Deep vein thrombosis and pulmonary embolism are clinical manifestations of venous thromboembolism, and they necessitate anticoagulant therapy in most cases. The duration of treatment is predicated on a balance between the risk of recurrent disease and the risk of bleeding inherent to anticoagulant therapy. It is important that physicians are aware of evidence-based guidelines that can enhance decision-making discussions with patients about the risks and benefits of the different durations of treatment. Keeping patients well informed as they consider these difficult choices helps them assume responsibility and may improve compliance in accordance with the tenets of osteopathic principles of care.


Deep vein thrombosis and pulmonary embolism (VTE) affects approximately 360,000 patients in the United States each year as either deep vein thrombosis (DVT) or pulmonary embolism (PE). The pathophysiologic characteristics and the treatment of VTE are the same regardless of whether the symptoms manifest in the extremities, the lungs, or both.

The duration of anticoagulant therapy with warfarin or another vitamin K antagonist is determined with the goal of preventing recurrent events, which can be fatal. However, the likelihood of VTE recurrence depends on certain clinical attributes or clinical scenarios. VTE theoretically could be classified on the basis of the initial site of manifestation, such as upper extremity, proximal lower extremity, distal lower extremity, pelvis, or visceral veins; cerebral or cavernous vein; or lungs. However, investigations to determine the optimal duration of treatment for VTE have primarily studied DVT of the lower extremities or PE. The clinical scenarios that have been studied and are incorporated into evidence-based guidelines are provoked VTE, cancer-related VTE, idiopathic VTE, recurrent VTE, and thrombophilia-related VTE. This review is not a general overview of the treatments for VTE, but instead focuses on the likelihood of recurrence of each clinical type of VTE to assist clinicians and their patients in optimally balancing the risk of recurrent VTE with the risk of anticoagulation-related bleeding.

**Provoked VTE**

Recurrent of an initial VTE that was related to recent surgery, trauma, or lower extremity fracture is much less likely than recurrence of other types of clinical thrombosis, as shown in a landmark cohort study by Prandoni et al. In another observational study, by Baglin et al., VTE that was provoked by surgery or pregnancy and that was treated in the usual manner did not recur during 24 months of follow-up. The low rate of recurrence of provoked VTE in these epidemiologic studies suggested that treatment may be shortened to less than the traditional 3 to 6 months of anticoagulant therapy. In a small trial, however, patients with provoked VTE who were randomly assigned to undergo 1 month of anticoagulant therapy had higher rates of recurrence than those who underwent...
3 months of therapy. A meta-analysis that attempted to identify only patients with provoked VTE showed similar results.

One of the most important difficulties in classifying patients with provoked VTE is the lack of a consistent definition of “provoked” in trials that compare different durations of VTE treatment (Figure 1).

The American College of Chest Physicians’ (ACCP’s) evidence-based clinical practice guidelines state that “for patients with DVT secondary to a transient (reversible) risk factor, we recommend treatment with a VKA [vitamin K antagonist] for 3 months over treatment for shorter periods (Grade 1A).” The ACCP guidelines’ grades of recommendations are outlined in Figure 2.

Cancer-Related VTE
Patients with cancer-related VTE are at a substantially higher risk of developing recurrence, and they present a unique set of clinical challenges. Compared with patients without malignancy, patients with cancer and venous thrombosis are 3 times more likely to experience recurrent thromboembolic disease (21% vs 7%) and are twice as likely to have major bleeding complications while receiving anticoagulant therapy. Moreover, oral anticoagulant therapy with warfarin can cause problems in patients with cancer because the drug may interact with the chemotherapeutic agents; may cause vomiting, which could alter the vitamin K intake; and may cause liver dysfunction, which may variably affect warfarin pharmacokinetics and lead to unpredictable levels of anticoagulation. Low-molecular-weight heparin (LMWH) has been compared to warfarin during the first 3 to 6 months of therapy, and a pooled analysis of 4 studies demonstrated a reduction in VTE recurrence of approximately 50% without an increased likelihood of major bleeding. The results of this meta-analysis were driven primarily by the CLOT trial (Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer), in which patients with cancer-related VTE were randomly assigned to receive either dalteparin (a LMWH) or warfarin for 6 months; they demonstrated an 8% absolute risk reduction in recurrence (number needed to treat, 13) without a statistically significant increase in bleeding.

