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Clinical Guide - Duration of Anticoagulant Therapy for VTE

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Summary of Recommendations

Categories of VTE	Durations of treatment (Target INR 2.5, range 2.0-3.0)
Provoked by a transient risk factor *	3 months of treatment
Unprovoked VTE†	Minimum of 3 months of treatment and then reassess
First unprovoked proximal DVT or PE WITH no risk factors for bleeding AND if good anticoagulant control is achievable AND if anticoagulation is not a major burden for the patient.	Indefinite therapy with annual review
Isolated distal DVT as a first event	3 months of treatment
Second unprovoked VTE	Indefinite therapy with annual review
Cancer-associated VTE	Indefinite treatment‡

* 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 (e.g., such as recent major surgery), the lower the expected risk of recurrence after stopping anticoagulant therapy.

† Absence of a transient risk factor or active cancer

‡ Initial treatment with a low-molecular-weight-heparin for at least 3 months is recommended, followed by long-term treatment with either low-molecular-weight-heparin or warfarin (cross-reference TIG guideline on Cancer and Thrombosis).

Background

Initial demonstration that 3 months of warfarin markedly reduced the frequency of recurrent DVT compared to 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.(1) Subsequently, high-dose subcutaneous heparin and low-molecular-weight-heparin (LMWH; 50-75% of the acute treatment dose) were shown to be as effective as warfarin for this phase of treatment.(1) Early studies did not follow patients after anticoagulant therapy was withdrawn to determine if the risk of recurrent VTE remained acceptable, and did not compare the risk of recurrence after completion of different durations of therapy in order to identify the optimal duration of therapy .

Recurrent episodes of VTE appear to fall into two categories. First, recurrences may be due to reactivation and extension of the original thrombosis; this risk, which is very high when patients present with acute thrombosis appears to persist for about 3 months. Second, 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) or indefinitely (e.g., patients with unprovoked VTE).[2-4] The risk of bleeding during anticoagulant therapy also differs with the duration of therapy, and among patients.[5-7]

Anticoagulant therapy should be stopped when it's benefits no longer clearly outweigh it's risks, or it is patient preference to stop treatment 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%).[8;9]

Factors that influence the duration of anticoagulant therapy

During the last decade, a series of well-designed studies have helped to define the optimal duration of anticoagulation. Their findings can be summarized as follows:

- During the last two decades, a series of well designed studies have helped to define the optimal duration of anticoagulation. Their findings can be summarized as follows:

- Shortening the duration of anticoagulation from 3[10;11] or 6[12] months to 4[10;11] or 6[12] weeks results in a doubling of the frequency of recurrent VTE during one[10;11] to two[12] years of follow-up.

- Patients with VTE provoked by a transient risk factor have a lower (about one-third) risk of recurrence than those with an unprovoked VTE or a persistent risk factor.[10-14] The greater the provoking reversible risk factor (e.g., such as recent major surgery), the lower the expected risk of recurrence after stopping anticoagulant therapy.

- 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 3% if VTE was provoked by a major transient risk factor (e.g., recent surgery) and about 5% after a minor risk factor.[10;11;13-15]

- The risk of recurrent VTE appears to be similar if anticoagulant therapy is stopped after 3 months of treatment compared to 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.[1;13;16-18]

- 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 in patients with a first unprovoked episode of proximal DVT or PE.[1;19]

- After 3 months of initial treatment of unprovoked VTE with oral anticoagulants targeted at an INR of 2.5 (INR range 2.0-3.0), continuing treatment with:

  • Oral anticoagulants targeted at an INR of ~2.5 reduces the risk of recurrent VTE by over 90%.[1;20;21]
  • Oral anticoagulants targeted at an INR of ~1.75 reduces the risk of recurrent VTE by about 75%.[22]
  • Oral anticoagulants targeted to an INR of ~2.5 have been shown to be more effective than therapy targeted to an INR of ~1.75, without having increased the risk of bleeding.[23]

- A second episode of VTE suggests a higher risk of recurrence (increased by about 50%).[12;24] 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 VTE is s strong argument for indefinite anticoagulant therapy.[1]

- Risk of recurrence is lower (about half) following an isolated calf (distal) DVT than after proximal DVT or PE.[12;13;25] This argues against longer than 3 months of treatment for unprovoked isolated calf DVT.

