

Optimal Duration of VTE Treatment Samuel Z. Goldhaber, MD

Advising patients and referring physicians about the optimal duration of anticoagulation following acute VTE is the most common PE/DVT consultation question posed. Evaluation is complex and requires balancing the risks of recurrent VTE in the absence of anticoagulation versus the risks of bleeding complications with continued pharmacological therapy.¹ Discussion with our patients must include their preferences, and the message that we communicate must be nuanced but yet understandable.

Risk Factors for Recurrent VTE

Risk factors for VTE recurrence during anticoagulation include: immobilization, cancer, and chronic obstructive pulmonary disease.² Risk factors for recurrence after anticoagulation is discontinued include: male gender,³ elevated body mass index,⁴ low levels of HDL cholesterol,⁵ as well as initial presentation with symptomatic PE rather than symptomatic DVT.⁶ 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.⁷ The most important predictors were male gender, 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 County⁸ and Padua, Italy⁹ both demonstrate a 30% recurrence rate in patients with an initial DVT who were followed for 8-10 years after discontinuing anticoagulation. The largest cohort with long-term follow-up comprises 1,626 DVT patients with either idiopathic or provoked thrombosis.¹⁰ 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 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 classical 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 prescribed to manage circumscribed straightforward infectious diseases such as cellulitis 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, 3,456 patients aged 18-56 years were identified with idiopathic PE.¹¹ There was no specific information available regarding the duration or intensity of oral anticoagulation. The recurrence rate within six 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 six months after the index event. During the 6-60 months after the index event, the recurrence rate was 2.9% per year. Almost half of the fatal recurrent events occurred within one month after the index PE. Among those who died of recurrent PE more than one month following 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.¹² The number needed to treat to prevent 1 VTE event with lifelong anticoagulation was approximately 9 patients.

Population-Based versus Individualized Strategy

To determine the optimal duration of anticoagulation, two 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 upon 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 etiology 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.¹³⁻¹⁵ Those with provoked episodes are labeled as low risk and receive time-limited anticoagulation, usually 3-6 months of warfarin. The advantage is that a recommendation for optimal duration of anticoagulation can be generated quickly, depending only upon 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 usual 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 based upon 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, protein C or S deficiency, or those homozygous for factor 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.¹⁶ Patients with DVT were assigned to fixed dosing (duration dependent upon idiopathic versus provoked etiology) 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 3-6 months of anticoagulation is to discontinue anticoagulation, allow about one month to elapse, and then obtain a plasma D-dimer test to assess residual hypercoagulability.¹⁷ 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.¹⁸ 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 for noncancer patients. Yet their bleeding risk while being anticoagulated is higher than that of noncancer patients. In a cohort of 842 patients with acute DVT, 181 had known cancer at the time of DVT diagnosis. The one-year incidence of recurrent thrombosis was 21% for cancer patients compared with 6.8% for noncancer patients. The 12-month cumulative incidence of major bleeding was 12.4% in patients with cancer and 4.9% in patients without cancer.¹⁹ 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.²⁰ Whether patients should continue on low molecular weight heparin or be switched to warfarin after the initial 3-6 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.²¹ However, many patients who we evaluate in the office setting fall into a “gray zone” where it is not certain whether they had a provoked or idiopathic VTE. Some have features of a provoked VTE (e.g., 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 utilize a population approach as our default strategy for patients with clear cut idiopathic or provoked VTE. For patients where the classification is not straightforward, we utilize a hybrid approach and incorporate features of an individualized strategy. For example, if an overweight individual has adopted a heart-healthy lifestyle with proper nutrition and exercise, with 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 upon the duration of anticoagulation. In the future, more sophisticated models will be developed for predicting risk of recurrence after cessation of anticoagulation. Genetic testing and discovering of additional mutations that predict recurrence will play an increasingly important role in determining the optimal duration of anticoagulation.

References

1. Zhu T, Martinez I, Emmerich J. Venous thromboembolism: risk factors for recurrence. *Arterioscler Thromb Vasc Biol.* 2009;29:298-310.
2. Nijkeuter M, Sohne M, Tick LW, Kamphuisen PW, Kramer MH, Laterveer L, van Houten AA, Kruip MJ, Leebeek FW, Buller HR, Huisman MV. The natural course of hemodynamically stable pulmonary embolism: Clinical outcome and risk factors in a large prospective cohort study. *Chest.* 2007;131:517-523.
3. Kyrle PA, Minar E, Bialonczyk C, Hirschl M, Weltermann A, Eichinger S. The risk of recurrent venous thromboembolism in men and women. *N Engl J Med.* 2004;350:2558-2563.
4. Eichinger S, Hron G, Bialonczyk C, Hirschl M, Minar E, Wagner O, Heinze G, Kyrle PA. Overweight, obesity, and the risk of recurrent venous thromboembolism. *Arch Intern Med.* 2008;168:1678-1683.

