Apixaban for Extended Treatment of Venous Thromboembolism

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Treatment for venous thromboembolism (VTE) involves anticoagulation, often with warfarin, for 3 or more months. Warfarin requires laboratory monitoring for dosage adjustments and dietary restrictions, which often limits its usefulness to 6 to 12 months. If warfarin therapy is stopped, the risk of recurrent VTE is 6% to 10% per year in patients without reversible risk factors. Apixaban is an oral factor Xa inhibitor that can be given in fixed doses without requiring laboratory monitoring. Doses of 2.5 and 5 mg have been effective in studies on thromboprophylaxis after major orthopedic surgery and on prevention of stroke in patients with atrial fibrillation. This current randomized, double-blind study was designed to compare the efficacy and safety of these 2 doses of apixaban with those of placebo for extended treatment of VTE.

Patients had confirmed, symptomatic deep vein thrombosis or pulmonary embolism and had been treated for 6 to 12 months with standard anticoagulant therapy or with apixaban or enoxaparin and warfarin as participants in the AMPLIFY (Apixaban after the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis With First-Line Therapy) trial. Patients were enrolled within ~7 days after they received the last dose of previous anticoagulant medication and when the INR (international normalized ratio) was 2.0 or less. Patients were assigned to receive 2.5 or 5 mg apixaban or placebo, all given twice daily. The primary efficacy outcome was the composite of symptomatic recurrent VTE or death from any cause. The prespecified secondary efficacy outcome was symptomatic recurrent VTE or death related to VTE. Another secondary outcome, added after the trial began, was the composite of symptomatic recurrent VTE, death related to VTE, myocardial infarction, stroke, or death related to cardiovascular disease. The primary safety outcome was major bleeding, with secondary outcomes of the composite of major or clinically relevant nonmajor bleeding. Patients were assessed monthly during the intended 12-month treatment period and 30 days after the end of the 1-year study period.

A total of 2486 patients were enrolled, with 2482 included in the intention-to-treat analyses. A primary efficacy outcome event occurred in 11.6% of patients given placebo (96/829), 3.8% (32/840) receiving 2.5 mg apixaban, and 4.2% (34/813) given 5 mg apixaban. Symptomatic recurrent VTE or death related to VTE occurred in 8.8%, 1.7%, and 1.7% of patients receiving placebo, 2.5 mg, or 5 mg apixaban, respectively. Rates for the composite outcome of all thromboembolic events were 10.0%, 2.3%, and 2.1%, respectively. Major bleeding occurred in 4 (0.5%), 2 (0.2%), and 1 patient (0.1%) receiving placebo, 2.5, or 5 mg apixaban, respectively. Clinically relevant nonmajor bleeding occurred in 2.3%, 3.0%, and 4.2%, respectively. Rates for the composite outcome of major bleeding or clinically relevant nonmajor bleeding were 10.04%, 2.4%, and 2.5% for placebo, 2.5, and 5 mg apixaban groups, respectively. The rates for the composite secondary efficacy outcome were 10.4% (86 patients) given placebo, 2.4% (20 patients) receiving 2.5 mg apixaban, and 2.5% (20 patients) given 5 mg apixaban. Rates of death from any cause were 1.7%, 0.8%, and 0.5%, respectively. Rates of adverse events were similar in the 3 groups. During the 30-day follow-up, symptomatic recurrent VTE occurred in 2, 3, and 5 patients (0.2%, 0.4%, and 0.6%, respectively) who received placebo and the 2.5- or 5-mg doses of apixaban.

Either of the 2 doses of apixaban can reduce the risk of recurrent VTE without increasing the rate of major bleeding. Future studies are needed to determine the net benefit and risk of extending treatment beyond 18 to 24 months.

COMMENT

Patients with provoked VTE triggered by temporary risk factors can typically stop anticoagulation after 3 months of therapy. However, for patients with unprovoked VTE, for which the risk of recurrence can approach 40% at 5 years,1 it may be prudent to consider a longer course of treatment. Nonetheless, balancing the risks and benefits of extended anticoagulation is challenging. Although the efficacy of warfarin in preventing recurrences is greater than 90%, the drug is associated with a risk of major bleeding of 1% to 2% per year.2 Moreover, the logistics of warfarin management are cumbersome, given the need for frequent monitoring and the many associated food and drug interactions that must be considered.

This current study showed that, compared with placebo, both the 2.5- and 5-mg doses of apixaban reduced the risk of recurrent VTE (fatal or nonfatal). Importantly, these benefits were observed with rates of major bleeding that were encouragingly low and similar to those in the placebo group.

