

High- and moderate-intensity warfarin regimens did not differ for preventing thrombosis in the antiphospholipid antibody syndrome

Crowther MA, Ginsberg JS, Julian J, et al. A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. *N Engl J Med.* 2003;349:1133-8.

QUESTION

In patients with previous arterial or venous thrombosis and the antiphospholipid antibody syndrome, is high-intensity warfarin more effective than moderate-intensity warfarin for preventing recurrent thrombosis?

DESIGN

Randomized (allocation concealed*), blinded {patients, clinicians, data collectors, outcome assessors, and monitoring committee}†, controlled trial with mean 2.7-year follow-up.

SETTING

13 clinical centers in Canada and the United States.

PATIENTS

114 patients (mean age 42 y, 60% women) who had an objectively confirmed arterial or venous thrombosis and a positive test for antiphospholipid antibodies (lupus anticoagulant [defined by the International Society on Thrombosis and Haemostasis], moderate or high titer of IgG anticardiolipin antibody, or both) on 2 occasions \geq 3 months apart. Exclusion criteria were IgM anticardiolipin antibodies only; clinically significant bleeding diathesis; intracranial hemorrhage, stroke, or

gastrointestinal bleeding in the previous 3 months; contraindication to warfarin; objectively confirmed recurrent thrombosis while receiving warfarin (target international normalized ratio [INR] \geq 2.0); pregnancy or planning pregnancy; or geographic location that would prevent follow-up. All patients were included in the analysis.

INTERVENTION

Patients were allocated to moderate-intensity warfarin (target INR 2.0 to 3.0) ($n = 58$) or high-intensity warfarin (target INR 3.1 to 4.0) ($n = 56$).

MAIN OUTCOME MEASURES

Episodes of recurrent thrombosis (stroke or transient ischemic attack, myocardial infarction, peripheral arterial thrombosis, cerebral venous thrombosis, deep venous thrombosis, or pulmonary embolism).

MAIN RESULTS

The rate of recurrent thrombosis did not differ between patients who received high-intensity warfarin and those who received moderate-intensity warfarin (Table). The groups did not differ for major bleeding ($P = 0.96$).

CONCLUSION

In patients with previous arterial or venous thrombosis and antiphospholipid antibody syndrome, high-intensity warfarin was not better than moderate-intensity warfarin for preventing recurrent thrombosis.

Source of funding: Canadian Institutes for Health Research.

For correspondence: Dr. M.A. Crowther, St. Joseph's Hospital, Hamilton, Ontario, Canada. E-mail crowthrm@mcmaster.ca.

*See Glossary.

†Information provided by author.

High-intensity warfarin (INR 3.1 to 4.0) vs moderate-intensity warfarin (INR 2.0 to 3.0) for the antiphospholipid antibody syndrome at mean 2.7 years‡

Outcome	High-intensity warfarin	Moderate-intensity warfarin	RRI (95% CI)	NNH
Recurrent thrombosis	10.7%	3.4%	199% (-40 to 1091)	Not significant

‡INR = international normalized ratio. Other abbreviations defined in Glossary; RRI, NNH, and CI calculated from data in article using Cox proportional-hazards model.

COMMENTARY

Patients with antiphospholipid antibodies who develop thrombosis are at greater risk for recurrent thrombosis than those without antiphospholipid antibodies (1). Therefore, it is generally recommended that such patients continue warfarin therapy indefinitely (2). However, uncertainty remains concerning the optimum intensity of warfarin therapy for preventing recurrent thrombosis. Retrospective studies suggest that increasing the intensity of warfarin (target INR $>$ 3.0) may reduce the risk for recurrence (3), although this may increase the risk for bleeding (2).

The study by Crowther and colleagues is the first randomized trial to determine whether high-intensity warfarin is more effective than moderate-intensity warfarin for preventing recurrent thrombosis in patients with antiphospholipid antibodies. Unfortunately, the study lacked the power to reliably answer the question because the observed incidence of recurrent thrombosis was much lower than expected. As a result, the null hypothesis of no difference in effectiveness between high- and moderate-intensity warfarin could not be rejected. This lack of statistical power is reflected by the wide CIs around the point estimate for the primary efficacy outcome, which do not exclude a 40% reduction or a 1000% increase in the risk for recurrent thrombosis with high- versus moderate-intensity warfarin.

What are the implications for clinical practice? The low incidence of recurrent thrombosis in patients who received moderate-intensity warfarin might suggest that a target INR of 2 to 3 is sufficient to prevent recurrence at least in some patients with thrombosis and antiphospholipid antibodies. However, until more data become available, the optimal intensity of warfarin therapy in these patients remains uncertain, and clinicians will need to continue treatment recommendations according to the patient's individual risk factors for bleeding and thrombosis.

*John W. Eikelboom, MD
Royal Perth Hospital
Perth, Western Australia, Australia*

References

- Schulman S, Svenungsson E, Granqvist S. Anticardiolipin antibodies predict early recurrence of thromboembolism and death among patients with venous thromboembolism following anticoagulant therapy. Duration of Anticoagulation Study Group. *Am J Med.* 1998;104:332-8.
- Brunner HI, Chan WS, Ginsberg JS, Feldman BM. Longterm anticoagulation is preferable for patients with antiphospholipid antibody syndrome. Result of a decision analysis. *J Rheumatol.* 2002;29:490-501.
- Khamashta MA, Cuadrado MJ, Mujic F, et al. The management of thrombosis in the antiphospholipid-antibody syndrome. *N Engl J Med.* 1995; 332:993-7.