5. Eichinger S, Pecheniuk NM, Hron G, Deguchi H, Schemper M, Kyrle PA, Griffin JH. High-density lipoprotein and the risk of recurrent venous thromboembolism. *Circulation*. 2007;115:1609-1614.
6. Eichinger S, Weltermann A, Minar E, Stain M, Schonauer V, Schneider B, Kyrle PA. Symptomatic pulmonary embolism and the risk of recurrent venous thromboembolism. *Arch Intern Med*. 2004;164:92-96.
7. Eichinger S, Heinze G, Jandeck LM, Kyrle PA. Risk assessment of recurrence in patients with unprovoked deep vein thrombosis or pulmonary embolism: the Vienna prediction model. *Circulation*. 2010;121:1630-1636.
8. Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. *Arch Intern Med*. 2000;160:761-768.
9. Prandoni P, Lensing AW, Cogo A, Cuppini S, Villalta S, Carta M, Cattelan AM, Polistena P, Bernardi E, Prins MH. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med*. 1996;125:1-7.
10. Prandoni P, Noventa F, Ghirarduzzi A, Pengo V, Bernardi E, Pesavento R, Iotti M, Tormene D, Simioni P, Pagnan A. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. *Haematologica*. 2007;92:199-205.
11. White RH, Zhou H, Murin S. Death due to recurrent thromboembolism among younger healthier individuals hospitalized for idiopathic pulmonary embolism. *Thromb Haemost*. 2008;99:683-690.
12. Ost D, Tepper J, Mihara H, Lander O, Heinzer R, Fein A. Duration of anticoagulation following venous thromboembolism: a meta-analysis. *JAMA*. 2005;294:706-715.
13. Kearon C, Ginsberg JS, Kovacs MJ, Anderson DR, Wells P, Julian JA, MacKinnon B, Weitz JI, Crowther MA, Dolan S, Turpie AG, Geerts W, Solymoss S, van Nguyen P, Demers C, Kahn SR, Kassis J, Rodger M, Hambleton J, Gent M. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. *N Engl J Med*. 2003;349:631-639.
14. Ridker PM, Goldhaber SZ, Danielson E, Rosenberg Y, Eby CS, Deitcher SR, Cushman M, Moll S, Kessler CM, Elliott CG, Paulson R, Wong T, Bauer KA, Schwartz BA, Miletich JP, Bounameaux H, Glynn RJ. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. *N Engl J Med*. 2003;348:1425-1434.
15. Schulman S, Wahlander K, Lundstrom T, Clason SB, Eriksson H. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. *N Engl J Med*. 2003;349:1713-1721.
16. Prandoni P, Prins MH, Lensing AW, Ghirarduzzi A, Ageno W, Imberti D, Scannapieco G, Ambrosio GB, Pesavento R, Cuppini S, Quintavalla R, Agnelli G. Residual thrombosis on

ultrasonography to guide the duration of anticoagulation in patients with deep venous thrombosis: a randomized trial. *Ann Intern Med.* 2009;150:577-585.

17. Palareti G, Cosmi B, Legnani C, Tosetto A, Brusi C, Iorio A, Pengo V, Ghirarduzzi A, Pattacini C, Testa S, Lensing AW, Tripodi A. D-dimer testing to determine the duration of anticoagulation therapy. *N Engl J Med.* 2006;355:1780-1789.
18. Bruinstroop E, Klok FA, Van De Ree MA, Oosterwijk FL, Huisman MV. Elevated D-dimer levels predict recurrence in patients with idiopathic venous thromboembolism: a meta-analysis. *J Thromb Haemost.* 2009;7:611-618.
19. Prandoni P, Lensing AW, Piccioli A, Bernardi E, Simioni P, Girolami B, Marchiori A, Sabbion P, Prins MH, Noventa F, Girolami A. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood.* 2002;100:3484-3488.
20. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, Rickles FR, Julian JA, Haley S, Kovacs MJ, Gent M. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med.* 2003;349:146-153.
21. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008;133:454S-545S.