EDITORIALS

Reduced-Intensity Rivaroxaban for the Prevention of Recurrent Venous Thromboembolism

Mark A. Crowther, M.D., and Adam Cuker, M.D.

Warfarin and direct oral anticoagulant agents prevent recurrent venous thromboembolism. When a first episode of venous thromboembolism occurs in association with a transient risk factor (e.g., surgery), treatment can be stopped after 3 months. With persistent and strong risk factors, such as cancer, therapy should be continued indefinitely.[1] Prolonged anticoagulation therapy is now suggested for most patients with unprovoked venous thromboembolism. Cessation of therapy after 3 to 6 months may be recommended in some female patients who are judged to be at low risk for recurrence,[2] in patients at high risk for bleeding, and in patients with poor adherence or an aversion to anticoagulation therapy.

Various strategies have been studied to reduce the cost, complexity, and toxicity of long-term anticoagulation therapy. Reduced-intensity warfarin proved to be less efficacious than standard-intensity warfarin in randomized, controlled trials.[3,4] Aspirin reduces the risk of recurrent venous thromboembolism, as compared with placebo, but recurrence rates remain substantial (5.1% per year) with aspirin.[5]

The direct oral anticoagulant agents do not require routine laboratory monitoring or dose adjustment, have fewer interactions with other drugs or food than warfarin, and are associated with a lower risk of most forms of bleeding.[6] These advantages render this class of drugs attractive for long-term secondary prevention of venous thromboembolism.

Agnelli and colleagues assigned patients with venous thromboembolism who had received 6 to 12 months of anticoagulation therapy to receive apixaban at a dose of 2.5 mg or 5 mg twice daily or placebo.[7] Symptomatic recurrent fatal or nonfatal venous thromboembolism occurred in 1.7% of the patients who received either of the two doses of apixaban and in 8.8% of those who received placebo. Major bleeding was numerically more common in the placebo group but was infrequent in all three groups.

Weitz and colleagues now report in the *Journal* additional information on a reduced-dose direct oral anticoagulant agent for the prevention of recurrent venous thromboembolism.[8] They enrolled 3365 patients who had undergone 6 to 12 months of initial anticoagulation therapy and in whom there was equipoise with respect to the need for ongoing treatment. Patients were randomly assigned to receive once-daily rivaroxaban at doses of 20 mg or 10 mg or aspirin. After a median of 351 days, symptomatic recurrent fatal or nonfatal venous thromboembolism or unexplained death occurred in 17 of the 1107 patients (1.5%) who were assigned to receive 20 mg of rivaroxaban, in 13 of 1127 (1.2%) who were assigned to receive 10 mg of rivaroxaban, and in 50 of 1131 (4.4%) who were assigned to receive aspirin. Major or clinically relevant nonmajor bleeding occurred in 3.3%, 2.4%, and 2.0% of the patients, respectively.

How should clinicians interpret the results of this trial? First, after an initial treatment course at usual therapeutic doses, clinicians now have good-quality evidence to support the use of long-term, reduced-intensity anticoagulation therapy with rivaroxaban. Such treatment reduces the risk of recurrent venous thromboembolism, as compared with low-dose aspirin, without increasing major bleeding. Second, the favorable safety and

efficacy profile of reduced-intensity rivaroxaban may lead to questions about how patients with provoked venous thromboembolism should be treated. After a first provoked event, recurrent venous thromboembolism occurred in 9 of 666 patients (1.4%) who were assigned to receive 20 mg of rivaroxaban, in 6 of 647 (0.9%) who were assigned to receive 10 mg of rivaroxaban, and in 24 of 663 (3.6%) who were assigned to receive aspirin. Given the protection from recurrent venous thromboembolism afforded by reduced-dose rivaroxaban, extending treatment beyond 3 months could be considered in patients with provoked venous thromboembolism who are at average risk for bleeding and who are strongly averse to having another episode of venous thromboembolism. In light of the safety profile of low-dose rivaroxaban, the benefit of this strategy does not need to be large in order to justify the extension of therapy. Third, this trial suggests that it would be helpful to evaluate the effect of reduced doses of rivaroxaban within 6 months after an episode of venous thromboembolism.

The results of this trial cannot be extended to patients who have an unequivocal indication for long-term anticoagulation therapy and who thus were ineligible to participate in the trial. Such patients are an important group in whom the efficacy of reduced-intensity therapy remains untested. For patients who are unable to afford direct oral anticoagulant agents, adjusted-dose warfarin remains an acceptable alternative for long-term secondary prevention of venous thromboembolism.

The emergence of rivaroxaban and other direct oral anticoagulant agents has altered the standard of care among patients with venous thromboembolism. For patients without cancer, the use of direct oral anticoagulant agents might be considered as first-line treatment for those with acute venous thromboembolism.[1] Full-dose treatment could be continued for a minimum of 3 to 6 months. In patients in whom there is equipoise with respect to continuing anticoagulant therapy beyond this period, the use of a reduced-intensity direct oral anticoagulant agent might be considered. Clinicians who choose this strategy can be confident of excellent efficacy and low bleeding risk similar to that observed with aspirin or placebo.

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From the Departments of Pathology and Molecular Medicine, Medicine, and Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada (M.A.C.); and the Departments of Medicine and Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia (A.C.).

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Ensuring Vaccine Safety in Pregnant Women

Kathryn M. Edwards, M.D.

In this issue of the *Journal*, investigators from Denmark present a comprehensive review of the adverse pregnancy outcomes encountered in women who received quadrivalent human papillomavirus (HPV) vaccine during pregnancy, as compared with those who did not.[1] The investigators assembled data on all the pregnancies in Denmark that occurred within a 7-year period,