Conventional-intensity was more effective than low-intensity warfarin therapy for preventing recurrent venous thromboembolism

Kearon C, Ginsberg JS, Kovacs MJ, et al. **Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism.** N Engl J Med. 2003;349:631-9.

QUESTION

In patients with unprovoked venous thromboembolism (VTE), is low-intensity warfarin therapy as effective as conventional-intensity warfarin therapy for the long-term prevention of recurrent VTE?

DESIGN

Randomized {allocation concealed*}†, blinded {clinicians, patients, outcome assessors, data collectors, monitoring committee, and data analysts}†,* controlled trial with mean follow-up of 2.4 years (Extended Low-Intensity Anticoagulation for Thrombo-Embolism [ELATE] study).

SETTING

16 academic clinical centers in Canada and the United States.

PATIENTS

738 patients (mean age 57 y, 55% men) with ≥ 1 episode of unprovoked VTE (defined as objectively confirmed, symptomatic, proximal deep venous thrombosis or pulmonary embolism that occurred in the absence of a major risk factor for thrombosis) who had completed ≥ 3 months of oral anticoagulant therapy at the conventional intensity. Exclusion criteria were other indications for warfarin therapy, contraindication to long-term warfarin therapy, known antiphospholipid antibodies, allergy to contrast medium, or life expectancy < 2 years. Follow-up was 99.9%.

INTERVENTION

After stratifying for clinical center and whether the patient had completed 3 to 4 or > 4 months of initial anticoagulant therapy, patients were allocated to warfarin therapy with a target international normalized ratio (INR) of 1.5 to 1.9 (low-intensity warfarin group, n = 369) or warfarin therapy with a target INR of 2.0 to 3.0 (conventional-intensity warfarin group, n = 369).

MAIN OUTCOME MEASURES

Recurrent VTE, major bleeding episodes, any bleeding episodes, and death.

MAIN RESULTS

Analysis was by intention to treat. The mean INR was 1.8 in the low-intensity warfarin group and 2.4 in the conventional-intensity warfarin group. Patients in the low-intensity warfarin group had a greater risk for recurrent VTE than did those in the conventional-intensity warfarin group. Groups did not differ for major or any bleeding episodes, or death (Table).

CONCLUSIONS

In patients with unprovoked venous thromboembolism (VTE), conventional-intensity warfarin therapy was more effective than low-intensity warfarin therapy for long-term prevention of recurrent VTE. Low-intensity warfarin therapy did not reduce the risk for bleeding.

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*See Glossary.

†Information provided by author.

Low-intensity vs conventional-intensity warfarin therapy in unprovoked venous thromboembolism at mean 2.4 years‡

Outcomes	Low-intensity warfarin	Conventional-intensity warfarin	RRI (95% CI)	NNH (CI)
Recurrent venous thromboembolism	4.3%	1.6%	176% (10 to 567)	35 (11 to 620)
Major bleeding episode	2.4%	2.2%	20% (–60 to 194)	Not significant
Any bleeding episode	10.6%	8.4%	28% (–19 to 100)	Not significant
Death	4.3%	2.2%	107% (–10 to 361)	Not significant

‡Abbreviations defined in Glossary; RRI, NNH, and CI calculated from data in article using Cox proportional-hazards model.

COMMENTARY

In patients with unprovoked (or idiopathic) VTE who have received 3 months of vitamin K antagonists (VKAs) with a target INR of 2.0 to 3.0, uncertainty exists about the intensity and duration of anticoagulation. The study by Kearon and colleagues has strengthened the evidence that lowering INR below 2.0 for extended secondary prophylaxis results in more recurrences without diminishing the risk for bleeding. Higher-intensity anticoagulation (INR > 3.0) offers no advantage in preventing recurrent disease, but increases the risk for bleeding (1). This evidence coupled with another study (2) has resolved the uncertainty about the optimal intensity of extended secondary prophylaxis: the target INR should be 2.0 to 3.0.

Now the uncertainty about the optimal duration of anticoagulation needs to be addressed. Although the use of VKAs reduces the risk for recurrence, the absolute incidence of recurrence for unprovoked VTE rebounds in the 6 to 12 months after stopping therapy to 5% to 10% regardless of whether VKAs were used for 3, 6, or 12 months (3). Thereafter, the annual incidence for recurrent VTE stabilizes at 1% to 2%. Thus, prolonging the duration of VKAs in this setting merely delays rather than reduces the risk for recurrence. Clinical decision making for secondary prophylaxis of unprovoked VTE will need a shift in thinking about VTE as an acute event to a chronic disease and consideration of the risk for bleeding and patient preference.

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References

1. **Hull R, Hirsh J, Jay R, et al.** Different intensities of oral anticoagulant therapy in the treatment of proximal-vein thrombosis. N Engl J Med. 1982; 307:1676-81.
2. **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.
3. **van Dongen CJ, Vink R, Hutten BA, Buller HR, Prins MH.** The incidence of recurrent venous thromboembolism after treatment with vitamin K antagonists in relation to time since first event: a meta-analysis. Arch Intern Med. 2003;163:1285-93.