Venous Thromboembolism: Duration of Treatment

Objective:

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

Background:

Determining the duration of anticoagulant therapy depends on an assessment of an individual's **risk of recurrent thrombosis off anticoagulation** versus the **risk of major bleeding on anticoagulation**. While case-fatality rates of recurrent VTE and major bleeding events are similar during the initial period of VTE treatment, the case fatality rate of recurrent VTE is lower after completion of 3 to 6 months of anticoagulation compared to that for major bleeding. This means that long-term therapy is not always associated with a net mortality benefit, especially in patients at lower risk of recurrent VTE or higher bleeding risk. There are unfortunately no long-term randomized studies comparing short term to indefinite anticoagulation duration.

Risk of VTE Recurrence

The risk of recurrent VTE <u>after stopping anticoagulation</u> 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. **Three months is the minimum duration of treatment** for proximal deep vein thrombosis (DVT) or pulmonary embolism (PE) because shortening the duration of anticoagulation from 3 or 6 months to 4 or 6 weeks results in doubling of the frequency of recurrent VTE during the first 6 months after stopping anticoagulant therapy.

After 3 months, a decision must be made about whether to continue anticoagulation. This decision will depend on balancing the risk of recurrence (which depends mainly on whether the VTE was provoked by a transient risk factor, unprovoked, or related to a major persistent risk factor such as active cancer) and the risk of bleeding (see below).

Other considerations:

- Type of index event: the risk of VTE recurrence is similar after an episode of proximal DVT versus 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. The risk of recurrence is lower (by 50%) after an isolated calf (distal) DVT than after a proximal DVT or PE.
- Burden of anticoagulation (financial, functional, and psychological), and quality of life
- Patient preference: 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.

Bleeding Risk Estimation

The risk of anticoagulant-induced bleeding varies markedly among patients and must be balanced against the benefits of continuing anticoagulation. The risk of anticoagulant-induced bleeding is highest during the first 3 months of treatment and stabilizes after the first year.

Unfortunately, we do not currently have adequately validated bleeding risk tools to provide accurate estimates of bleeding risk in patients with VTE. Bleeding risk scores such as HASBLED were derived in patients with atrial fibrillation (AF), who generally have higher baseline bleeding risk, so major bleeding estimates from these studies may not apply to patients on anticoagulation for VTE prevention who have already completed 3 to 6 months of therapy. Major bleeding is variably defined in studies, but contemporary studies usually define it as bleeding that is fatal, occurs in a critical organ/space, results in a reduction of hemoglobin of at least 20 g/L, and/or results in the transfusion of at least 2 units of blood.

One pragmatic approach is to identify variables that appear to be predictors of bleeding in multiple studies in both AF and VTE, to form an overall impression of bleeding risk (see **Table 1**). Patients with two or more such risk factors may be considered to be at least moderate bleeding risk. One should carefully consider whether extended anticoagulant therapy is warranted in such individuals.

TABLE 1: BLEEDING RISK FACTORS

- Age > 65
- Anemia
- Antiplatelet therapy
- Chronic kidney disease
- Chronic liver disease
- Prior history of bleeding
- Thrombocytopenia

Long term use of direct oral anticoagulants (DOACs) (as opposed to warfarin) may provide a better safety profile in terms of major bleeding.

In patients who have completed 6 months of anticoagulant therapy, the rate of major bleeding with DOACs approximates the major bleeding risk associated with ASA while having a superior efficacy to ASA in terms of reduction in recurrent VTE.

Patients with VTE Provoked by a Transient Risk Factor:

Patients with VTE provoked by a transient risk factor (**Table 2**) in the 3 months prior to the event have a much lower risk of recurrence than those with an unprovoked VTE or a persistent risk factor. Patients with VTE provoked by a transient risk factor which has resolved should generally receive only 3 months of anticoagulation.

TABLE 2: EXAMPLES OF TRANSIENT VTE RISK FACTORS

CATEGORY OF TRANSIENT RISK FACTOR	EXAMPLES OF RISK FACTORS
Major	• Surgery with general anesthetic for ≥30 minutes • Admission to hospital for an acute illness with confinement to bed for at least 3 days
Minor	• Surgery with general anesthetic for <30 minutes • Admission to hospital with an acute illness for less than 3 days • Confined to bed out of hospital for at least 3 days with an acute illness • Hormonal therapy • Pregnancy or the puerperium • Leg injury associated with reduced mobility for at least 3 days

The stronger the provoking reversible risk factor, the <u>lower</u> the expected risk of recurrence after stopping anticoagulant therapy. As shown in **Table 3**, the risk of recurrence is lower for VTE provoked by a surgical (i.e. major) risk factor than for those associated with non-surgical (i.e. minor) risk factors. For both, the risk of recurrence is lower than for an unprovoked event or one associated with a persistent strong risk factor.