Current wisdom suggests that VTE should be treated until a patient’s cancer is resolved; however, this hypothesis has not been adequately tested and results in a weak recommendation from the ACCP. In addition, the trial that compared warfarin to dalteparin lasted only 6 months, and the safety of extending LMWH treatment past 6 months is currently unknown but is under active investigation.

The ACCP guidelines state that “for patients with DVT and cancer, we recommend LMWH for the first 3 to 6 months of long-term anticoagulant therapy (Grade 1A). For these patients, we recommend subsequent anticoagulant therapy with vitamin K antagonist or LMWH indefinitely or until the cancer is resolved [Grade 1C].”

Idiopathic VTE
A venous thromboembolic event is thought to be idiopathic if it occurs in the absence of a clearly identified provoking clinical factor. In an observational study that followed up patients for 2 years after they stopped anticoagulant therapy, no patient who had had surgery-related or peripartum VTE experienced a recurrent episode. In contrast, the recurrence rate was highest (19.4%) in patients with unprovoked VTE and modestly elevated (8.8%) in patients with nonsurgical risk factors such as fracture with a plaster cast, oral contraceptive use, transient illness with immobilization, or a history of travel.

In the group with nonsurgical risk factors, there is a lack of consensus on how to classify the nonsurgical risk factors, and some trials classify these nonsurgical conditions as provoking factors, whereas other trials do not.

Various trials have used different combinations of risk factors as exclusion criteria to define idiopathic (nonprovoked) VTE when assessing the length or intensity of anticoagulation.

KEY POINTS

- **Patients with Deep Vein Thrombosis or Pulmonary Embolism that is Clearly Provoked Should be Treated for 3 Months.**
- **Venous Thromboembolism (VTE) That is Related to Cancer Should be Managed Until the Cancer is Resolved, and the First 6 Months of Treatment Should Preferentially be with Low-Molecular-Weight Heparin.**
- **Patients with Idiopathic (Non-Provoked) VTE Should be Treated for at Least 3 Months. Indefinite Treatment Should be Considered. D-Dimer Testing Performed Approximately 1 Month After Completion of Anticoagulation May Help Identify Patients Who Require Long-Term Anticoagulation.**
- **Recurrent Idiopathic Proximal VTE Should Be Anticoagulated Indefinitely.**
- **Inherited Thrombophilia Testing Does Not Appear to Be Useful in Guiding the Duration of Anticoagulation Therapy for Patients with Idiopathic VTE.**
tion. While recent surgery, active cancer, and known thrombophilia have been commonly accepted as provoking risk factors, it is unclear whether immobilization, pregnancy, use of female hormones, or history of long distance travel should also be considered as provoking VTE. Figure 3 summarizes the clinical factors used as the exclusion criteria in major randomized controlled trials that evaluated the duration or intensity of anticoagulation for idiopathic VTE.15-20

The high rate of recurrence of idiopathic VTE, which is 4% to 27% after 3 months of anticoagulant therapy,15-17 suggests that a longer duration of treatment is reasonable. However, increasing the duration of therapy from 3 months to 12 months only delays, but does not prevent, recurrence.15,16 Several testing strategies have been evaluated to identify subgroups of patients with idiopathic VTE who are at highest risk of recurrence and who would gain the most benefit from prolonged anticoagulant therapy. The two most promising strategies are D-dimer testing in patients with VTE and evaluation for residual vein thrombosis in patients with DVT.

D-dimer is a degradation product of fibrin and is an indirect marker of residual thrombosis.21 In a systematic review of patients with a first episode of unprovoked VTE, a normal D-dimer level at the end of at least 3 months of anticoagulant therapy was associated with a 3.5% annual risk of VTE recurrence, whereas an elevated D-dimer level at that time was associated with an 8.9% annual risk of VTE recurrence.22 A randomized controlled trial23 demonstrated that patients with idiopathic VTE who had an elevated D-dimer level at 1 month after at least 3 months of anticoagulant therapy experienced a recurrence rate of 10.9% per year when anticoagulant therapy was not continued. When anticoagulant therapy was resumed, however, the recurrence rate improved to 2% per year without an increase in major bleeding.

