

Long-term management of venous thromboembolism: is there a role for low-intensity warfarin therapy?

The recently released PREVENT trial provides some answers

VENOUS THROMBOEMBOLISM (VTE) affects 1–2 people per 1000 in the general population each year.¹ It most commonly manifests as deep vein thrombosis of the leg, or as pulmonary embolism. There are many acute provoking factors or triggers (eg, major trauma, recent surgery), and many chronic predisposing factors, both genetic (eg, factor V Leiden) and acquired (eg, cancer).

Most patients with provoked VTE have a low risk of recurrence (0–4% per year without anticoagulation), presumably because most have no major predisposing factors for VTE.² Treatment for provoked VTE is short term and consists of giving intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin (LMWH) for at least 5 days, followed by warfarin (target international normalised ratio [INR], 2.0–3.0) for 3 months.³ Further antithrombotic therapy is usually not required unless patients are re-exposed to known triggers for VTE.

Most patients with unprovoked VTE, however, have a higher risk of recurrence ($\geq 5\%$ per year without anticoagulation) over many years.^{4,5} This is because they are chronically exposed to one or more underlying genetic or acquired predisposing factors for VTE, which may be identifiable from the clinical history or through laboratory testing. Furthermore, the absence of a provoking factor or trigger for VTE is the most important predictor of recurrence in these patients. They require longer-term or indefinite treatment, which consists of giving intravenous unfractionated heparin or subcutaneous LMWH for at least 5 days, followed by warfarin (target INR 2.0–3.0).³

This is standard-intensity anticoagulation therapy, and is highly effective in preventing recurrent episodes of VTE for as long as it is continued. In trials in which patients were treated for a median of 4–6 months, it reduced the absolute risk by 7.6%, which is equivalent to preventing one event for every 13 patients treated (odds ratio [OR], 0.15; 95% CI, 0.10–0.23).⁶ In patients considered at highest risk of recurrent unprovoked VTE (eg, $> 10\%$ per year; see Box), warfarin therapy is continued indefinitely, whereas in most patients, it is discontinued after 6–12 months.³ This is because long-term anticoagulation is associated with a cumulative risk of bleeding, which is perceived to outweigh its benefits in preventing recurrent VTE. Standard-intensity therapy with warfarin causes minor “nuisance” bleeding in 5%–15%, major bleeding in 2%–3%, and fatal bleeding in 0.2%–0.6% of patients each year.⁷

A hitherto burning question for patients with unprovoked VTE is whether there are other anticoagulant treatment regimens with a more acceptable benefit-to-harm ratio, such as lower-intensity oral anticoagulation therapy.

The recently reported Prevention of Recurrent Venous Thromboembolism (PREVENT) trial was initiated in July 1998 to test the hypothesis that long-term, low-intensity warfarin therapy (target INR, 1.5–2.0) might provide a safe and effective method of reducing the risk of recurrent VTE among patients who had a previous idiopathic (unprovoked) venous thrombosis.⁸ After completing at least 3 months of standard-intensity warfarin therapy (target INR, 2.0–3.0), 508 patients were randomly allocated to receive low-intensity warfarin therapy or placebo in a double-blinded fashion. The trial was terminated after a mean follow-up duration of 2.1 years because there was strong evidence of efficacy of warfarin.

Of 253 patients assigned to placebo, 37 had recurrent venous thromboembolism (7.2 per 100 person-years), compared with 14 of 255 patients assigned to low-intensity warfarin therapy (2.6 per 100 person-years). This represents a relative risk reduction of 64% (hazard ratio [HR], 0.36; 95% CI, 0.19–0.67; $P < 0.001$), and an absolute risk reduction of 4.6%, equivalent to one event prevented for every 22 patients treated for 1 year. Bleeding episodes necessitating hospitalisation occurred in two patients in the placebo group (0.4 per 100 person-years), and five patients in the warfarin group (0.9 per 100 person-years); this difference was non-significant ($P = 0.25$).⁸ Although the PREVENT trial showed no significant excess of major bleeding with low-intensity warfarin therapy compared with placebo, event rates were low (5 v 2), and the 95% confidence intervals do not reliably exclude even a 13-fold increase in risk of major bleeding (HR, 2.53; 95% CI, 0.49–13.03). Yet, there is no doubt that low-intensity warfarin causes bleeding. In the PREVENT trial, “minor” bleeding was significantly increased in the warfarin group compared with the placebo group (12.8% v 6.7%; HR, 1.92; 95% CI, 1.26–2.93), with an increase in absolute risk of 6.1%, equivalent to one minor bleed caused for every 16 patients treated for 1 year.