TABLE 3: ESTIMATED RISK OF RECURRENCE AFTER STOPPING ANTICOAGULATION FOR A FIRST VTE

	1 YEAR AFTER STOPPING ANTICOAGULANTS	5 YEARS AFTER STOPPING ANTICOAGULANTS
Surgical/Major	1-2%	3%
Non-surgical/Minor (e.g., hospitalization, plaster cast immobilization, hormonal therapy*, flight of > 8 hours, medical illness with immobilization)	5%	15%

*The risk of recurrence in women with a first VTE associated with estrogen-containing contraceptive use (4% by 5 years off anticoagulation) may be lower than that seen with VTE provoked by other minor risk factors.

Patients with an Unprovoked VTE:

Patients with a first episode of unprovoked VTE should receive at least 3 months of anticoagulation, with the decision to continue anticoagulation longer term dependent on the estimated risk of recurrence, the risk of bleeding, and patient preference. In patients with a first unprovoked VTE, the decision to stop anticoagulant therapy 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.

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, 25% in the first 5 years and 36% in the first 10 years after stopping anticoagulant therapy.

Long-term anticoagulation should be considered for these patients, based on the risks of recurrent VTE and bleeding.

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** versus negative D-dimer have ~2-fold higher risk of recurrence;
- the predictive values 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.

These estimates can be used when discussing recommendations for duration of anticoagulation after unprovoked VTE, in conjunction with an estimate of bleeding risk and patient preference.

Prognostic models:

Three models to predict the risk of recurrent VTE after anticoagulation discontinuation following a **first unprovoked DVT or PE** have undergone external validation (e.g., in a patient population or data set separate from which they were derived). However, each have significant limitations as discussed below, which limit broad applicability.

HERDOO2

PREDICTORS OF RECURRENCE	RULE
• Hyperpigmentation, edema or redness in either leg • VIDAS D-dimer ≥250 ug/L during anticoagulation • Body mass index (BMI) ≥30 kg/m^2 • Age ≥65 years	• Female patients with <2 predictors of recurrence have a low risk of recurrence (3.0% per patient year) and may consider anticoagulant discontinuation • Women with ≥2 predictors of recurrence and all men are classified as high risk of recurrence

Unlike other investigators, the HERDOO2 investigators classified unprovoked VTE as all VTE (including estrogen- and pregnancy-related) not occurring in the setting of a major reversible provoking risk factor or

cancer. As such, the risk of recurrence in women with less than 2 predictors of recurrence in this model is likely to be higher in those who are older. In low risk women under 50 years of age who discontinued anticoagulants, the risk of recurrent VTE was low regardless of whether their initial event was estrogen associated. However, in women 50 years of age or older with less than 2 predictors of recurrence who stopped anticoagulants, the risk of recurrence was 5.7% per patient year. Therefore, further research is required before this rule can be confidently used in women ≥50 years of age. A subsequent analysis has shown that the HERDOO2 D-dimer cutpoint (and, therefore, rule) is not valid with D-dimer assays other than the VIDAS D-dimer. It is noteworthy that most patients in the HERDOO2 studies had D-dimer testing on a vitamin K antagonist rather than a DOAC.

DASH

PREDICTORS OF RECURRENCE	RULE
• Abnormal D-dimer level after approximately 1 month off anticoagulation (+2 points) • Male sex (+1 point) • Age ≤50 years (+1 point) • Hormone use at VTE diagnosis (-2 points)	Those with a DASH score of ≤1 have a risk of recurrence of 3.5% per year

It should be noted that the risk of recurrence in those >65 years was >5% even in those with the lowest DASH score. As with the HERDOO2 rule, further research is needed in older patients.

The **Vienna prediction model**, which includes sex, site of index event and D-dimer, uses a nomogram to calculate risk of recurrence at 1 year and 12 years after anticoagulant discontinuation (risk calculator available at http://www.meduniwien.ac.at/user/georg.heinze/zipfile/ViennaPredictionModel.html). Although this model has been validated in a separate pooled data set, its safety and efficacy have not been formally assessed in a clinical impact study in which the results of the model are used to guide patient management decisions.