Residual vein thrombosis after treatment of DVT has been shown to be a risk factor for DVT recurrence24 and is another clinical consideration that may help establish the optimal duration of anticoagulant therapy. Randomized controlled trials of patients with DVT have shown reduction in recurrence of DVT when patients with residual vein thrombosis received extended anticoagulant therapy24 or when the duration of anticoagulant therapy was tailored to findings that show recanalization of the thrombosed vein.25 One possible weakness of these studies is that patients with both provoked DVT and idiopathic DVT were studied as one group. Nevertheless, in the subset of patients with idiopathic DVT and residual thrombosis, the recurrence rate was 17% per year when the DVT was treated for only 3 months but was 10% when anticoagulant therapy was extended for up to 1 year.24

Finally, the relative location of a DVT influences the likelihood of recurrence and may influence the optimal duration of anticoagulant therapy. Patients with an isolated distal (calf) DVT are less likely to experience recurrent VTE than are patients who present with proximal DVT. Two randomized controlled trials23,26 used different durations of anticoagulant therapy and studied the recurrence rates of isolated distal DVT and of proximal DVT. These studies included both idiopathic DVT and provoked DVT, and no subgroup analysis was performed to compare idiopathic isolated distal DVT
against idiopathic proximal DVT. In one of the randomized trials, patients with either an initial isolated distal DVT or a proximal DVT underwent 6 weeks of anticoagulant therapy; the annual recurrence rates after treatment were approximately 5.7% and 10.6%, respectively; after 6 months of anticoagulant therapy, the rates were 2.9% and 5.6%, respectively. In the other randomized trial, which compared findings after 6 weeks of anticoagulant therapy versus 12 weeks for isolated distal DVT and 12 weeks of anticoagulant therapy versus 24 weeks for proximal DVT, the annual rates of recurrence after

<table>
<thead>
<tr>
<th>Grade of Recommendation*</th>
<th>Benefit vs Risk and Burdens</th>
<th>Methodologic Quality of Supporting Evidence</th>
<th>Implications</th>
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<tbody>
<tr>
<td>Strong recommendation, high-quality evidence, Grade 1A</td>
<td>Desirable effects clearly outweigh undesirable effects, or vice versa</td>
<td>Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies</td>
<td>Recommendation can apply to most patients in most circumstances; further research is very unlikely to change our confidence in the estimate of effect</td>
</tr>
<tr>
<td>Strong recommendation, moderate-quality evidence, Grade 1B</td>
<td>Desirable effects clearly outweigh undesirable effects, or vice versa</td>
<td>Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies</td>
<td>Recommendation can apply to most patients in most circumstances; higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate</td>
</tr>
<tr>
<td>Strong recommendation, low- or very low-quality evidence, Grade 1C</td>
<td>Desirable effects clearly outweigh undesirable effects, or vice versa</td>
<td>Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence</td>
<td>Recommendation can apply to most patients in many circumstances; higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate</td>
</tr>
<tr>
<td>Weak recommendation, high-quality evidence, Grade 2A</td>
<td>Desirable effects closely balanced with undesirable effects</td>
<td>Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies</td>
<td>The best action may differ depending on circumstances or patient or society values; further research is very unlikely to change our confidence in the estimate of effect</td>
</tr>
<tr>
<td>Weak recommendation, moderate-quality evidence, Grade 2B</td>
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<tr>
<td>Weak recommendation, low- or very low-quality evidence, Grade 2C</td>
<td>Desirable effects closely balanced with undesirable effects</td>
<td>Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence</td>
<td>Other alternatives may be equally reasonable; higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate</td>
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Figure 2. American College of Chest Physicians grades of recommendations for antithrombotic agents. *We use the wording we recommend for strong (Grade 1) recommendations and we suggest for weak (Grade 2) recommendations. Abbreviation: RCTs, randomized controlled trials. Source: Reprinted with permission from Guyatt GH, Cook DJ, Jaeschke R, Pauker SG, Schünemann HJ. Grades of recommendation for antithrombotic agents: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest. 2008;133(6 suppl):123S-131S.10

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12 weeks of treatment were approximately 3.4% for isolated distal and 8.1% for proximal DVT. These findings suggest that a patient with a first episode of isolated distal DVT may be at low risk for recurrence of DVT and that the risk-benefit ratio may be tipped to support limiting anticoagulant therapy to only 3 months for this indication. However, trials focused specifically on the precise subset of patients with idiopathic isolated distal DVT are lacking.

