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


**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 ± 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 ≥ 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] ≥ 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.

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*See Glossary.
†Information provided by author.

**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.

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**References**

