Duration of anticoagulant therapy for venous thromboembolism

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The risk of bleeding, as well as patient preferences, must be considered when deciding duration of warfarin therapy

Venous thromboembolism (VTE) affects about 17 000 Australians each year, usually as deep vein thrombosis (DVT) of the legs or pulmonary embolism (PE).[1] The sequelae of VTE include death, post-thrombotic syndrome, chronic pulmonary thromboembolic disease and recurrent VTE. Anticoagulation with an oral vitamin K antagonist (warfarin), overlapped for the first 5–7 days with unfractionated heparin, low-molecular-weight heparin or fondaparinux, prevents thrombus progression and reduces the risk of recurrent VTE and death during the acute phase.[2,3] When treatment is continued beyond the acute phase, warfarin reduces the risk of recurrent VTE but increases the risk of bleeding and requires frequent laboratory monitoring, which is inconvenient for patients. Thus, decisions regarding the optimal duration of anticoagulant therapy must balance the increased risk and sequelae of recurrent VTE when warfarin is stopped against the risk of bleeding and the inconvenience of continuing treatment.[3]

Many randomised controlled trials have evaluated the optimal duration of anticoagulant therapy in patients with VTE, and their results can be summarised as follows:

- In patients with a first episode of VTE that is provoked by a reversible risk factor, 3 months of anticoagulant therapy halves the risk of recurrence compared with the level of risk achieved with 1 month of therapy.[4] The risk of recurrence beyond 3 months is low.[4]
- In patients with isolated provoked or unprovoked calf DVT, 6 weeks of anticoagulant therapy is as effective as 3 months' therapy.[5]
- In patients with a first episode of unprovoked VTE, 3 months of anticoagulant therapy is as effective as 6 months' therapy,[5,6] but there is a high rate of recurrence (about 10%) during the first year after stopping warfarin; in subsequent years, the recurrence rate decreases to 3%–4% per annum.[7,8]

Continuing warfarin treatment beyond the acute phase for 1–2 years reduces the risk of recurrence during treatment by as much as 90% compared with no warfarin, but a "catch-up" phenomenon occurs after stopping warfarin, so that after several years the risk of recurrence is similar in patients who are treated for 3 months compared with those treated for 12 months.[9]

Although the efficacy of long-term treatment with vitamin K antagonists for preventing recurrent VTE is impressive and consistent,[7,8,10] pooled data from 10 trials involving 4833 participants provide no evidence that long-term anticoagulant therapy reduces fatal PE.[8] Trial data show that continuing warfarin treatment beyond 3 months is associated with an annual risk of major bleeding of 1%–3%,[11] and the incidence of major bleeding is likely to be even higher in unselected patients not enrolled in a clinical trial. Long-term warfarin therapy targeting an international normalised ratio (INR) of 1.5–2.0 is less effective for the prevention of recurrent VTE than warfarin therapy targeting an INR of 2.0–3.0; nor does the lower target ratio reduce the risk of bleeding.[12]

Several new oral anticoagulants (eg, rivaroxaban, apixaban, dabigatran etexilate) that selectively target coagulation factor Xa or factor IIa (thrombin) are in advanced stages of clinical development.[13] These agents appear to be attractive alternatives to warfarin for long-term management of patients with VTE because they can be given in fixed daily or twice-daily doses without laboratory monitoring. However, it remains to be seen whether the new oral anticoagulants will provide a more favourable risk–benefit profile than warfarin during long-term treatment.

Our recommendations for duration of anticoagulant therapy for VTE (Box) are generally consistent with those of the 2008

Recommended duration of anticoagulant therapy

Condition	Recommended duration	Evidence grade*
Provoked VTE (transient risk factor)	3 months	1A
Isolated calf DVT	6 weeks†	1B
First unprovoked proximal DVT or PE	Minimum 3 months Consider long-term‡	1A 2B
Recurrent unprovoked VTE	Long-term	1A
Cancer-related VTE	Minimum 3 months§ Continue during treatment for cancer and while cancer is active	1A 1C
VTE with high-risk thrombophilia¶ **	Minimum 3 months; consider long-term	2C
Limb- or life-threatening VTE**	Minimum 3 months; consider long-term	2C
Chronic thromboembolic pulmonary disease	Long-term	1C
Severe post-thrombotic syndrome**	Consider long-term	2C

DVT = deep vein thrombosis. PE = pulmonary embolism.
VTE = venous thromboembolism.
* Based on the grading system used by the American College of Chest Physicians (ACCP) guidelines.[13] Strong (Grade 1) recommendations can be applied uniformly to most patients. Weak (Grade 2) suggestions require more judicious application. Level A denotes high-quality evidence; Level B, moderate-quality evidence; and Level C, low-quality evidence. Risk of bleeding, as well as patient values and preferences, must be taken into account.
† Unlike the ACCP guidelines, which do not provide a separate recommendation for calf vein thrombosis, we recommend 6 weeks, based on the results of the Durée Optimale du Traitement AntiVitamines K trial.[5] There is no evidence to guide the treatment of calf vein thrombosis limited to muscle veins; if anticoagulants are used, we suggest that the duration of use does not exceed 6 weeks (Grade 2, Level C).
‡ Unlike the ACCP guidelines, we do not explicitly recommend long-term treatment after a first episode of unprovoked VTE. Our recommendation attaches a relatively high value to the burden of long-term anticoagulant therapy and a lower value to preventing recurrence beyond the acute phase.
§ Low-molecular-weight heparin is the preferred treatment.
¶ Includes patients with antiphospholipid antibody syndrome, antithrombin deficiency and multiple thrombophilic defects.
** The ACCP guidelines do not provide guidance for these categories of patients. ◆

American College of Chest Physicians guidelines.[14] The risk of bleeding and patient values and preferences must be taken into account when making treatment decisions. Patients with acute DVT or PE or both should receive warfarin for a minimum of 3 months. An exception is patients with isolated calf DVT, for whom 6 weeks of warfarin treatment is adequate. Patients whose first episode of proximal DVT or PE is provoked by a transient risk factor (eg, surgery) can stop treatment after 3 months because they have a relatively low risk of recurrence after warfarin is discontinued. Patients with a persisting reversible risk factor should continue taking warfarin until the risk is no longer present. Compared with those who experience provoked VTE, patients with a first episode of unprovoked proximal DVT or PE have a substantially higher risk of recurrence after warfarin treatment is discontinued, presumably because they have a chronic propensity to thrombus formation. However, there is little point in continuing treatment beyond 3–6 months in these patients unless a decision is made to treat indefinitely, as the benefits of extended treatment are lost when warfarin is discontinued.

Long-term or indefinite warfarin therapy seems reasonable for patients with a history of limb- or life-threatening VTE, chronic pulmonary thromboembolism or severe post-thrombotic syndrome, and for patients who prefer to continue anticoagulant treatment. Indefinite treatment also seems reasonable for patients at very high risk of recurrence, such as those with a history of recurrent unprovoked VTE, high-risk thrombophilia (eg, antiphospholipid antibody syndrome, antithrombin deficiency, multiple thrombophilic defects) or active cancer (or those receiving treatment for cancer). Other tests (eg, for residual thrombus detected by compression sonography, or D-dimer) might also identify patients at increased risk of recurrence, but their utility in determining the optimal duration of anticoagulant therapy remains uncertain. Ultimately, the question of which patients will benefit from indefinite anticoagulant therapy requires evaluation in large randomised controlled trials that have sufficient power to show a worthwhile reduction in morbidity or mortality or an improvement in quality of life.

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