated body mass index, low levels of high-density lipoprotein cholesterol, and initial presentation with symptomatic PE rather than asymptomatic DVT. The Vienna Prediction Model was developed to assess the risk of recurrent VTE after discontinuation of oral anticoagulation in patients with a first idiopathic, unprovoked PE or DVT. The most important predictors were male sex, PE rather than DVT, and elevated D-dimer levels.
**High Risk of Recurrent VTE**

Recurrent VTE after discontinuing anticoagulation occurs with surprising frequency. Observational studies from Mayo Clinic’s Olmsted County, Minnesota, and Padua, Italy, demonstrate a 30% recurrence rate in patients with an initial DVT who were followed up for 8 to 10 years after discontinuing anticoagulation. The largest cohort with long-term follow-up comprises 1626 DVT patients with either idiopathic or provoked thrombosis. After 10 years of follow-up, the cumulative incidence of recurrence was 40%. When the DVT population was dichotomized into idiopathic versus provoked initial events, the 10-year recurrence rate was 52% for idiopathic DVT versus 22% for provoked DVT. These data force us to question the notion that time-limited anticoagulation is an effective strategy because the rate of recurrence is high, even among those with provoked VTE.

These high recurrence rates for both idiopathic and provoked VTE require a paradigm shift in our thinking about PE and DVT. In many instances, VTE appears to be similar to chronic illnesses such as coronary artery disease or diabetes mellitus because VTE recurs so frequently. In the absence of a clinical recurrence, it is likely that many patients remain hypercoagulable after discontinuing anticoagulation. We must question and probably discard the classic teaching that most PE or DVT can be safely treated in a time-limited fashion. Therapy used to be considered analogous to a short course of antibiotics such as cephalosporins or streptococcal pharyngitis. The strategy for managing VTE must be long term. Advances in our understanding of the epidemiology of VTE indicate that the high recurrence rate demands a more sophisticated management approach.

**Weighing Risks of Recurrent VTE Versus Bleeding Complications**

Recurrent VTE can be fatal. For patients being anticoagulated, the toll of bleeding complications must be weighed when making recommendations for future management. In the California Patient Discharge Data Set, 3456 patients 18 to 56 years of age with idiopathic PE were identified. No specific information was available regarding the duration or intensity of oral anticoagulation. The recurrence rate within 6 months of diagnosis was 13.1%. The rate of hospitalization with a principal diagnosis of bleeding was 13 bleeds per 100 person-years in the first 6 months after the index event. During the 6 to 60 months after the index event, the recurrence rate was 2.9%/y. Almost half of the fatal recurrent events occurred within 1 month after the index PE. Among those who died of recurrent PE >1 month after the index event, 28% had developed pulmonary hypertension.

It is clear that patients who receive extended anticoagulation are protected from recurrent VTE while receiving long-term therapy. The number needed to treat to prevent 1 VTE event with lifelong anticoagulation was ≈9 patients.

**Population-Based Versus Individualized Strategy**

To determine the optimal duration of anticoagulation, 2 opposing approaches are possible: (1) a population-based strategy that attempts to dichotomize all VTE as either idiopathic or provoked and (2) an individualized strategy that attempts to generate a personalized recommendation based on specific risk factors and risk profile.

**Population-Based Strategy**

The implication of the population-based strategy is that virtually all patients can be dichotomized with respect to the pathogenesis of venous thrombosis. The attraction of this approach is its simplicity and economy. Virtually no additional testing is required for risk profiling, which is established almost completely on the basis of a detailed patient history. Those with idiopathic events are considered at high risk for recurrence and benefit from indefinite duration anticoagulation. Those with provoked episodes are labeled as low risk and receive time-limited anticoagulation, usually 3 to 6 months of warfarin. The advantage is that a recommendation for optimal duration of anticoagulation can be generated quickly, depending only on the circumstances under which the VTE initially occurred. When idiopathic and provoked events can be readily identified, this population-based strategy is simple and straightforward.

The disadvantage of the population-based strategy is that it is inflexible and overlooks patients who remain at high risk for recurrence even though their initial VTE was provoked. Such a patient might, for example, be overweight and have a sibling or parent who died of massive PE. There are also low-risk patients with idiopathic VTE who will be placed on lifelong anticoagulation with the population-based strategy. For example, patients with idiopathic isolated calf DVT will receive indefinite duration anticoagulation. From a clinical viewpoint, this therapeutic recommendation seems too intensive, given the usually benign clinical course of such a small thrombus burden.

**Individualized Strategy**

The individualized strategy, like the population-based strategy, requires a detailed patient history. However, the individualized approach is usually accompanied by an extensive, expensive, and time-consuming additional workup. The philosophy supporting this strategy advocates “personalized medicine” and is analogous to tailoring chemotherapy for cancer patients on the basis of the analysis of their specific tumors. Another analogy is rapid turnaround genetic testing to prescribe initial doses of warfarin to achieve more rapid therapeutic levels of anticoagulation. However, with respect to predicting recurrent VTE, we do not have access to elegant predictive tools.

Profiling the risk for recurrent VTE events with the individualized strategy almost always includes detailed laboratory evaluation for thrombophilia and hypercoagulability. Patients with lupus anticoagulant or protein C or S deficiency and those homozygous for factor
D-dimer serves as a nonspecific global indicator of coagulation activation and of endogenous fibrinolysis. If the D-dimer level is elevated, anticoagulation is resumed; if the level is normal, no further anticoagulation is prescribed. High levels are associated with high recurrence rates. With this strategy, patients who have high D-dimer levels are restarted on warfarin anticoagulation and continue taking it indefinitely, whereas those with normal levels do not resume anticoagulation therapy. This algorithm is not generally recommended but is widely practiced.

