



Duration of therapy for acute venous thromboembolism

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Following an episode of venous thromboembolism (VTE), treatment should be continued until the benefits of anticoagulation no longer outweigh the risks of therapy. The optimal duration of anticoagulation needs to be individualized. This assessment is dominated by the risk of recurrent VTE if anticoagulation is stopped and the risk of bleeding if treatment is continued. After considering these two competing risks, if the benefits of remaining on anticoagulant therapy are small or uncertain, patient preference and the cost of therapy also strongly influence this decision, particularly if indefinite anticoagulant therapy is being considered.

Risk factors for recurrent venous thromboembolism after stopping anticoagulant therapy

Reversibility of risk factors for venous thromboembolism

Probably the greatest advance in the assessment of the risk for recurrent VTE after anticoagulant therapy is stopped is the recent recognition that patients who have thrombosis provoked by a major reversible risk factor, such as surgery, have a low risk of recurrence (ie, approximately 3% per year), whereas patients with an unprovoked (idiopathic) episode of VTE or a persistent risk factor (eg, cancer) have a high risk (ie, approximately 10% per year) (Table 1) [1–7].

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Thrombophilia

Hereditary and acquired biochemical states that are associated with VTE (thrombophilia) are heterogeneous in terms of the frequency with which they occur in the normal population and the strength of their association with thrombosis [8–11] (Table 1). Although the presence of one of these abnormalities is often assumed an important risk factor for recurrent VTE and a strong indication for prolonged treatment, the evidence supporting this assumption is inconsistent.

Antiphospholipid antibodies

Antiphospholipid antibodies (anticardiolipin antibody [12,13] or lupus anticoagulant [13]) are associated with a twofold or greater risk of recurrent thrombosis after stopping anticoagulant therapy [12,13]. One study found that, owing to an excess of subsequent venous and arterial thrombosis following a first episode of VTE, the presence of an anticardiolipin antibody was associated with a higher mortality. Remaining on anticoagulant therapy seemed to reduce this risk [12].

Factor V Leiden and the G20210A prothrombin gene mutation

Factor V Leiden and the prothrombin gene mutation, singly in a heterozygous state, are of uncertain importance as risk factors for recurrent VTE. Two prospective studies found that factor V Leiden was associated with a twofold increase in the risk of recurrence [14,15], whereas three other studies found no such association [13,16,17]. Similarly, the prothrombin gene mutation was associated with an increase in the risk of recurrent VTE in two prospective studies [18,19], whereas it was not in two others [17,20]. Patients who are heterozygous for factor V

Table 1
Risk of recurrent venous thromboembolism after stopping anticoagulant therapy

Variable	Relative risk
Transient risk factor [1–5,7]	≤ 0.5
Persistent risk factor [1–5,7]	≥ 2
Unprovoked VTE [1–3,7,13]	≥ 2
Protein C, protein S, and antithrombin deficiencies [23]	1.4
Heterozygous for factor V Leiden [13–17]	1–2
Homozygous for factor V Leiden [17]	4.1
Heterozygous for G20210A mutation in the prothrombin gene [13,14,17–20]	1–2
Heterozygous for factor V Leiden and G20210A prothrombin gene [18,21,22]	2–5
Factor VIII level > 200 IU/dL [25,26]	~ 6
Antiphospholipid antibodies [12,13]	2–4
Mild hyperhomocysteinemia [28]	2.7
Family history of VTE [3,17]	~ 1
Cancer [7,23,34]	~ 3
Chemotherapy [34]	~ 2
Discontinuation of estrogen [34,68,69]	< 1
Proximal DVT versus PE [3,13]	~ 1
Distal DVT versus proximal DVT or PE [3,6]	0.5
Residual thrombosis [2,3,13,33,51]	1–2
Vena caval filter [38,53,54]	~ 1.8
Second versus first episode of VTE [38,52]	~ 1.4
Age [13,17,34,38]	~ 1
Gender [13,17,38]	~ 1
Asian [38]	~ 0.8

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Leiden and the prothrombin gene mutations [18, 21,22] or homozygous for factor V Leiden [17] seem to have a high risk for recurrent VTE (Table 1).

