DURATION OF ANTICOAGULANT THERAPY FOR VENOUS THROMBOEMBOLISM

Thrombosis Canada
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TARGET AUDIENCE: All Canadian health care professionals.

OBJECTIVE:

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

ABBREVIATIONS:

APS	antiphospholipid antibody syndrome
DVT	deep vein thrombosis
CVAD	central venous access device
INR	international normalized ratio
LMWH	low-molecular-weight heparin
MTFHR	methylene tetrahydrofolate reductase
PE	pulmonary embolism
UFH	unfractionated heparin
VKA	vitamin K antagonist
VTE	venous thromboembolism

BACKGROUND:

The initial demonstration that 3 months of warfarin markedly reduced the frequency of recurrent deep vein thrombosis (DVT) compared with 3 months of low-dose subcutaneous heparin established the need for a prolonged phase of treatment for venous thromboembolism (VTE) after initial treatment with full-dose intravenous heparin (see DVT: Treatment guide). 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. This risk decreases progressively during the first 3 months of treatment (corresponding to treatment of the acute episode).

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 patients underlying predisposition to VTE, persists as long as an acquired risk factor is active (e.g. patients with cancer [see Cancer and Thrombosis guide]) or indefinitely (e.g. patients with unprovoked VTE).

The risk of bleeding during anticoagulant therapy also differs with the duration of therapy, and among patients. 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 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 appears to be similar whether anticoagulant therapy is stopped after 3 months of treatment or after 6 or 12 months of treatment; this suggests that 3 months of treatment is as long as is needed to treat the acute episode of VTE. However, shortening the duration of anticoagulation from 3 or 6 months to 4 or 6 weeks results in doubling the frequency of recurrent VTE during follow-up.

b) 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 greater the provoking reversible risk factor (e.g. recent major surgery), the lower the expected risk of recurrence after stopping anticoagulant therapy.

c) 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 major transient risk factor (e.g. recent surgery) and about 5% after a minor risk factor.

d) In patients with a first unprovoked episode of proximal DVT or pulmonary embolism (PE), the risk of recurrence is about 10% in the first year, 30% in the first 5 years and 50% in the first 10 years after stopping anticoagulant therapy.

e) 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. 3 months of therapy, 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.

f) Risk of recurrence is lower (about half) following an isolated calf (distal) DVT than after proximal DVT or PE. This argues against longer than 3 months of treatment for unprovoked isolated calf DVT.

g) Risk of recurrence is similar after an episode of proximal DVT or PE.

h) Risk of recurrence is about 3-fold higher in patients with active cancer. The risk is higher in patients with metastatic compared with localized disease, and is expected to be lower if VTE occurred while patients were receiving chemotherapy and chemotherapy was subsequently stopped.

i) The presence of a hereditary predisposition 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 (see Homocysteinemia-MTFHR, Factor V Leiden, Protein C, S & AT guides) is not required in order to select duration of therapy.

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

k) Factors such as D-dimer levels measured a month after stopping anticoagulant therapy, gender and residual abnormalities on ultrasound may influence the risk of recurrence but there is insufficient evidence to make recommendations regarding duration of therapy.

l) The presence of an inferior vena cava filter increases the risk of having DVT, decreases the risk of having a PE, and does not appear to have an effect on the overall risk of recurrent VTE. Consequently, the presence of an inferior vena caval filter need not influence the duration of anticoagulant therapy.

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

n) Risk of bleeding differs markedly among patients depending on the prevalence of risk factors (e.g. age >65 years; age >75 years; previous bleeding; cancer; metastatic cancer; renal failure; liver failure; thrombocytopenia; previous stroke; diabetes; anaemia; 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 $\geq$2 factors (annual risk of major bleeding of 6.5%; will vary with number and severity of factors).

Summary of Recommendations

Categories of VTE	Duration of Treatment
Provoked by a transient risk factor*	3 months
First unprovoked VTE†	Minimum of 3 months and then reassess
Proximal DVT or PE with no or only minor risk factors for bleeding	Indefinite therapy with annual review

Categories of VTE	Duration of Treatment
Isolated distal DVT	3 months, depending on patient preference
Second unprovoked VTE	Minimum of 3 months, then reassess. For patients with no or only minor risk factors for bleeding, indefinite therapy with annual review‡
Cancer-associated VTE	Minimum 3 months, then reassess and continue if active cancer (overt evidence of cancer) or continuing to receive anticancer therapy

* Transient risk factors include: surgery, hospitalization or plaster cast immobilization, all within 3 months; estrogen therapy, pregnancy, prolonged travel (e.g. longer than 8 hours), lesser leg injuries or immobilizations more recently (e.g. within 6 weeks). The greater 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

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

PEDIATRICS:

Pediatricians with expertise in thromboembolism should manage, where possible, pediatric patients with thromboembolism. When this is not possible, a combination of a neonatologist/pediatrician and an adult hematologist, supported by consultation with an experienced pediatric hematologist, is recommended. In children with a first VTE (central venous access device [CVAD] [see Central Venous Catheter-Related DVT guide]and non-CVAD related), acute anticoagulant therapy with either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) is recommended for at least 5 days, following which LMWH, UFH or a vitamin K antagonist (VKA) should be continued for 3 months. In patients transitioning to a VKA, these should be initiated on day 1 with LMWH/UFH discontinued on day 6 or when the international normalized ratio (INR) is $\geq$ 2.0, whichever is longer.

It is recommended that children with unprovoked VTE receive anticoagulant therapy for 6-12 months following an event and indefinite treatment if recurrent. In children with secondary VTE (i.e. VTE that has occurred in association with a clinical risk factor) who have ongoing, but potentially reversible risk factors, continue anticoagulant therapy beyond 3 months in either therapeutic or prophylactic doses until the risk factor has resolved. See Pediatrics guide.

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