The ACCP guidelines state that for “patients with unprovoked DVT, we recommend treatment with a VKA [vitamin K antagonist] for at least 3 months (Grade 1a). We recommend that after 3 months of anticoagulant therapy, all patients with unprovoked DVT should be evaluated for the risk-benefit ratio of long-term therapy (Grade 1c). For patients with a first unprovoked distal DVT that is unprovoked, we suggest that 3 months of anticoagulant therapy is sufficient rather than indefinite therapy (Grade 2B).”

Recurrent VTE

It is clinically sensible that patients with a second episode of VTE should be treated indefinitely, and this concept has been proved in a randomized controlled trial. Patients with provoked or idiopathic VTE were randomly assigned after their second episode to receive anticoagulant therapy for either 6 months or an indefinite period of time. After 4 years of follow-up, 20.7% of patients in the 6-month group and 2.6% in the indefinite-period group experienced recurrent VTE. The percentage of patients who experienced major hemorrhage was 2.7% in the 6-month group and 8.6% in the indefinite-period group. Of note, only 20% of the patients in this study had provoked VTE, and these results should be applied to patients with only unprovoked recurrent VTE.

The ACCP guidelines state that for “patients with a second episode of unprovoked VTE, we recommend long-term treatment (Grade 1a).”

Thrombophilia-related VTE

Patients with inherited thrombophilia are at greater than average risk of experiencing an initial VTE event. Common inherited thrombophilic conditions include deficiencies in protein C, protein S, and antithrombin and gene mutations for factor V Leiden and prothrombin.

One retrospective study involved examination of a large cohort of families of patients who already had experienced a first episode of either idiopathic or provoked VTE. The study revealed high annual risks of recurrent VTE associated with hereditary deficiencies of protein S (8.4%), protein C (6.0%), or antithrombin (10%). However, a systematic review performed in patients with the more commonly occurring genetic thrombophilias, factor V Leiden and prothrombin

It is unclear whether immobilization, pregnancy, use of female hormones, or history of long distance travel should also be considered as provoking VTE.
G20210A mutation, revealed VTE recurrence rates ranging from 1.1% to 5.8% per year, which are similar to that of patients with idiopathic VTE. Also, the family members of the patients included in the review had low rates of VTE, which suggests that testing of relatives of probands may not be clinically useful.30

Lastly, a prospective study28 that evaluated the effect of thrombophilia and clinical factors on the recurrence of VTE revealed that prothrombotic abnormalities do not appear to play an important role in the risk of a recurrent event. However, clinical factors, such as whether the first event was idiopathic or provoked, appear to be more important in determining the duration of anticoagulant therapy.28

In the absence of strong evidence, the ACCP guidelines do not include a recommendation on the duration of anticoagulation treatment specific to patients with inherited thrombophilia. However, the guidelines recognize the increased risk of recurrent thrombosis from acquired thrombophilia associated with antiphospholipid antibodies.2 Results of one study31 indicated that the risk of recurrence is doubled in patients with anticardiolipin antibodies (29% in patients with the antiphospholipid antibodies vs 14% in patients without), and a systematic review32 found that warfarin (adjusted to a target international normalized ratio of 2.0-3.0) is effective in preventing recurrent VTE in these patients. Although the optimal duration of treatment is unknown, most experts agree that patients with thrombophilia-related VTE require anticoagulation indefinitely.33

There are still areas of uncertainty, including clinical factors that have not yet been clearly classified as either provoking or not provoking and the role of thrombophilia in the recurrence of VTE. Also, the development of novel oral anticoagulant medications may tilt the balance of benefits and burdens and thus lead to better therapeutic recommendations in the future.

References

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