Deficiency of protein C, protein S, and antithrombin

Limited prospective data are available regarding the risk for recurrent VTE in patients with antithrombin, protein C, or protein S deficiency. One prospective study identified a hazard ratio of 1.4 for recurrent VTE in patients with one of these abnormalities or a lupus anticoagulant [23]. A retrospective family cohort study estimated that the presence of one of these abnormalities was associated with a 10% cumulative frequency of a recurrent VTE 1 year after diagnosis, rising to 23% after 5 years [24]. Nevertheless, because these three deficiency states are associated with a 20 to 50 fold increase in the risk for a first episode of VTE [8], they are thought to be clinically important risk factors for recurrent VTE.

Factor VIII

A markedly elevated level of factor VIII is a risk factor for recurrent thrombosis (Table 1) [25,26].

Hyperhomocysteinemia

Hyperhomocysteinemia, a condition that is related to hereditary and acquired risk factors [27], was associated with a 2.7-fold increased risk of recurrent VTE in one study of patients with unprovoked VTE [28]. Reversal of hyperhomocysteinemia with vitamin therapy may reduce the risk of recurrent VTE, a hypothesis that is currently being tested [29].

Cancer

Cancer is associated with a threefold increased risk of recurrent VTE during [30–33] and following [7,23,33,34] oral anticoagulant therapy (Table 1). Some evidence suggests that anticoagulant therapy may favorably alter the natural history of some cancers [35,36]. Schulman and colleagues [36] found that treatment of a first episode of VTE with oral anticoagulant therapy for 6 months versus 6 weeks was associated with a lower frequency of cancer (odds ratio, 0.6), especially urogenital, during 8 years of follow-up. This observation must be confirmed in other studies before it can be considered an argument in favor of more prolonged anticoagulant therapy for patients with VTE.

Pulmonary embolism versus deep vein thrombosis

Patients who present with pulmonary embolism (PE) have the same risk for a recurrent episode of

VTE as patients who present with proximal deep vein thrombosis (DVT) [3,34,37,38]. Nevertheless, patients with PE are about four times as likely to have a recurrence as PE when compared with patients who present initially with DVT [37–39], and this pattern of recurrence seems to persist long-term [38,39]. Approximately 10% of symptomatic PEs are thought to be rapidly fatal [40–42], and 5% or more of patients who have PE diagnosed and treated die of PE [38,39,43–46]. These observations suggest that, in patients who have completed 3 or more months of therapy for DVT or PE, recurrent VTE presenting as PE has a case–fatality rate of approximately 15%. The risk of dying of acute DVT because of subsequent PE or other complications (eg, bleeding, precipitation of myocardial infarction) seems to be 2% or less [23,38,39,44,47]. Based on these estimates for the proportion of recurrences that will be PE and DVT and the case–fatality rate associated with each presentation, the case–fatality rate associated with recurrent VTE that occurs 3 or months after a preceding PE is expected to be approximately 12% and the rate after a preceding DVT approximately 5%. Consistent with the latter estimate, an overview of randomized trials calculated a 5.1% case–fatality rate for recurrent VTE in patients with DVT who had completed 3 months of treatment [37]. Although the risk of a recurrence is the same after PE and proximal DVT, the consequence of a recurrence, including events that occur after the initial phase of treatment, seems to be much more severe after PE than after DVT.

Because they frequently have sustained recurrent episodes of PE and have a poor tolerance for further episodes of PE, patients with chronic thromboembolic pulmonary hypertension generally should be treated indefinitely [48].

Residual deep vein thrombosis

The resolution of DVT is often slow and incomplete. Approximately half of patients with proximal DVT have an abnormal compression ultrasound of the proximal veins 1 year after diagnosis and treatment [33,49,50]. The significance of residual DVT as a risk factor for recurrent VTE is unclear. After 3 months of treatment for unprovoked proximal DVT or PE in one study, residual DVT was not associated with subsequent recurrence (hazard ratio, 1.25; 95% confidence interval [CI], 0.5–3.3) [13]. Nevertheless, in a heterogeneous group of patients with proximal DVT, including those with asymptomatic thrombi or cancer, residual DVT after 3 months of treatment was associated with recurrence after stopping therapy (75% risk

in the ipsilateral leg) [33]. In that study, residual thrombosis was associated with initial large and symptomatic DVT and cancer [33].