The results of the PREVENT trial indicate that low-intensity warfarin therapy is effective for long-term prevention of recurrent VTE. However, it was not shown to be sufficiently superior to placebo for low-intensity warfarin to be adopted for this indication. Standard-intensity warfarin is also superior to placebo when continued for up to 4 years after an initial thrombotic event.^{6,9–11} Indeed, it almost eliminates the risk of recurrent VTE in patients who continue the therapy, but is not routinely used because of the bleeding risks. Mini-dose warfarin therapy (fixed-dose, 1–2 mg daily) has never been shown to be effective for this indication, while low-intensity warfarin therapy is unlikely to offer any advantages over standard-intensity therapy in terms of convenience, and would only be a viable alternative if it were significantly safer.

Standard-intensity therapy with warfarin remains the treatment of choice for the long-term prevention of recurrent VTE in patients who are at highest risk of recurrence

Major determinants of the risk of recurrent venous thromboembolism

Low risk (0–4% per year)

- Provoked event*
- Isolated distal deep vein thrombosis

Intermediate risk (5%–10% per year)

- First unprovoked event
- Major predisposing factor(s)[†]

Highest risk (> 10% per year)

- More than one unprovoked event
- First unprovoked event plus major predisposing factor(s)[†]
- Active cancer

*Provoking factors include, in the last 3 months: hospitalisation, major surgery, trauma, leg fracture, plaster cast, puerperium.

[†]Major predisposing factors include: prolonged immobility, neurological disease with paresis, homozygosity for factor V Leiden, combined (multiple) thrombophilic abnormalities, antiphospholipid antibody syndrome, inferior vena caval filter. Cancer is also a major predisposing factor but is mentioned separately because it is such a strong predisposing factor in its own right.

Indirect comparisons of the relative effectiveness and safety of low-intensity and standard-intensity therapy with warfarin, compared with placebo, are unreliable.^{8–11} For example, the apparently lower rates of bleeding in the PREVENT trial when indirectly compared with previous trials of warfarin might simply be explained by differences in patient selection. The PREVENT trial randomly allocated patients to treatment or placebo after they had completed a median of 6.5 months of warfarin treatment, and also included a 28-day run-in phase. It is thus likely that patients at increased risk of bleeding were excluded from the long-term phase of the study. By contrast, in most previous trials of long-term standard-intensity therapy with warfarin, patients were randomly allocated after no more than 3 months of treatment. This is as unreliable as comparing two sporting teams by their respective performances against another team rather than having them oppose each other directly. Indeed, the results of a recent direct head-to-head randomised comparison showed that low-intensity warfarin therapy was not only less effective than standard-intensity therapy for preventing recurrent VTE (absolute risk increase of 1.3% per patient year, equivalent to one event caused for every 77 patients treated for 1 year), but provided no advantage in terms of major bleeding (1.0% v 0.9% per patient-year; HR, 1.0; 95% CI, 0.4–2.7) or minor bleeding (4.9% v 3.6% per patient-year; HR, 1.3; 95% CI, 0.8–2.1).¹²

Taken together, these results indicate that standard-intensity therapy with warfarin is more effective for preventing recurrent VTE than low-intensity warfarin therapy, which, in turn, is more effective than placebo. However, because low-intensity warfarin therapy does not appear to be any safer in terms of bleeding and still requires close laboratory monitoring, it is difficult to justify this approach as an alternative to standard-intensity therapy for the long-term prevention of VTE, irrespective of a patient's baseline risk of recurrence or bleeding.

The implications of these results for clinicians are that standard-intensity therapy with warfarin (target INR, 2.0–

3.0) remains the treatment of choice for the long-term prevention of recurrent VTE in patients who are at highest risk of recurrence (eg, history of recurrent unprovoked VTE, major predisposing factor such as cancer; see Box) or with an initial life-threatening event (eg, major pulmonary embolism), and low risk of haemorrhagic complications. For patients with a first episode of unprovoked VTE or at increased risk of haemorrhagic complications, to decide about long-term treatment, doctors need to weigh the absolute risks of recurrent VTE and bleeding complications with and without warfarin treatment in each patient. In most cases, this is likely to result in the discontinuation of treatment after 6–12 months.

The implications of these results for researchers are that more data are required to improve the reliability of clinical and laboratory predictors of recurrent VTE and haemorrhagic complications in individual patients, and that randomised controlled trials are required to evaluate the effectiveness and safety of alternative long-term antithrombotic therapies (eg, ximelagatran,¹³ antiplatelet agents) that are likely to be more convenient or have a more favourable benefit-to-risk profile than either standard-intensity or low-intensity warfarin therapy.

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