Patients with Persistent Risk Factors:

Patients with strong persistent risk factors (active cancer, high risk thrombophilia) should remain on anticoagulation indefinitely if the bleeding risk is acceptable.

a) Persistent risk factors that usually prompt continuation of anticoagulation:

- **Active cancer:** The risk of recurrent VTE is markedly increased in patients with **active cancer.** This risk is higher in patients with metastatic disease (compared with localized disease) and in patients on chemotherapy [See **Clinical Guide: Cancer and Thrombosis**]

- **Antiphospholipid antibody positivity:** The presence of persistently positive moderate-to-high titre antiphospholipid antibodies and/or a lupus anticoagulant and VTE (fitting the criteria for **antiphospholipid antibody syndrome**) is considered high risk for VTE recurrence (and arterial thrombosis) and these patients should generally receive anticoagulant therapy indefinitely. Consultation with a Thrombosis specialist or Hematologist is suggested. [See **Clinical Guide: Thrombophilia: Antiphospholipid Antibody Syndrome**]
- **High risk hereditary thrombophilia:** Given the low prevalence of the higher risk thrombophilias, screening for hereditary thrombophilia is generally not recommended to determine duration of anticoagulation. 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 the patient may be a candidate for indefinite anticoagulant therapy. Consultation with a Thrombosis specialist or Hematologist is suggested. [See **Clinical Guides: Thrombophilia: Deficiencies in Protein C, Protein S, and Antithrombin** and **Thrombophilia: Factor V Leiden and Prothrombin Gene Mutation**]

b) Persistent risk factors that do not usually influence duration of anticoagulation:

- **Low risk hereditary thrombophilia and/or family history of VTE:** The presence of one of the common hereditary thrombophilia conditions (i.e. heterozygosity 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. A positive family history alone does not increase the risk of recurrent VTE.
- **Presence of an inferior vena cava filter:** The presence of an inferior vena cava filter (IVF) alone should not influence the duration of anticoagulant therapy beyond the duration of treatment for the VTE that triggered the filter insertion.
- **Residual abnormalities on ultrasound: T**hese are detected in approximately one third of patients. Although these findings may slightly increase the likelihood of recurrence after stopping anticoagulants, the associated risk is not sufficient to make this a deciding factor in determining duration of anticoagulant therapy.

Patients with a second episode of VTE

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

TABLE 4: SUMMARY RECOMMENDATIONS FOR DURATION OF TREATMENT

CATEGORIES OF VTE	DURATION OF TREATMENT
First VTE provoked by a transient risk factor	3 months
Second VTE provoked by a transient risk factor	Same as for first VTE provoked by a transient risk factor
First unprovoked VTE†	Minimum of 3 months and then reassess.
With low or moderate bleeding risk	Indefinite therapy with periodic reviews¶‡
With high bleeding risk	3 months, especially if recurrent VTE risk is relatively lower and/or bleeding risk factors cannot be mitigated
Second unprovoked VTE	Same as for first unprovoked VTE; this is a strong indication for indefinite anticoagulant therapy unless there is a very high bleeding risk¶‡
Isolated distal DVT	3 months
Central venous catheter(CVC)-associated VTE	3 months; longer if CVC remains in place
VTE associated with ongoing non-cancer-related risk factors (e.g. paraplegia or other significant immobility, active inflammatory bowel disease, high risk thrombophilia)	Indefinite therapy with periodic reviews or as long as the risk factor persists¶
Cancer-associated VTE	3 to 6 months, then reassess and continue if active cancer or patient continuing to receive anticancer therapy

† Absence of a transient risk factor, active cancer or other ongoing clinical risk factor for recurrent VTE.

¶ Patients who have been recommended indefinite anticoagulant therapy should be reassessed periodically (e.g. yearly) to re-estimate the VTE versus bleeding risk balance and review patient preferences.

‡ For patients continuing on long term rivaroxaban (Xarelto®) or apixaban (Eliquis®) beyond 6 months, dose reduction of rivaroxaban to 10 mg once daily or apixaban to 2.5 mg twice daily can be considered based on the results of the EINSTEIN CHOICE and AMPLIFY Extend studies in which these lower doses were as effective and safe as standard dosing.

Special Considerations:

Pediatrics

If possible, pediatric hematologists with experience in thromboembolism should manage children with or at risk for thrombosis, as well as those receiving antithrombotic therapy. When this is not possible, a combination of a neonatologist/pediatrician and an adult hematologist, supported by consultation with an experienced pediatric hematologist, should manage these children.

Central venous catheter (CVC) associated VTE

CVC-associated VTE should be treated like a provoked VTE. [See **Clinical Guide: [Central Venous Catheter-Related Thrombosis]**].

Other Relevant Thrombosis Canada Clinical Guides:

- [Apixaban (Eliquis®)](#)
- [Cancer and Thrombosis](#)
- [Central Venous Catheter-Related Venous Thrombosis](#)
- [Deep Vein Thrombosis (DVT): Treatment](#)
- [Pregnancy: Venous Thromboembolism Treatment](#)
- [Pulmonary Embolism (PE): Treatment](#)
- [Rivaroxaban (Xarelto®)](#)
- [Thrombophilia: Antiphospholipid Antibody Syndrome](#)
- [Thrombophilia: Deficiencies in Protein C, Protein S, and Antithrombin](#)
- [Thrombophilia: Factor V Leiden and Prothrombin Gene Mutation](#)

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