In the duration of anticoagulation (DURAC) study that compared 6 weeks and 6 months of anticoagulant therapy for a first VTE, 59% of recurrent DVTs within 6 months of diagnosis involved the ipsilateral leg, whereas 31% of late recurrences were in the initially affected limb [51]. Most of the early recurrences were seen in patients who had stopped anticoagulants after 6 weeks of treatment. These observations suggest that early ipsilateral recurrences reflect inadequate initial treatment (ie, 6 weeks), whereas recurrences after adequate initial therapy (ie, 6 months) reflect a systemic predisposition to thrombosis. Patients with abnormal impedance plethysmography after 3 months of treatment for proximal DVT were not found to have a higher risk for recurrent VTE when compared with patients with normal plethysmography (relative risk, 1.3). This observation argues against residual DVT and local venous obstruction as a risk factor for recurrence [2].

Multiple previous episodes of venous thromboembolism

Intuitively, patients who have had more than one VTE, particularly if the interval between episodes is not long, are expected to have a higher risk of recurrence than patients with a first VTE. Contrary to this expectation, the DURAC investigators found a similar risk of recurrence during 2 years of follow-up after 6 months of treatment for a first and a second episode of VTE [3,52]. In contrast, in a large epidemiologic study of linked hospital discharge records, the risk of recurrence was approximately 50% higher during 2 years of follow-up after a second versus first DVT [53].

Vena caval filters

In a randomized trial that evaluated routine placement of vena caval filters as an adjunct to anticoagulant therapy in patients with proximal DVT, filters were shown to reduce the frequency of PE acutely (during the first 12 days) but almost doubled the long-term risk of recurrent DVT [54]. Despite increasing the risk of recurrent DVT, filters were not associated with more frequent PE. These findings are supported by another large epidemiologic study of linked hospital discharge records. In that study, a vena caval filter was an independent risk factor for recurrent DVT (odds ratio, 1.8) but not a risk factor for PE (odds ratio, 1.0) [38]. The filter-associated

increase in DVT was largely confined to patients who presented initially with PE [53]. The findings of these two studies support the use of anticoagulant therapy in patients who have had a filter inserted when such therapy becomes safe (eg, bleeding risk resolves), and favor a more prolonged, but not necessarily indefinite, duration of such treatment (Table 1).

D-dimer and other factors

Laboratory evidence of increased activation of coagulation after withdrawal of anticoagulants may identify patients who are at a higher risk for recurrent VTE. A positive D-dimer level 1 or 3 months after stopping anticoagulant therapy was found to be associated with a two to threefold increase in recurrent VTE and seemed to be predictive of recurrence regardless of whether the initial VTE was unprovoked or provoked by a transient or persistent risk factor [7]. This approach to stratifying the risk for recurrent VTE requires confirmation and standardization before it can be recommended.

The influence of several other factors on the risk for recurrent VTE is noted in Table 1.

Risk factors for bleeding during anticoagulant therapy

Long-term anticoagulation targeted to an International Normalized Ratio (INR) of 2.0 to 3.0 is generally associated with an annual risk for major bleeding of approximately 3% [13,52,55,56]. Of these major bleeds, about one fifth are expected to be fatal (annual rate of fatal bleeding of approximately 0.6%) [55]. The risk of bleeding for individual patients may differ markedly from these estimates depending on the prevalence of risk factors for bleeding, such as the patient's age and gender (ie, female), the prevalence of certain comorbid conditions (eg, previous gastrointestinal bleeding or stroke, chronic renal disease, malignancy, alcohol-related disease, diabetes), and the use of concomitant antiplatelet therapy [55–60]. The risk of bleeding is highest shortly after starting anticoagulant therapy [55–57] and is higher if oral anticoagulation is difficult to control [56].

Recent randomized trials have demonstrated that better control of anticoagulant therapy can be achieved with computer-assisted dosing of warfarin versus traditional dosing by experienced medical staff alone [61] and by using a multicomponent intervention that promotes patient education and participation in anticoagulant management versus usual care [62].

