Long-term, low-intensity warfarin after idiopathic venous thromboembolism

Ridker PM, Goldhaber SZ, Danielson E, Rosenberg Y, Eby CS, Deitcher SR, for the Prevention of Recurrent Venous Thromboembolism (PREVENT) Investigators. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. To be published in *N Engl J Med* 2003; 348(15).

Background: Current guidelines recommend that full-dose warfarin be continued for 6–12 months after an idiopathic episode of venous thromboembolism (VTE), with a target international normalized ratio (INR) of between 2.0 and 3.0.[1] The annual risk of major hemorrhage in patients prescribed warfarin is 5%–9%, whereas the long-term risk of recurrent VTE after cessation of anticoagulation is 6%–9% per year, and may be as high as 10%–27% in the first 12 months following cessation of warfarin for idiopathic deep vein thrombosis (DVT).[2] Low-intensity warfarin (INR 1.5–2.0) may carry a lower risk of bleeding and appears to suppress biochemical markers of coagulation; however, this strategy to prevent recurrence of VTE has not been tested in randomized controlled trials.

Question: Does long-term, low-intensity warfarin therapy safely and effectively reduce the risk of recurrent VTE in patients who have had a previous idiopathic VTE?

Design: This randomized, double-blind, placebo-controlled trial enrolled patients with a documented, idiopathic VTE (DVT or pulmonary embolism), who had already successfully completed 3 or more months of uninterrupted, full-dose oral anticoagulant therapy. Exclusion criteria were a history of metastatic cancer, major gastrointestinal bleeding, hemorrhagic stroke, life expectancy less than 3 years, antiphospholipid antibody syndrome, or treatment with an antiplatelet or anticoagulant agent other than low-dose ASA (≤ 325 mg). Patients were randomly allocated to low-intensity warfarin (INR 1.5–2.0) or matching placebo. All participants attended office visits every 2 months at which blinded INR evaluation and dose adjustments occurred. To ensure blinding, sham dose adjustments were made in the placebo group.

Patients were followed for recurrent, symptomatic VTE, which was considered confirmed only if objective imaging tests were abnormal. The primary end point was defined as the time to first confirmed recurrent VTE. A composite secondary end point was recurrent VTE, major hemorrhage or death from any cause. Results were analyzed according to the intention-to-treat principle.

Results: The trial was terminated early by the data and safety monitoring committee because of strong evidence of efficacy, by which time 508 patients had been enrolled and followed for a mean of 2.1 years. The mean duration of full-dose anticoagulant therapy before enrolment was 6.5 months. The median age of study participants was 53 years; 47% were female and 38% had had 2 or more previous episodes of VTE. The median INR of patients in the placebo and warfarin groups was 1.0 and 1.7 respectively.

Thirty-seven of the 253 patients (14.6%) assigned to placebo had a recurrent VTE compared with 14 of the 255 patients (5.5%) on low-intensity warfarin, a relative risk reduction of 64% ($p < 0.001$). Ten patients would have to be treated for 3 years to prevent 1 recurrent event. The risk of major hemorrhage was similar in the placebo and warfarin groups (2 of 253 patients in the placebo group v. 5 of 255 patients in the warfarin group had major bleeding episodes respectively, $p = 0.25$). The composite secondary end point was reduced by 48% in the warfarin group ($p = 0.01$).

Commentary: For patients presenting with idiopathic VTE, extended therapy with conventional-intensity warfarin (INR 2.0–3.0) is effective in preventing recurrent thromboembolic events, but is associated with an increased risk of major bleeding, even in the setting of controlled clinical trials. Thus, the risk–benefit ratio of chronic, full-dose warfarin therapy may not be favourable, particularly considering that 20% of major bleeding episodes related to warfarin are fatal.[2]

This well-conducted study convincingly demonstrates that low-dose, long-term anticoagulation with warfarin (following at least 3 months of standard, full-dose anticoagulation) substantially reduces the risk of recurrent events after idiopathic VTE, without increasing the risk of major hemorrhage. Strengths of the trial include the magnitude of benefit, the consistency of effect across all identified subgroups, the assessment of only clearly symptomatic thromboembolic events during follow-up, and the use of masking for patients, caregivers and outcome adjudicators in order to minimize bias. Low-intensity oral anticoagulation has also been successfully employed to prevent VTE in patients with indwelling venous catheters[3] and in women with advanced breast cancer.[4]

Because low-intensity warfarin was not compared with the strategy of conventional-intensity warfarin in the PREVENT trial, the best approach for long-term secondary prevention in patients with idiopathic VTE is still somewhat uncertain. Kearon and colleagues recently presented the preliminary results of a randomized, double-blind study directly comparing these 2 strategies, following at least 3 months of full-dose warfarin for unprovoked VTE.[5] Conventional-intensity warfarin (INR 2.0–3.0) was found to be superior to low-intensity

warfarin (INR 1.5–1.9), with a reduction of 69% in the risk of recurrent VTE and no increase in major bleeding.

Practice implications: Patients with an unprovoked episode of DVT or pulmonary embolism should still receive at least 6 months of conventional-intensity warfarin, with current guidelines stressing longer periods for higher-risk patients.[1] Thereafter, low-intensity, long-term anticoagulation (target INR 1.5–2.0) is a reasonable option. For selected patients at particularly high risk of thrombosis (e.g., those with multiple previous episodes, underlying thrombophilia), and in whom the risks of bleeding are acceptable, conventional-intensity anticoagulation should still be considered.

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