Cancer and Concomitant VTE
Patients with cancer and concomitant VTE pose a special challenge. The consensus is that these patients should continue anticoagulation for as long as their cancer is active. Their risk of recurrence after discontinuing anticoagulation is higher than that of noncancer patients. Yet, their bleeding risk while being anticoagulated is higher than that of noncancer patients. The 12-month cumulative incidence of major bleeding was 12.4% in patients with cancer and 4.9% in patients without cancer. Cancer patients with VTE have fewer recurrent events with low-molecular-weight heparin as monotherapy without warfarin, as opposed to low-molecular-weight heparin as a “bridge” to warfarin. Whether patients should continue on low-molecular-weight heparin or be switched to warfarin after the initial 3 to 6 months of anticoagulation remains unknown.

Reconciliation of Diverse Approaches
The clinician is confronted with a wide array of conflicting, confusing, and overlapping suggested strategies for determining the optimal duration of anticoagulation. Committee guidelines currently favor a population-based rather than individualized approach (Table 2). However, many patients whom we evaluate in the office setting fall into a “gray zone” in that it is not certain whether they had a provoked or idiopathic VTE. Some have features of a provoked VTE (eg, oral contraceptive use) with superimposed long-haul travel, which is classified in VTE algorithms as unprovoked. Others suffer PE or DVT in the setting of an acute medical illness characterized by immobilization and dehydration.

To reconcile these ambiguities, we use a population approach as our default strategy for patients with clear-cut idiopathic or provoked VTE. For patients in whom the classification is not straightforward, we use a hybrid approach and incorporate features of an individualized strategy (Figure). For example, if an overweight individual has adopted a heart-healthy lifestyle with proper nutrition and exercise and consequent marked weight loss, this improvement would favor a time-limited rather than lifelong course of anticoagulation. For patients with some ambiguous features of presentation regarding idiopathic versus provoked VTE, patient preference may be a stronger-than-usual factor in deciding on the duration of anticoagulation. In the future, more sophisticated models will be developed for predicting risk of recurrence after cessation of an-

Table 2. Consensus Guidelines for Optimal Duration of Anticoagulation

| For provoked VTE, 3 months of anticoagulation |
| For unprovoked proximal DVT or PE and low bleeding risk, indefinite duration anticoagulation if consistent with patient preference |

V Leiden or the prothrombin gene mutation are predisposed to recurrent VTE if anticoagulation is stopped.

It is also common to reimage previously thrombosed deep leg veins to ascertain whether recanalization has occurred. Some advocate that anticoagulation should continue in DVT patients until recanalization has been demonstrated on venous ultrasound examination. This strategy uses “flexible dosing” and has been popularized by Prandoni et al, who conducted a randomized controlled trial. Patients with DVT were assigned to fixed dosing (duration dependent on idiopathic versus provoked pathogenesis) versus flexible dosing, with anticoagulation continued until vein recanalization, which was assessed at 3, 9, 15, and 21 months. The recurrent VTE rate with flexible dosing (12%) was lower than with fixed dosing (17%). Nevertheless, this strategy has not been endorsed by any major guideline committee.

Another individualized approach among patients who have completed at least 3 to 6 months of anticoagulation is to discontinue anticoagulation, allow ≥1 month to elapse, and then obtain a plasma D-dimer test to assess residual hypercoagulability. D-dimer serves as a nonspecific global indicator of coagulation activation and of endogenous fibrinolysis. If the D-dimer level is elevated, anticoagulation is resumed; if the level is normal, no further anticoagulation is prescribed. High levels are associated with high recurrence rates. With this strategy, patients who have high D-dimer levels are restarted on warfarin anticoagulation and continue taking it indefinitely, whereas those with normal levels do not resume anticoagulation therapy. This algorithm is not generally recommended but is widely practiced.

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Anticoagulation. Genetic testing and discovery of additional mutations that predict recurrence will play an increasingly important role in determining the optimal duration of anticoagulation.

Case 1
This 79-year-old woman was not having any problems with her warfarin prescription. She had suffered an idiopathic DVT, but a repeat venous ultrasound 2 years later showed recanalization of leg veins. This finding on venous ultrasound examination implies that her risk of recurrent DVT is lower than average. We recommended extended indefinite duration anticoagulation. However, we suggested that the intensity of anticoagulation be loosened from the standard range international normalized ratio of 2.0 to 3.0 to a lower goal of 1.5 to 2.0. This suggestion to lower anticoagulation intensity was based on the results of the Prevention of Recurrent Venous Thromboembolism (PREVENT) Trial, which tested low-intensity indefinite duration anticoagulation versus placebo in idiopathic VTE patients who had received at least 6 months of warfarin. In this trial, recurrent VTE was reduced by 68% in the warfarin group compared with recurrent VTE was reduced by 68% in receiving lifelong anticoagulation.

Case 2
This 24-year-old woman had features of both a provoked and an idiopathic event. We discontinued anticoagulation and instructed her to return in 6 weeks for D-dimer testing. Her D-dimer was low normal (243 ng/mL, with normal <500 ng/mL). We phoned her and provided reassurance that her risk was low and that she could remain off anticoagulation. Three months later, she presented that she could remain off anticoagulation/mL). We phoned her and provided normal (243 ng/mL with normal.

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Disclosures
None.

References

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