The multicomponent intervention halved the frequency of major bleeding during the 6 months after anticoagulant therapy was started [62].

Two prospectively validated prediction rules have been published for assessing an individual's risk of major bleeding during the first 3 months of anticoagulant therapy [58,59] and thereafter [58]. Hereditary factors, such as polymorphisms that affect the cytochrome P-450 system of the liver, may increase sensitivity to warfarin and predispose the patient to anticoagulant-induced bleeding [63,64].

Relative importance of an episode of recurrent venous thromboembolism and an episode of major bleeding

When weighing the risks and benefits of anticoagulation in an individual patient, in addition to considering the absolute risk of thrombosis and major bleeding with and without anticoagulant therapy, the consequences associated with each of these outcomes need to be considered.

The consequences of recurrent VTE depend on whether the recurrence is a PE or DVT. Death is expected to result from 15% of PEs and 2% or less of DVTs. Initial presentation as a PE rather than DVT is the only factor other than previous insertion of a vena caval filter (risk factor for DVT only) that seems to influence markedly whether recurrent VTE is a PE versus DVT [38]. After the patient has completed 3 or more months of anticoagulant therapy, the case-fatality rate for recurrent VTE is expected to be 12% following PE and 5% following DVT.

The case-fatality rate associated with major bleeding during anticoagulant therapy is approximately 20% [55]. This rate is likely to be higher in patients with a history of ischemic stroke that is not caused by atrial fibrillation, because these patients are at a greater risk for intracerebral bleeding (case-fatality rate of approximately 50% [65]) than for other types of bleeding [65,66].

A comparison of associated case-fatality rates suggests that, on average, the consequence of a major bleed during long-term anticoagulation is about twice as severe as the consequence of a recurrent episode of VTE that occurs after a PE, and about four times as severe as the consequence of a recurrent episode of VTE that occurs after a DVT. The annual risk of recurrent VTE needs to exceed 6% after a PE and 12% after a DVT before one should consider long-term anticoagulation in patients with an average risk of bleeding (ie, approximately 3% per year [13,52,55,56]).

Direct comparisons of different durations of anticoagulant therapy

Short versus conventional durations of anticoagulant therapy

Four large trials have assessed the safety of shortening the duration of oral anticoagulant therapy from 3 or 6 months to 4 or 6 weeks [1–3,6]. The three studies that enrolled patients primarily with proximal DVT or PE found that shortening the duration of anticoagulation was associated with about double the frequency of recurrent VTE during follow-up [1–3]. Regardless of the duration of anticoagulation, major bleeding was uncommon in these three studies; therefore, it can be concluded that anticoagulant therapy should not be shortened to 4 or 6 weeks in patients with a first episode of VTE. Subgroup analyses of one study suggested that isolated calf vein thrombosis provoked by a major transient risk factor could be treated safely with only 6 weeks of therapy [3]. The fourth of these studies, which compared 6 versus 12 weeks of therapy in patients with isolated calf DVT (idiopathic or secondary), found that shortening therapy did not increase the risk of recurrence (relative risk, 0.58; 95% CI, 0.01–3.36) and was associated with a low frequency of recurrent VTE during follow-up (approximately 1.3% per year) [6].

Six or 12 months versus 3 months of anticoagulant therapy

Pinede and colleagues [6] compared 6 and 3 months of anticoagulant therapy in patients with a first episode of proximal DVT or PE (unprovoked or secondary). After 15 months of follow-up, the frequency of recurrent VTE did not differ between the two groups (relative risk, 0.93 in favor of 3 months; 95% CI, 0.53–1.65).

Agnelli and colleagues [67] compared stopping anticoagulant therapy at 3 months with continuing it for another 9 months after a first episode of unprovoked DVT. At the end of the first year, recurrent VTE was less frequent in the group that remained on anticoagulant therapy (3.0% versus 8.3%), but this benefit was lost 2 years after anticoagulant therapy was stopped (16% rate of recurrent VTE in both groups).

