

Does warfarin prevent venous thromboembolic events in aPL-positive patients?

Evidence-based answer

Yes, warfarin is effective in the secondary prevention of venous thromboembolic events (VTEs) for patients positive for lupus anticoagulant or anticardiolipin antibody (also known as antiphospholipid antibodies [aPL]) (strength of recommendation [SOR]: **B**, single cohort study, extrapolation from other RCTs). Patients should be treated for at least a year (SOR: **C**, consensus statement), and possibly indefinitely, with warfarin (SOR: **B**, small clinical trials and cohort studies). Moderate-intensity therapy (international normalized ratio [INR] range, 2.0–3.0) appears to be the best balance between

risks and benefits (SOR: **B**, based on meta-analysis of 2 small randomized control trials).

Little evidence exists regarding primary prevention for patients with an incidental finding of either aPL. For these individuals, the risks of warfarin may outweigh any benefits. Many experts recommend primary prevention with aspirin for those individuals who are aPL positive and who do not have contraindications to aspirin or another compelling reason for warfarin use (malignancy, family history, or accompanying hypercoagulable state) (SOR: **C**, expert opinion).

Clinical commentary

Consider this syndrome when a younger patient has had an idiopathic thromboembolism episode

Antiphospholipid antibodies have a prevalence rate of 1% to 5% in the general population, and 12% to 34% among patients with systemic lupus erythematosus.¹ The prevalence of antiphospholipid antibodies increases with age, especially among elderly patients with coexistent chronic illness.

Patients with antiphospholipid antibodies are not always symptomatic. Common manifestations may include arterial and venous thromboembolic events, frequent miscarriage, thrombocytopenia,

hemolytic anemia, and livedo reticularis.²

Family physicians should consider this syndrome when a patient ≤ 50 years old has had an episode of idiopathic thromboembolism, or an unexplained elevated activated partial-thromboplastin time, or a history of miscarriage. A previous study³ reported that presence of lupus anticoagulant is associated with increased risk of recurrent thromboembolic events. Therefore, it's reasonable to continue anticoagulation with warfarin indefinitely for these patients, after their first episode of a thromboembolic event.

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FAST TRACK

Moderate-intensity warfarin (to an INR of 2–3) appears to be the best balance between risks and benefits

CONTINUED

FAST TRACK

American College of Chest Physicians advisory: 12 months of warfarin, and indefinite therapy if a VTE patient has antiphospholipid antibodies

Evidence summary

Lupus anticoagulant and anticardiolipin antibodies are known to increase risk of both arterial and venous thromboembolic events.

One study prospectively followed patients ≥ 15 years old recruited from 16 hospitals in Sweden, who had their first or second episode of a VTE. Patients with malignancy or a known congenital deficiency of an inhibitor of coagulation were excluded. These patients were followed for 4 years. Each received at least 6 months of warfarin therapy (INR=2.0–2.85) after initial diagnosis of a VTE.

After treatment, the 4-year recurrence rate for VTEs was 29% for patients with aPL (20/68) vs 14% for patients without (47/344) (relative risk [RR]=2.1; 95% confidence interval [CI], 1.3–3.3). The risk of death for those patients with aPL was 15% (10/68) vs 6% for those without (20/324) (RR=1.8; 95% CI, 0.9–3.6).

In the same study, those with an aPL and a second clot were randomized to a second 6 months of therapy vs indefinite therapy (INR=2.0–2.85). After 4 years, their risk of another recurrence was 20% (3/15) with 6 months of therapy vs 5% (1/19) with indefinite therapy. This underpowered study did not show a statistical difference under intention-to-treat analysis; however, the single failure in the treatment group had stopped the warfarin prior to the event.⁴

Moderate intensity therapy does the job

Two recent randomized controlled trials have shown that moderate-intensity warfarin therapy (INR=2.0–3.0) is equally efficacious to high-intensity therapy (INR=3.0–4.0).^{5,6} In these small studies, those with aPL were randomized to moderate-intensity vs high-intensity therapy and followed for approximately 3 years. A meta-analysis of these studies (done in conjunc-

tion with the second study) remained insufficiently powered to show any significant differences between high- and moderate-intensity therapy, but there was a trend towards increased thrombosis and bleeding events in the high-intensity groups.⁶ Of note, the relative risk for developing a VTE was lower in these studies than in those with time-limited treatment, suggesting that indefinite treatment may be indicated.

Warfarin probably isn't best for primary prevention

Wahl et al⁷ constructed a decision analysis of antithrombotic therapy for patients with systemic lupus erythematosus with and without aPL. They compared observation alone with aspirin and with warfarin for the primary prevention of VTE. Using a decision analysis based on the best available efficacy rates, they recommended that the benefits of prophylactic aspirin outweigh the risks. However, due to high complication rates, warfarin's benefits are outweighed by the risks. This analysis has not been validated in an actual patient population and remains theoretical in nature, but is the best available evidence regarding primary prevention of VTE for patients with aPL.

Recommendations from others

Guidelines from the American College of Chest Physicians recommend at least 12 months of treatment with warfarin and suggest indefinite treatment for patients with a VTE and antiphospholipid antibodies. The guidelines also suggest a target INR of 3.0 (range, 2.5–3.5) for patients with recurrent VTEs or additional risk factors, and a therapeutic INR of 2.5 (range, 2.0–3.0) for patients with a VTE and lupus anticoagulant but no additional risk factors.⁸

The Thrombosis Interest Group of Canada also recommends considering indefinite treatment for those with a VTE and a positive test for any of the antiphospholipid antibodies.⁹ ■

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