EDITORIAL

Can We Rely on RE-LY?

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In patients with atrial fibrillation, warfarin prevents 64% of strokes.[1] Thus, warfarin has become the recommended treatment for candidates for anticoagulation therapy who have atrial fibrillation and at least one additional risk factor for stroke.[2]

Despite clear and consistent recommendations,[3] warfarin is prescribed to only two thirds of appropriate candidates.[4] Several factors contribute to suboptimal use of warfarin therapy: drug and dietary interactions, inconvenience of monitoring the international normalized ratio (INR), risk of hemorrhage, and concerns about real-world effectiveness, which averages 35%.[4] Thus, new oral anticoagulants are needed.

Dabigatran etexilate, an oral thrombin inhibitor, appears to be an anticoagulant that could fill this niche. After conversion to its active form, dabigatran competitively inhibits thrombin. This conversion is carried out by a serum esterase that is independent of cytochrome P-450. Therefore, dabigatran should be less susceptible to dietary and drug interactions and to genetic polymorphisms that affect warfarin. Furthermore, neither anticoagulation monitoring nor dose adjustments are necessary with dabigatran.

The results of a large, multicenter, randomized trial comparing dabigatran with warfarin are reported in this issue of the *Journal*.[5] The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) (ClinicalTrials.gov number, NCT00262600) steering committee and investigators enrolled 18,113 patients who had atrial fibrillation and were at risk for stroke. Two doses of dabigatran (110 mg twice daily and 150 mg twice daily), administered in a blinded fashion, were compared with adjusted-dose warfarin administered in an unblinded manner. Because warfarin use was not blinded and patients taking warfarin had regular follow-up evaluations for purposes of INR monitoring, reporting bias could have affected the detection of outcome events. To minimize this risk, each event was adjudicated by two independent investigators who were unaware of the treatment assignments, and all hospital records were reviewed to ensure complete detection of events.

The primary outcome of RE-LY was systemic embolism or stroke (including hemorrhagic stroke). The rate of the primary outcome (expressed as the percent per year) was significantly lower with dabigatran at a dose of 150 mg twice daily (1.11%) than with either dabigatran at a dose of 110 mg twice daily (1.53%) or warfarin (1.69%). The rate of nonhemorrhagic (i.e., ischemic or unspecified) stroke also was significantly lower with 150 mg of dabigatran (0.92%) than with either 110 mg of dabigatran (1.34%) or warfarin (1.20%). To prevent one nonhemorrhagic stroke, the number of patients who would need to be treated with dabigatran at a dose of 150 mg twice daily, rather than warfarin, is approximately 357.

The rates of hemorrhagic stroke with the 110-mg and 150-mg dabigatran doses (0.12% and 0.10%) were significantly lower than that with warfarin (0.38%). Given these rates, the number of patients who would need to be treated with dabigatran (rather than warfarin) to prevent one hemorrhagic stroke is approximately 370. The rate of extracranial hemorrhage was similar in all three groups: 2.51% with 110 mg of dabigatran, 2.84% with 150 mg of dabigatran, and 2.67% with warfarin.

The quality of warfarin management in RE-LY was assessed by measuring the percentage of

time (excluding the first week of therapy) during which the INR was within the therapeutic range, which averaged 64%. This value is similar to the percentage of time within the therapeutic range in warfarin groups of contemporary trials: 64% in ACTIVE (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) W[6,7] and 66% to 68% in the SPORTIF (Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation) trials.[8,9] The slightly lower rate of INR control in RE-LY reflects the higher enrollment of RE-LY participants who had not received long-term vitamin K–antagonist therapy. On the basis of a published equation,[7] one can estimate that RE-LY participants who were randomly assigned to receive warfarin would have needed to have an INR within the therapeutic range approximately 79% of the time to have a stroke rate as low as that in the group receiving 150 mg of dabigatran. Even with patients' self monitoring or pharmacogenetic dosing, such tight control is unlikely.

Myocardial infarction and gastrointestinal side effects were significantly more common with dabigatran than with warfarin. Rates of myocardial infarction were 0.72% and 0.74% with 110 mg and 150 mg of dabigatran, respectively, and 0.53% with warfarin; approximately 500 patients would have to receive dabigatran for 1 patient to have an event. Whether thrombin inhibition contributes to the risk of myocardial infarction is unclear. As compared with warfarin, ximelagatran (another oral thrombin inhibitor that is not available for clinical use) was associated with a significantly increased risk of myocardial infarction in patients who had acute deep-vein thrombosis[10] or were undergoing joint arthroplasty.[11] However, in another study, ximelagatran prevented reinfarction after an acute myocardial infarction.[12] In RE-LY, rates of dyspepsia (including abdominal pain) were elevated with dabigatran (11.8% in the 110-mg group and 11.3% in the 150-mg group) as compared with warfarin (5.8%), and it contributed to the greater second-year rate of dropout with dabigatran (approximately 21%) than with warfarin (16.6%).

RE-LY participants underwent monitoring of aspartate aminotransferase and alanine aminotransferase to detect possible hepatotoxicity. The fraction of participants whose aminotransferase levels were elevated to more than three times the upper limit of the normal range was approximately 2% in each dabigatran group — no higher than in the warfarin group and one third that associated with ximelagatran.[8,9] In RE-LY, the fraction of patients requiring hospitalization for a hepatobiliary disorder was equivalent in the three treatment groups. The median duration of follow-up in RE-LY was 2.0 years, so the hepatic risks of long-term use are unclear, but they are being quantified in a follow-up study (NCT00808067). Also unclear is how often aminotransferases should be monitored during the initial months of therapy and whether subsequent monitoring will be needed.

Dabigatran is not without important drug interactions. P-glycoprotein inhibitors — including verapamil, amiodarone, and especially quinidine — raise dabigatran serum concentrations considerably. This interaction may have contributed to the trend toward greater efficacy of dabigatran in the subgroup of patients taking amiodarone, but it could elevate the risk of hemorrhage in such patients.

In conclusion, as compared with adjusted-dose warfarin, dabigatran given at a dose of 150 mg twice daily prevented more strokes and dabigatran at a dose of 110 mg twice daily caused fewer hemorrhages. The 150-mg dose appears to be more efficacious and the 110-mg dose appears to be safer, especially in patients taking amiodarone or other P-glycoprotein inhibitors. A future subgroup analysis could test the hypothesis that the 110-mg dose also is safer in patients who are petite or elderly or who have renal impairment. Patients who had a creatinine clearance of less than 30 ml per minute or liver disease were excluded from RE-LY and should not receive the drug. Noncompliant patients also were excluded from RE-LY, and they might receive less (if any) benefit from dabigatran, because the longer half-life of warfarin could provide them with a more consistent anticoagulant effect. Because of dabigatran's twice-daily dosing and greater risk of nonhemorrhagic side effects, patients already taking warfarin with excellent INR control have little to gain by switching to dabigatran. In contrast, many other patients who have atrial fibrillation and at least one additional risk factor for stroke could benefit from dabigatran. In summary, although there are qualifications, we can rely on RE-LY.

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