Is Aspirin an Alternative Therapy for Venous Thromboembolism Prevention?

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The management of venous thromboembolism (VTE) has dramatically changed over the past 5 to 10 years. With the advent of direct-acting oral anticoagulants (DOACs), health care providers have a variety of agents that can safely and effectively treat and prevent both deep vein thrombosis (DVT) and pulmonary embolism (PE). While the evidence supporting the use of these agents is clear, the decision on when to discontinue anticoagulation is much more complicated.

While guidelines traditionally recommend at least 3 months of anticoagulation, the risk of recurrent VTE remains, prompting providers to consider extension of therapy. Additionally, guidelines recommend extending therapy beyond 3 months in patients with a first unprovoked VTE who are at low to moderate risk of a hemorrhagic event. However, many patients prefer to discontinue anticoagulation due to safety and lifestyle concerns.

Is there an alternative to traditional oral anticoagulation for the prevention of recurrent VTE that is associated with fewer adverse effects?

PATIENT CASE

FR is a 51-year-old man with a history of hypertension, stage 2 chronic kidney disease, and left lower-extremity DVT. He had received a diagnosis of an unprovoked DVT 12 months ago, and he has been treated with warfarin since then. He presents to the clinic for monitoring of his international normalized ratio, which is 2.3 today. During his visit, he states that he would like to discontinue warfarin but would consider preventive treatment that would not require monitoring and that has a relatively low risk of bleeding. How do you respond?

THE EVIDENCE

Two randomized placebo-controlled trials have evaluated the efficacy of aspirin for the reduction of recurrent VTE. The first of these, the WARFASA trial,[1] evaluated the use of aspirin, 100 mg, or placebo in 403 patients with a first unprovoked VTE who had been treated with oral vitamin K antagonists for 6 to 18 months. Patients were treated with aspirin for 2 years with the option of extending treatment. The investigators found that treatment with aspirin significantly reduced the rate of recurrent VTE (6.6% vs 11.2% per year; $P = .02$). This composite outcome was driven by a significant reduction in DVT. Additionally, major bleeding or clinically relevant nonmajor bleeding was not different between groups (4 vs 4, $P = .97$).

The ASPIRE trial[2] was carried out in a similar manner, enrolling 822 patients with unprovoked VTE who had received treatment with warfarin for 6 weeks to 24 months. These patients were randomly assigned to aspirin, 100 mg, once daily or placebo for a minimum of 2 years and maximum of 4 years. The primary outcome was the rate of recurrent VTE. Unfortunately, because of slow recruitment, the study did not achieve the desired statistical power. As a result, the use of aspirin did not show a significant reduction in the overall rate of recurrent VTE (4.8% vs 6.5% per year; $P = .09$). However, the study did note a significant reduction in the rate of major vascular events defined as myocardial infarction, stroke, or cardiovascular death (5.2% vs 8.0% per year; $P = .01$).

During the interim analysis of the ASPIRE trial, the investigators decided to combine the results from the ASPIRE trial with those of the WARFASA trial (the INSPIRE collaboration). The combined analysis solidified the results of the WARFASA trial.[3] The rate of recurrent VTE was significantly reduced with the use of aspirin (5.1% vs 7.5% per year; $P = .008$). Aspirin also reduced the rate of major vascular events (5.7% vs 8.7% per year; $P = .002$) and was not associated with a significant increase in major bleeding (0.5% vs 0.4% per year; $P = .60$).

As a result of these studies, the most recent American College of Chest Physicians CHEST guideline[4] addresses the use of aspirin in the setting of secondary VTE prevention. Specifically, the guideline states, "In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, we suggest aspirin over no aspirin to prevent recurrent VTE." The guideline estimates 60 fewer VTE events per 1000 with the use of aspirin, with an expected major bleeding rate of 4 per 1000 patients. However, the guideline does not recommend aspirin in patients wishing to extend anticoagulation therapy, since the reduction in VTE is much greater with anticoagulant therapy than with aspirin.

CLINICAL APPLICATION

FR has completed 12 months of treatment for his first unprovoked VTE, and he would like to discontinue his warfarin treatment. He says he wants something that does not have to be monitored but

that also is associated with a low rate of bleeding. A DOAC seems to fit the patient's request for no routine monitoring, but these agents do carry a significant risk for bruising and bleeding, similar to that of warfarin (with the exception of apixaban and edoxaban, which have lower bleeding risks compared with warfarin). Because his VTE was unprovoked, FR could be considered for complete discontinuation of anticoagulation (which would confer zero risk for bleeding), but he prefers to take something to help reduce his chances for a future clot.

The results of the WARFASA trial and the INSPIRE collaboration confirm the safety of aspirin in this setting as well as its benefits in reducing recurrent VTE events. Furthermore, the CHEST guideline recommends continued aspirin therapy over placebo in this setting. Aspirin therapy is inexpensive, is convenient (once daily), and does not require routine monitoring. Moreover, in patients with comorbid cardiovascular disease, aspirin may also provide additional risk reduction for vascular events. Because FR desires an agent that is convenient and safer than anticoagulation, aspirin seems to be a reasonable option for him. However, if his risk for recurrent VTE is judged to be sufficiently high enough to warrant continued anticoagulation, aspirin would not represent a viable option due to its inferior efficacy compared with the anticoagulants.

FR would be counseled to discontinue his warfarin today and to begin taking aspirin, 81 mg, daily the following day. He also would be counseled to monitor closely for bruising, bleeding, or signs of VTE, and to avoid using nonsteroidal anti-inflammatory drugs. He would be advised to return in 6 months for a reassessment of his aspirin therapy and the overall risks and benefits of his current VTE treatment. ■

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