Low-intensity warfarin therapy prevented recurrent venous thromboembolism

Ridker PM, Goldhaber SZ, Danielson E, et al. **Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism.** N Engl J Med. 2003;348:1425-34.

QUESTION

In patients with idiopathic venous thromboembolism (VTE), is long-term, low-intensity warfarin therapy more effective than placebo for preventing recurrent VTE?

DESIGN

Randomized (unclear allocation concealment*), blinded (clinicians, patients, outcome assessors, and monitoring committee),* placebo-controlled trial with mean 2.1-year follow-up (The Prevention of Recurrent Venous Thromboembolism [PREVENT] trial).

SETTING

Centers in the United States, Canada, and Switzerland.

PATIENTS

After completing a 28-day, open-label run-in phase to ensure ≥ 85% patient compliance and a stable warfarin titration level (international normalized ratio [INR] 1.5 to 2.0 with warfarin dose ≤ 10 mg/d), 508 patients (median age 53 y, 53% men) with documented idiopathic VTE were randomized. Exclusion criteria were metastatic cancer; major gastrointestinal bleeding; hemorrhagic stroke; life expectancy < 3 years; treatment with dipyridamole, ticlopidine, clopidogrel, heparin, > 325 mg of aspirin, or drugs that affect the prothrombin time; or known lupus anticoagulant antibodies or antiphospholipid antibodies. All patients were included in the analysis.

INTERVENTION

Patients were stratified by clinical site, time since the index event (≤ 6 mo or > 6 mo), and if the index event was the patient's first VTE, and were allocated to low-intensity warfarin (target INR 1.5 to 2.0) (n = 255) or placebo (n = 253).

MAIN OUTCOME MEASURES

Recurrent VTE (confirmed by objective testing) including deep venous thrombosis and pulmonary embolism; major hemorrhage; and a composite endpoint of recurrent VTE, major hemorrhage, and death from any cause.

MAIN RESULTS

Analysis was by intention to treat. Fewer patients in the warfarin group had recurrent VTE than did those in the placebo group (Table). The net clinical benefit was greater for patients who received warfarin (Table). The groups did not differ for any other endpoints. Adjusting for patients with factor V Leiden or the prothrombin mutation did not alter the results (P for interaction = 0.51).

CONCLUSION

In patients with idiopathic venous thromboembolism, long-term, low-intensity warfarin was effective for preventing recurrent venous thromboembolism.

Sources of funding: National Heart, Lung and Blood Institute and Bristol-Myers Squibb.

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*See Glossary.

Warfarin vs placebo for prevention of recurrent venous thromboembolism (VTE) at mean 2.1 years†

Outcomes	Warfarin	Placebo	RRR (95% CI)	NNT (CI)
Recurrent VTE	5.5%	14.6%	62% (33 to 79)	11 (7 to 25)
Death	1.6%	3.2%	50% (–53 to 84)	Not significant
Composite endpoint	8.6%	16.2%	47% (14 to 67)	14 (7 to 53)
			RRI (CI)	NNH
Major bleeds	2.0%	0.8%	148% (–44 to 1001)	Not significant

†Composite endpoint = recurrent VTE, major bleeding episode, or death. Abbreviations defined in Glossary; RRR, RRI, NNT, NNH and CI calculated from data in article.

COMMENTARY

In patients with idiopathic VTE, 3 studies previous to the PREVENT study addressed the question of secondary prophylaxis with low-intensity warfarin (1–3). 1 trial comparing low- and standard-intensity warfarin therapy showed safety similar to that of the PREVENT trial, but was underpowered to assess the efficacy of these 2 regimens (1). Another study showed no recurrence or major bleeding, but it was uncontrolled (2). The ELATE trial (3), which so far has only been published as an abstract, included 739 patients (similar to those in the PREVENT trial) who were randomized to warfarin, with a target INR of 1.5 to 1.9 or 2.0 to 3.0. After a mean follow-up of 2.3 years, the low-intensity group had more recurrent VTE than the conventional-intensity group (1.9% vs 0.6% per patient-y; hazard ratio 3.3, 95% CI 1.2 to 9.1), but did not differ for major bleeding (1.0% vs 0.9% per patient-y). However, as in the ELATE trial, the PREVENT trial had a lower incidence of major bleeding than that seen in other long-term studies (4–6), thereby suggesting that patients at higher risk for bleeding may have been underrepresented. It would be important to know how many patients were removed by this process.

Low-intensity warfarin therapy is beneficial because the interval between INR tests can be extended to about 2 months. However, the ELATE trial may trump this benefit if its published results favor high-intensity warfarin. In any event, because of a paucity of evidence, patients with a high risk for recurrence (e.g., cancer or severe thrombophilic defects) should not be switched to low-intensity warfarin. Finally, the optimal duration of anticoagulation therapy for patients with idiopathic VTE remains unresolved, although evidence exists that indefinite antithrombotic therapy is needed. Clinical trials are ongoing to assess other antithrombotic strategies with direct thrombin inhibitors or antiplatelet agents that do not require laboratory monitoring.

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