VENOUS THROMBOEMBOLISM: DURATION OF TREATMENT

OBJECTIVE:
To provide guidance on the recommended duration of anticoagulant therapy for venous thromboembolism (VTE).

BACKGROUND:
Making a decision on the duration of anticoagulant therapy depends on the assessment of an individual’s risk of recurrent thrombosis off anticoagulation versus the risk of major bleeding on anticoagulation. It is also important to take into consideration that the consequences of a major bleed are generally more severe than the consequences of a recurrent episode of VTE (e.g. case-fatality of ~10% versus ~5%, respectively). Other factors to consider include the burden of anticoagulation (financial, functional, and psychological), quality of life, and patient preference.

Recurrent episodes of VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), may be due to reactivation and extension of the original thrombosis or may be due to a new episode of VTE that is not directly related to the initial episode of thrombosis. The risk of recurrence reflects the patient’s underlying predisposition to VTE and persists as long as an acquired risk factor is active (e.g. patients with cancer) or indefinitely (e.g. patients with unprovoked VTE).

The risk of bleeding during anticoagulant therapy also differs among patients and with the duration of therapy, with the risk being highest in older patients and during the first month of anticoagulation. Anticoagulant therapy should be stopped when its benefits no longer clearly outweigh its risks, or when patients, who have a good understanding of the associated risks, want to stop even if continuing treatment is expected to be of net benefit.

FACTORS THAT INFLUENCE THE DURATION OF ANTICOAGULANT THERAPY:

a) The risk of recurrent VTE after stopping anticoagulation appears to be similar whether anticoagulant therapy is stopped after 3 months vs. after 6 to 24 months of treatment; this suggests that 3 months of treatment is sufficient to treat the acute episode of VTE if the decision is to not continue anticoagulation long-term. Because shortening the duration of anticoagulation from 3 or 6 months to 4 or 6 weeks results in doubling the frequency of recurrent VTE during the first 6 months after stopping anticoagulant therapy, 3 months is the minimum duration of treatment for VTE.

b) If the risk of recurrence is expected to be unacceptably high if anticoagulants are stopped, treatment should be continued indefinitely (i.e., without a scheduled stopping date). Therefore, patients with VTE are usually treated for either 3 months or indefinitely.

c) Patients with VTE provoked by a transient risk factor have a much lower (about one-third) risk of recurrence than those with an unprovoked VTE or a persistent risk factor. Transient risk factors
include: surgery, hospitalization or plaster cast immobilization, all within 3 months; estrogen therapy, pregnancy, flight of > 8 hours, recent leg injuries or immobilizations (e.g. within 6 weeks). The stronger the provoking reversible risk factor is (e.g. recent major surgery), the lower the expected risk of recurrence after stopping anticoagulant therapy.

d) In the first year after stopping therapy for VTE with a transient risk factor, the risk of recurrence is about 1-2% if VTE was provoked by a surgical (i.e., major) risk factor and about 5% if VTE was provoked by a non-surgical (i.e., minor) risk factor. By 5 years, the risk of recurrence is approximately 3-old higher (3% for major risk factor, 15% for minor risk factor).

e) Patients with a first unprovoked episode of proximal DVT or PE, on average, have a risk of recurrence of about 10% in the first year, 30% in the first 5 years and 50% in the first 10 years after stopping anticoagulant therapy.

f) The risk of recurrence after a first unprovoked proximal DVT or PE can be further stratified according to the patient's sex and D-dimer results measured 1 month after stopping anticoagulant therapy:

- men have ~1.5-fold higher risk of recurrence than women (~12% vs. ~8% in the first year after stopping therapy);
- patients with a positive D-dimer vs. negative D-dimer have ~2-fold higher risk of recurrence; and
- the predictive value of sex and D-dimer results for recurrent VTE are additive: male and D-dimer negative: ~8% in the first year; male and D-dimer positive: ~16% in the first year; female and D-dimer negative: ~5% in the first year; female and D-dimer positive: ~10% in the first year.

g) The presence of residual abnormalities on ultrasound is detected in approximately one-third of patients and does not appear to be a clinically-important risk factor for recurrence after stopping anticoagulant therapy.

h) Risk of recurrence is similar after an episode of proximal DVT vs PE. However, patients who presented initially with PE are more likely to recur with PE than DVT, while those who present initially with DVT are more likely to recur with DVT.

i) Risk of recurrence is lower (by 50%) after an isolated calf (distal) DVT than after a proximal DVT or PE.

j) Central venous catheter (CVC) associated VTE should be treated like a provoked VTE. [see Clinical Guide: Central Venous Catheter-Related Thrombosis]

k) A second episode of VTE suggests a higher risk of recurrence. However, the recommendation for duration of anticoagulant therapy is dependent on whether the VTE was provoked or unprovoked.

l) Risk of recurrent VTE is markedly increased in patients with active cancer (perhaps 20% per patient-year, initially); the risk is higher in patients with metastatic compared with localized disease. The risk of recurrent VTE may be lower if it occurred while patients were receiving chemotherapy and chemotherapy was subsequently stopped. [see Clinical Guide: Cancer and Thrombosis]
m) The presence of one of the common hereditary thrombophilia conditions (i.e., heterozygous for factor V Leiden or prothrombin G20210A) does not appear to be a clinically important risk factor for recurrence of VTE either during or after anticoagulant therapy. However, if a patient is known to have antithrombin, protein C or protein S deficiency or is homozygous or compound heterozygous for factor V Leiden or prothrombin G20210A with a history of VTE, the risk of recurrent VTE is higher and they may be a candidate for indefinite anticoagulant therapy. However, given the low prevalence of the higher-risk thrombophilia, screening for hereditary thrombophilia is generally not recommended to determine duration of anticoagulation. A positive family history alone does not increase the risk of recurrent VTE.

