**OBJECTIVE:**

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

**BACKGROUND:**

Recurrent episodes of VTE appear to fall into two categories:

1) Recurrences may be due to reactivation and extension of the original thrombosis. This risk is very high when patients first present with acute thrombosis; the risk decreases progressively during the first 3 months of treatment.

2) Recurrences may be due to a new episode of VTE that is not directly related to the initial episode of thrombosis; this risk, which reflects the patient’s underlying predisposition to VTE, 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. The assessment of benefit, which is dominated by balancing the increase in risk of recurrent VTE if anticoagulation is stopped against the increase in risk of bleeding if anticoagulation is continued, needs to be individualized. When comparing the risk of recurrent VTE with the risk of anticoagulant-induced bleeding (each usually expressed as a percentage per patient-year or number of events per 100 patient-years), it is 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).

**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 of treatment 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. Since 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) Because the risk of recurrence after stopping anticoagulant therapy is similar if anticoagulants are stopped at 3 months or are stopped later, if a time-limited course of treatment is selected, anticoagulants usually should be stopped at 3 months.
c) 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.

d) 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. The stronger the transient provoking factor (e.g. recent major surgery), the lower the expected risk of recurrence after stopping anticoagulant therapy.

e) Three months of anticoagulation is adequate treatment for VTE provoked by a transient risk factor. In the first year after stopping therapy, 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.

f) Although 3 months is the usual length of time-limited treatment, 6 months may be preferred with combinations of the following factors: (i) the DVT or pulmonary embolism (PE) was very large or very symptomatic; (ii) symptoms of the initial DVT or PE persist; (iii) the VTE was unprovoked (with these 3 factors, it may take 6 months to reduce the risk of recurrence to the lowest achievable level); (iv) the patient is not ready (confident enough) to stop anticoagulant therapy at 3 months; and (v) the patient does not have a high risk for bleeding.

g) 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.

h) 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 about 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.

i) A **second episode of VTE** suggests a higher risk of recurrence (increased by about 50%). If both episodes of VTE were provoked by a transient risk factor, indefinite anticoagulant therapy is unlikely to be necessary (i.e. treat for 3 months, followed by aggressive intermittent prophylaxis with subsequent risk factors). A second episode of unprovoked proximal DVT or PE is a strong argument for indefinite anticoagulant therapy.

j) Risk of recurrence is lower (about half) after an **isolated calf (distal) DVT** than after a proximal DVT or PE. This argues against treating an unprovoked isolated calf DVT for longer than 3 months.
k) Risk of recurrence is similar after an episode of **proximal DVT or 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 than PE.

l) Risk of recurrence 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 VTE occurred while patients were receiving chemotherapy and chemotherapy was subsequently stopped.

m) The presence of one of the common **hereditary predispositions to VTE** does not appear to be a clinically-important risk factor for recurrence either during or after anticoagulant therapy. Consequently, testing for hereditary thrombophilias is not useful in order to select duration of therapy.

n) The presence of an **antiphospholipid antibody** has uncertain significance as a predictor of recurrence independently of clinical presentation (e.g. provoked versus unprovoked).

o) 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 anticoagulant therapy.

p) 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.

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

r) **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; co-morbidity and reduced functional capacity; recent surgery; frequent falls; alcohol abuse). A suggested (but unvalidated) categorization of the risk of bleeding during extended anticoagulant therapy according to the prevalence of these risk factors is: **Low risk** with 0 factors (annual risk of major bleeding of 0.8%); **Moderate risk** with 2 factors (annual risk of major bleeding of 1.6%); and **High risk** if ≥2 factors (annual risk of major bleeding of >6.5%; will vary with number and severity of factors).

s) In patients with a first unprovoked proximal DVT or PE, 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 illicit patient preferences for the purpose of joint decision making, the expected risk of recurrence with and without indefinite anticoagulant therapy, and the expected consequences of recurrent VTE and bleeding, need to be explained to the patient.
### Table 1: Summary of Recommendations

<table>
<thead>
<tr>
<th>Categories of VTE</th>
<th>Duration of Treatment</th>
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<tbody>
<tr>
<td>Provoked by a transient risk factor*</td>
<td>3 months</td>
</tr>
<tr>
<td>First unprovoked VTE†</td>
<td>Minimum of 3 months and then reassess</td>
</tr>
<tr>
<td>Proximal DVT or PE with no or only minor risk factors for bleeding¶</td>
<td>Indefinite therapy with annual review, depending on patient preference</td>
</tr>
<tr>
<td>Isolated distal DVT</td>
<td>3 months</td>
</tr>
<tr>
<td>Second unprovoked VTE</td>
<td>Minimum of 3 months, then reassess. For patients with no or only minor risk factors for bleeding, indefinite therapy with annual review‡</td>
</tr>
<tr>
<td>Cancer-associated VTE</td>
<td>Minimum 3 months, then reassess and continue if active cancer (overt evidence of cancer) or continuing to receive anticancer therapy</td>
</tr>
</tbody>
</table>

* Transient risk factors include: surgery, hospitalization or plaster cast immobilization, all within 3 months; estrogen therapy, pregnancy, leg injuries or immobilizations more recently (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.

† Absence of a transient risk factor or active cancer.

¶ As noted in h) above, patient sex, with or without D-dimer testing, may be used to further assess a patient’s risk of recurrence. D-dimer testing should not be done unless it has first been established with the patient that the results will influence the patient’s decision to stop or to continue treatment. For a man, this would be a decision to stop anticoagulants with a risk of recurrence of 8% in the first year (if the D-dimer is negative) and a decision to remain on therapy indefinitely with a risk of recurrence of 16% in the first year. For a woman, this would be a decision to stop anticoagulants with a risk of recurrence of 5% in the first year (if the D-dimer is negative) and a decision to remain on therapy indefinitely with a risk of recurrence of 10% in the first year.

‡ Indefinite therapy is suggested if there is a low or moderate risk of bleeding, and 3 months is suggested if there is a very high risk of bleeding; both of these decisions are sensitive to patient preference.

### Other Relevant Thrombosis Canada Clinical Guides:
- Cancer and Thrombosis
- Deep Vein Thrombosis (DVT): Treatment
- Pediatric Thrombosis
- Pregnancy: Venous Thromboembolism Treatment
- Pulmonary Embolism (PE): Treatment
REFERENCES:

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