Prolonged versus conventional durations of anticoagulant therapy

Two trials have assessed long-term anticoagulation in different groups of patients believed to have

a high risk for recurrent VTE. Schulman and colleagues [52] compared 6 months versus 4 years of warfarin therapy in patients with a second episode of VTE. Recurrent VTE was markedly reduced by long-term oral anticoagulant therapy (0.65% versus 5.2% per year), but such therapy was associated with a higher frequency of major bleeding (2.2% versus 0.45% per year). Overall, there was no convincing benefit of long-term anticoagulation in this patient population.

Kearon and colleagues [13] compared an additional 2 years of anticoagulant therapy with placebo in patients with a first episode of idiopathic VTE who had completed 3 months of warfarin therapy. The trial was stopped after an average of 10 months of follow-up when an interim analysis revealed unexpectedly high recurrence rates (27% per year) in patients who discontinued warfarin after 3 months of treatment. Long-term warfarin therapy resulted in a 95% reduction in the risk of recurrent VTE but was associated with a 3.8% per year risk of major bleeding. It is not known whether the benefit accrued from the extended duration of therapy in this study could be achieved with less than 2 additional years of anticoagulation, or whether anticoagulants can be been stopped safely at the end of this period.

Recommended duration of anticoagulation in individual patients

Based on the previous analysis of risk factors for recurrent thrombosis and the findings of studies that have compared different durations of anticoagulation, an approach to selecting the optimal duration of anticoagulation for individual patients with VTE is outlined in Table 2. Because the presence or absence of a major reversible risk factor at the time of thrombosis seems to have the greatest prognostic influence on the risk for recurrence, this clinical categorization is the starting point. Factors that may modify the duration of anticoagulation within each category are then considered.

For patients who have VTE associated with a major transient risk factor, stopping anticoagulant therapy after 3 months of treatment is expected to be associated with a subsequent low risk of recurrent VTE of approximately 3% per year [1,2,5–7,23]. For patients who have unprovoked VTE, stopping anticoagulant therapy after 6 or more months of treatment is expected to be associated with a subsequent risk of recurrent VTE of approximately 10% per year [3,6,7,67]. The recurrence rate in such patients has tended to be lower than this estimate in European studies [6,7,67], and the rate seems to decrease over

Table 2

Recommended duration of anticoagulant therapy for venous thromboembolism

Recommended duration of therapy	Type of VTE and associated risk factors
VTE provoked by a major transient risk factor ^a	
3 months	Proximal DVT or PE
6 weeks	Isolated distal DVT
6 months	Protein C, protein S, antithrombin deficiencies; homozygous factor V Leiden or G20210A mutation in the prothrombin gene; antiphospholipid antibodies; combined thrombophilic abnormalities; concomitant cancer with a normal functional status; inferior vena cava filter; patient preference
VTE not provoked by a major transient risk factor	
6 months	Minor reversible risk factor (estrogen therapy, prolonged travel [4 hours], treated hyperhomocysteinemia); moderate risk of bleeding; patient preference
Long-term therapy ^b	More than one episode of idiopathic VTE; active cancer; protein C, protein S, antithrombin deficiencies; homozygous factor V Leiden or G20210A mutation in the prothrombin gene; antiphospholipid antibodies; combined thrombophilic abnormalities; severe immobilization; pulmonary embolism; pulmonary hypertension; severe postthrombotic syndrome; inferior vena cava filter; low risk of bleeding; patient preference
3 months	High risk for bleeding; isolated distal DVT; patient preference

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

^a Major transient risk factors include hospitalization, general anesthesia, 3 days of bedrest, leg fracture with or without plaster immobilization, all within 3 months.

^b No upper limit to duration of anticoagulation. Decision to continue anticoagulant therapy may be changed if risk of bleeding increases or at patient's request.

time. For some patients, particularly those who have had a PE, this risk may be considered high enough to justify long-term therapy (Table 2). It is uncertain whether stopping anticoagulant therapy after 3 months rather than 6 months would be associated with a higher subsequent risk of recurrence in patients with unprovoked VTE. Although one study found a high risk of recurrence (approximately 27% per year) after 3 months of therapy in such patients [13], two others found much lower rates of recurrence after 3 months of treatment (approximately 7% per year), which were similar to the rates observed after 6 months [6] and 12 months [67] of treatment.