What are the ramifications of these results? For patients with VTE for whom there is ambiguity about the benefits and risks of continued therapy, the findings provide a rationale for continuing anticoagulation therapy for an additional 12 months. Clearly, both the 2.5-mg twice-daily regimen of apixaban and the 5-mg twice-daily regimen were safe, effective, and simple to use. The authors underscore that the number of patients who would need to be treated to prevent 1 episode of recurrent VTE (fatal or nonfatal) during the 1-year active study period was only 14, whereas the number needed for treatment to precipitate

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of clinically relevant nonmajor bleeding. The current double-blind, randomized studies were done to evaluate the efficacy and safety of dabigatran during long-term prophylaxis after VTE. In 1 trial, dabigatran was compared with warfarin (active-control study; RE-MEDY), and in the second, dabigatran was compared with placebo (placebo-control study; RE-SONATE).

Enrolled patients had completed 3 or more months of treatment for VTE. At randomization, previous anticoagulant therapy was halted, and the study drug started when the INR (international normalized ratio) was 2.3 or less. In the active-control study, patients received dabigatran (n = 1430) at a fixed dose of 150 mg twice a day, and a warfarin-like placebo or active warfarin (n = 1426) and a dabigatran-like placebo. The drug doses were adjusted to maintain INR at 2.0 to 3.0. In the placebo-control study, patients received the same fixed dose of dabigatran (n = 681) or a placebo (n = 662). Patients were evaluated 15 and 30 days after randomization and then monthly until day 180. Thereafter, those in the active-control study were assessed every 90 days until the end of treatment. In both studies, patients were evaluated at 30 days after the end of treatment. The primary efficacy outcome was recurrent symptomatic and verified VTE or death associated with VTE. Safety outcomes were major bleeding and clinically relevant nonmajor bleeding.

In the active control group, recurrent VTE occurred in 26 patients (1.8%) in the dabigatran group and 18 patients (1.3%) in the warfarin group. The overall hazard ratio (HR) with dabigatran for the time to first recurrent VTE was 1.44 (95% confidence interval [CI], 0.78–2.64). Major bleeding occurred in 13 patients (0.9%) in the dabigatran group and in 25 patients (1.8%) in the warfarin group (HR, 0.52; 95% CI, 0.27–1.02). Major or clinically relevant bleeding occurred in 80 patients (5.6%) and 145 patients (10.2%) in the dabigatran and warfarin groups, respectively (HR, 0.54; 95% CI, 0.41–0.71; P < 0.001). In the dabigatran group, 10 and 3 patients had myocardial infarction and unstable angina, respectively (0.9%); in the warfarin group, 1 had myocardial infarction, and 2 had unstable angina (0.2%) (P = 0.02). In the placebo-control study, recurrent VTE occurred in 3 patients (0.4%) in the dabigatran group and in 37 (5.6%) in the placebo arm (HR, 0.08; 95% CI, 0.02–0.25; P < 0.001). At the extended 12-month follow-up in 1323 patients, the cumulative incidence of recurrent VTE was 6.9% and 10.7% in the dabigatran and placebo groups, respectively (HR, 0.61; 95% CI, 0.42–0.88). Two patients had major bleeding, both in the dabigatran group. Major or clinically relevant nonmajor bleeding occurred in 36 patients (5.3%) in the dabigatran group and in 12 (1.8%) in the placebo group (HR, 2.92; 95% CI, 152–5.60; P = 0.001). One acute coronary event occurred in each group.

Dabigatran was noninferior to warfarin in preventing current VTE, with a lower risk of bleeding. However, although dabigatran reduced the rate of recurrent VTE compared with placebo, it had a higher risk of bleeding.

COMMENT

Neither dabigatran nor apixaban has been approved for short-term or extended treatment of VTE, but rivaroxaban recently became the first new anticoagulant approved for this indication in the United States and Europe. Because the current options for extended treatment after a first unprovoked VTE include aspirin, warfarin, and rivaroxaban, it seems likely that other new anticoagulants will soon be approved. It would be welcome news if specific antidotes for these new oral anticoagulants were developed as well.

A fter venous thromboembolism (VTE), most patients require anticoagulant treatment for 3 or more months. Long-term treatment is recommended if they have risk factors for recurrence. The risk of major bleeding and the need for frequent laboratory monitoring and dose adjustments make long-term treatment difficult. Dabigatran, a direct thrombin inhibitor, does not require frequent monitoring or dose adjustments. Previous studies found that 150 mg twice daily was noninferior to warfarin for the initial 6-month treatment and carried a lower rate of clinically relevant nonmajor bleeding. The current double-blind, randomized studies were done to evaluate the efficacy and safety of dabigatran during long-term prophylaxis after VTE. In 1 trial, dabigatran was compared with warfarin (active-control study; RE-MEDY), and in the second, dabigatran was compared with placebo (placebo-control study; RE-SONATE).

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