n) The presence of an antiphospholipid antibody and VTE (fitting the criteria for Antiphospholipid Antibody Syndrome) is considered high risk for VTE recurrence and these patients should receive anticoagulant therapy indefinitely.

o) The presence of an inferior vena cava filter (IVCF), beyond the first few months of implantation, does not appear to be associated with an increased risk of recurrent VTE. Consequently, the presence of an IVCF alone should not influence the duration of anticoagulant therapy beyond the duration of treatment for the VTE that triggered the filter insertion.

p) The risk of anticoagulant-induced bleeding is highest during the first 3 months of treatment and stabilizes after the first year.

q) Risk of bleeding differs markedly among patients depending on the prevalence of risk factors (e.g. age >75 years; previous bleeding; cancer; metastatic cancer; renal failure; liver failure; thrombocytopenia; previous stroke; diabetes; anemia; antiplatelet therapy; poor anticoagulant control; recent surgery; frequent falls; alcohol abuse). Patients without any risk factors have a low annual risk of major bleeding at 0.8% while those with two or more risk factors have an annual risk greater than 6%.

r) In patients with a first unprovoked VTE, the decision to stop anticoagulant therapy at 3 months or to continue treatment indefinitely is strongly influenced by the preferences of an informed patient. To elicit patient preferences for the purpose of joint decision making, the expected risks of recurrence with and without indefinite anticoagulant therapy, and the expected consequences of recurrent VTE and bleeding, need to be explained to the patient.

**Recommendations (see Table):**

a) Patients with their first VTE provoked by transient risk factor(s) should receive 3 months of anticoagulant therapy.

b) Although 3 months is the usual length of time-limited treatment, 6 months may be preferred if: (i) the DVT or PE was very large or very symptomatic; or (ii) symptoms of the initial DVT or PE persist; or (iii) the patient is not ready (confident enough) to stop anticoagulant therapy at 3 months; and (iv) the patient does not have a high risk for bleeding.

c) Patients with their first unprovoked episode of VTE should receive a minimum of 3 months anticoagulant therapy and then be reassessed for indefinite anticoagulant therapy. If patients have a high bleeding risk, anticoagulation should be stopped. All other patients should be considered for indefinite treatment.
d) For those patients with an isolated calf (distal) DVT for whom the decision was made to treat with anticoagulation vs watch and wait with follow-up ultrasound within a week, should be treated for 3 months.

e) Patients with CVC-associated VTE should receive 3 months of anticoagulation and longer if the patient continues to have a CVC.

f) For patients with a second episode of VTE, if both episodes were provoked by a transient risk factor which has resolved, treat for 3 months, followed by prophylaxis with subsequent risk factors.

g) A second episode of unprovoked VTE is a strong indication for indefinite anticoagulant therapy unless there is a very high bleeding risk.

h) Patients with active cancer and VTE should receive indefinite anticoagulant therapy. Cancer patients with potentially curable disease and VTE should be treated for a minimum of 3 months but should continue if they are undergoing chemotherapy until this is completed.

i) Patients who have been recommended indefinite anticoagulant therapy, should be reassessed periodically (eg. yearly) to re-estimate the VTE vs bleeding risk balance.

j) For patients with unprovoked VTE and not continuing on indefinite anticoagulant therapy, they should be considered for long-term low dose aspirin prophylaxis if no contraindications.

**TABLE: SUMMARY OF RECOMMENDATIONS**

<table>
<thead>
<tr>
<th>Categories of VTE</th>
<th>Duration of Treatment</th>
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</thead>
<tbody>
<tr>
<td>First provoked VTE</td>
<td>3 months</td>
</tr>
<tr>
<td>First unprovoked VTE†</td>
<td>Minimum of 3 months and then reassess</td>
</tr>
<tr>
<td>Low or moderate bleeding risk</td>
<td>Indefinite therapy with periodic review</td>
</tr>
<tr>
<td>High bleeding risk</td>
<td>3 months</td>
</tr>
<tr>
<td>Isolated distal DVT</td>
<td>3 months</td>
</tr>
<tr>
<td>CVC associated VTE</td>
<td>3 months</td>
</tr>
<tr>
<td>Second provoked VTE</td>
<td>3 months</td>
</tr>
<tr>
<td>Second unprovoked VTE</td>
<td>Same as for first unprovoked VTE</td>
</tr>
<tr>
<td>Cancer-associated VTE</td>
<td>Minimum 3 months, then reassess and continue if active cancer or continuing to receive anticancer therapy</td>
</tr>
</tbody>
</table>

† Absence of a transient risk factor or active cancer.

**OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES:**
- Cancer and Thrombosis
- Central Venous Catheter-Related Venous Thrombosis
- Deep Vein Thrombosis (DVT): Treatment
- Pediatric Thrombosis
- Pregnancy: Venous Thromboembolism Treatment
- Pulmonary Embolism (PE): Treatment

**REFERENCES:**


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