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Clinical Guide - Duration of Anticoagulant Therapy for VTE (April 2004)

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Summary of Recommendations

Categories of VTE	Durations of treatment (Target INR 2.5, range 2.0-3.0)
VTE provoked by a major transient risk factor *	**3 months of treatment**
VTE not provoked by a major transient risk factor* *If also:* *presentation as pulmonary embolism; or second unprovoked episode; or low risk of bleeding; or patient does not consider anticoagulant therapy a burden; or antiphospholipid antibody; or homozygous factor V Leiden; or heterozygous for both Factor V Leiden and G20210A prothrombin gene mutation; or deficiencies of protein C, S, or antithrombin*	**6 months of treatment** *consider indefinite rather than 6 months of therapy†*
VTE provoked by uncontrolled malignancy *If also:* *a high risk of bleeding; or an additional reversible provoking risk factor.*	**Indefinite treatment ‡** *consider 6 months rather than indefinite therapy*

* Major transient risk factors include: within 3 months: surgery with general anaesthesia; plaster cast immobilization of a leg; hospitalization.

† Indefinite therapy would usually not be considered if: there was also a minor transient provoking risk factor (e.g., estrogen therapy; prolonged travel [i.e. 6 hours]; pregnancy [see "Thrombosis in Pregnancy" guideline]; less marked leg injuries or immobilization) or a high risk for bleeding. Yearly review of this decision should be performed to consider new developments in antithrombotic therapy, or change in the patient's risk of bleeding

‡ Long term treatment with low-molecular-weight-heparin instead of warfarin may be preferred.

Background

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;2) 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.(2) However, whether 3 months of treatment is longer than necessary, or is long enough, for all patients with VTE has been uncertain.

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, persists for a limited period.(3;4) 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 for a longer period of time and often indefinitely.(3;5;6) The length of time after starting treatment that patients remain at risk of recurrence of their original thrombosis, and the magnitude of the long term risk for a new episode of VTE, is thought to differ among patients. The risk of bleeding during anticoagulant therapy also differs with the duration of therapy, and among patients.(7;8)

Anticoagulant therapy should be stopped when it's benefits no longer clearly outweigh it's risks.(9) This assessment, which is dominated by balancing the risk of recurrent VTE if anticoagulation is stopped against the risk of bleeding if anticoagulation is continued, needs to be individualized.(9) 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 mores severe than the consequences of a recurrent episode of VTE (e.g., case-fatality of ~20% versus ~5%).(9-11)

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:

- Shortening the duration of anticoagulation from 3(12;13) or 6(14) months to 4(12;13) or 6(14) weeks results in a doubling of the frequency of recurrent VTE during one(12;13) to two(14) 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.(5;12-15)
- Three months of anticoagulation is adequate treatment for VTE provoked by a transient risk factor; subsequent risk of recurrence is about 3% per patient-year.(12;13;15-17)
- Three months of anticoagulation may not be adequate treatment for an unprovoked ("idiopathic") episode of VTE; subsequent early risk of recurrence has varied from 5% to 25% per patient-year.(14;16;18;19)
- After six months of anticoagulation, recurrent DVT is at least as likely to effect the contralateral leg; this suggests that "systemic" rather than "local" (including inadequate treatment) factors are responsible for recurrences after 6 months of treatment.(4)
- There is a persistently elevated risk of recurrent VTE after a first episode; this appears to be 5 - 12% per year after six or more months of treatment for an unprovoked episode.(14;16;19-21)
- Extending duration of anticoagulation beyond 3 to 6 months may delay but, ultimately, not reduce the risk of recurrence if therapy is then stopped.(19;21)
- 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%.(6;18)
- 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 are more effective than using an INR target of ~1.75, without evidence of increased bleeding.(23)
- A second episode of VTE suggests a higher risk of recurrence but not necessarily high enough to justify indefinite anticoagulation.(24;25)
- Risk of recurrence is lower (about half) following an isolated calf (distal) DVT than after proximal DVT or PE; this favors a shorter duration of treatment.(14;16)

- Risk of recurrence is similar after an episode of proximal DVT or PE.(3;10;14;24)

- Recurrent VTE is usually (about 60% of episodes) a PE after an initial PE, and usually (about 80% of episodes) a DVT after an initial DVT(10;24;26); this effect is expected to increase mortality from recurrent VTE by 2 to 3-fold after a PE compared to after a DVT.(27)

- Risk of recurrence is about 3-fold higher in patients with active cancer.(3;5;28)

- Long term treatment with low-molecular-weight-heparin is more effective than warfarin in patients with VTE associated with cancer, and may be a preferred option for such patients (see "Cancer and Thrombosis" guideline).(29)

- Estrogen therapy is an important risk factor for first (30;31) and recurrent (32) episodes of VTE; consequently, if VTE occurred while on estrogen therapy, the risk of recurrent VTE is expected to be lowered by stopping estrogens.(3)

- Risk of recurrence is higher with antiphospholipid antibodies (anticardiolipin antibodies and/or lupus anticoagulants)(18;25), homozygous Factor V Leiden(33) and, probably, deficiencies of protein C, protein S and antithrombin(5;34), and combined heterozygous Factor V Leiden and heterozygous G20210A prothrombin gene mutations(35); these favor a longer duration of treatment.

- Heterozygous Factor V Leiden and the G20210A prothrombin gene mutations do not appear to be clinically important risk factors for recurrence.(33)

- Other risk factors for recurrences may include: advanced age; elevated levels of clotting factors VIII, IX, XI and homocysteine; elevated d-dimer levels after stopping anticoagulant therapy; venal caval filters; and residual deep vein thrombosis on ultrasound; they have uncertain implications for duration of treatment.(27)

- The risk of anticoagulant-induced bleeding is highest during the first three months of treatment and stabilizes after the first year.(7)

- Risk of bleeding differs markedly among patients depending on the prevalence of risk factors (e.g., advanced age; previous bleeding or stroke; renal failure; anaemia; antiplatelet therapy; malignancy; poor anticoagulant control).(7;8;23)

- 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.(7;23;36) The risk of major bleeding is expected to be at least 10-fold higher in patients with multiple risk factors for bleeding.(8)

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