- Risk of recurrence is similar after an episode of proximal DVT or PE.[2;8;12;26]

- Recurrent VTE is about three times as likely to be a PE after an initial PE (about 60% of episodes) compared to after an initial DVT (about 20% of episodes).[4;8;26] This effect is expected to increase mortality from recurrent VTE about 2-fold after a PE compared to after a DVT.

- Risk of recurrence is about 3-fold higher in patients with active cancer.[2;3;7] The risk is higher in patients with metastatic compared to localized disease, and is expected to be lower if VTE occurred while patients were receiving chemotherapy and chemotherapy was subsequently stopped.

- Long term treatment with low-molecular-weight-heparin, particularly for the first 3 or 6 months, is more effective than warfarin in patients with VTE associated with cancer and, therefore, is the preferred treatment for such patients (see "Cancer and Thrombosis" guideline).[1;27]

- Estrogen therapy is a risk factor for first [28;29] and recurrent [30] episodes of VTE; consequently, the risk of recurrent VTE after stopping anticoagulants is expected to be lower in women who had VTE while on estrogen therapy provided they are no longer taking estrogens.[2]

- 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.[1;31] Consequently, testing for hereditary thrombophilias is not required in order to select duration of therapy.

- The presence of an antiphospholipid antibody has uncertain significance as a predictor of recurrence independently of clinical presentation (e.g., provoked versus unprovoked).[4;32;33] Absence of an antiphospholipid antibody on routine testing is not a good reason to stop anticoagulant therapy at 3 months in a patient with unprovoked proximal DVT or PE, and presence of an antiphospholipid antibody is not a good reason to treat patients with VTE that was provoked by transient risk factor for longer than 3 months.

- D-dimer levels measured a month after stopping anticoagulant therapy predict the risk of recurrence in patients with a first episode of unprovoked VTE.[34;35] However, further studies are needed to determine if negative D-dimer results justify stopping anticoagulant therapy in all, or selected subgroups of, patients with unprovoked proximal DVT or PE after 3 months of treatment.

- Females appear to have a substantially lower risk of recurrence than males.[32;36] However, further studies are needed to determine if this risk is low enough to justify stopping anticoagulant therapy in females with unprovoked proximal DVT or PE who have completed 3 months of treatment.

- The presence of residual deep vein thrombosis on ultrasound appears to be a marker of a heightened risk of recurrence in patients with unprovoked VTE.[18;32;37] However, the strength of this relationship is uncertain and further studies are needed to determine if absence of residual DVT on ultrasound justifies stopping anticoagulant therapy in patients who have had an unprovoked proximal DVT.

- The presence of an inferior vena caval filter appears to increase the risk of having a DVT, decreases the risk of having a PE, and has no net effect on the risk of recurrent VTE.[26;38;39] Consequently, the presence of an inferior vena caval filter need not influence the duration of anticoagulant therapy.

- The risk of anticoagulant-induced bleeding is highest during the first three months of treatment and stabilizes after the first year.[5]

- Risk of bleeding differs markedly among patients depending on the prevalence of risk factors (e.g., advanced age; previous bleeding or stroke; renal failure; anemia; antiplatelet therapy; malignancy; poor anticoagulant control).[5-7]

- The risk of major bleeding in younger patients (e.g. less than 60 years) that do not have risk factors for bleeding and have good anticoagulant control (target INR 2-3) is about 1% per year.[21;23] The risk of major bleeding is expected to be at least 10-fold higher in patients with multiple risk factors for bleeding.[6]

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