Summary

Prospective studies are providing a better understanding of the relative risk for recurrent thrombosis and anticoagulant-related bleeding in subgroups of patients with VTE, particularly during the extended phase of therapy. These findings in conjunction with the results of randomized trials evaluating specific anticoagulant and nonanticoagulant therapies are resulting in improvements in the management of VTE (Box 1). It is anticipated that ongoing studies will continue to identify clinical and biochemical risk

factors for recurrent thrombosis and bleeding. Such research will determine whether lower intensities of oral anticoagulation (eg, INR < 2.0) are indicated for long-term secondary prophylaxis of VTE. The data obtained will clarify the role of extended-duration LMWH therapy in patients with and without cancer and may result in the development of novel antithrombotic agents that overcome the limitations of current therapies.

Box 1.

Key points

- Anticoagulant therapy should be stopped when its benefits (reduction of VTE) no longer clearly outweigh the risk of bleeding.
- Shortening the duration of anticoagulation from 3 [1,2] or 6 [3] months to 4 [1,2] or 6 [3] weeks results in a doubling of the frequency of recurrent VTE during 1 [1,2] to 2 [3] years of follow-up.

- Patients with VTE provoked by a transient risk factor have a lower (about one-third) risk of recurrence than do patients with an unprovoked VTE or a persistent risk factor [1–3, 5,7,23].
- Three months of anticoagulation is adequate treatment for VTE provoked by a transient risk factor; the subsequent risk of recurrence is 3% or less per patient-year [1,2,5–7,70].
- Three months of anticoagulation may not be adequate treatment for an unprovoked (idiopathic) episode of VTE; the subsequent early risk of recurrence has ranged from 5% to 25% per patient-year [3,6,7,13,67].
- After 6 months of anticoagulation, recurrent DVT is at least as likely to affect the contralateral leg; this observation suggests that systemic rather than local factors (including inadequate treatment) are responsible for recurrences after 6 months of treatment [51].
- There is a persistently elevated risk of recurrent VTE after a first episode; this risk is thought to be 5% to 12% per year after 6 or more months of treatment for an unprovoked episode [3,6,67].
- Oral anticoagulants targeted at an INR of approximately 2.5 are effective (risk reduction $\geq 90\%$) in preventing recurrent unprovoked VTE after the first 3 months of treatment [13,52].
- Indefinite anticoagulation is an option for patients with a first unprovoked VTE who have a low risk of bleeding.
- A second episode of VTE suggests a higher risk of recurrence but not necessarily high enough to justify indefinite anticoagulation [13,38].
- The risk of bleeding during anticoagulant therapy differs markedly among patients depending on the prevalence of risk factors (eg, advanced age, previous bleeding or stroke, renal failure, diabetes, anemia, antiplatelet therapy, malignancy, poor anticoagulant control) [57,58,60].

- The risk of PE is higher after an initial PE than after a DVT; this observation favors a longer duration of anticoagulation [38,39].
- The risk of recurrence is lower (about half) following an isolated calf (distal) DVT; this observation favors a shorter duration of treatment [3,6].
- The risk of recurrence is higher with antiphospholipid antibodies (anticardiolipin antibodies with or without lupus anticoagulants) [12,13], homozygous factor V Leiden [17], cancer [23], and, probably, antithrombin deficiency. These risk factors favor a longer duration of treatment.
- Heterozygous factor V Leiden and the G20210A prothrombin gene mutations do not seem to be clinically important risk factors for recurrence [17].
- Other abnormalities, such as elevated levels of clotting factors VIII, IX, and XI and homocysteine, and deficiencies of protein C and protein S, may be risk factors for recurrence; they have uncertain implications for the duration of treatment.
- For the purpose of influencing the duration of anticoagulant therapy, thrombophilia screening can be limited to situations in which the results of testing will change management, that is, (1) clinical assessment suggests an equivocal risk-to-benefit ratio for remaining on anticoagulants; and (2) test results have clear prognostic significance.

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