

Here Come the Alternatives to Warfarin!

Dabigatran or other oral clotting inhibitors might be better choices for some patients.

FDA approval of a drug is not usually sufficient impetus for a Journal Watch Top Story of the year. An exception to this informal policy is the recent approval of dabigatran (Pradaxa) for stroke prophylaxis in patients with atrial fibrillation, because it portends the eventual decline of warfarin, a notoriously frustrating drug to manage. Dabigatran is an oral thrombin inhibitor that does not require international normalized ratio (INR) monitoring ([JW Gen Med Oct 28 2010](#)).

FDA approval was based on the RE-LY trial, in which 18,000 participants were randomized to one of two twice-daily doses of dabigatran (110 or 150 mg) or dose-adjusted warfarin and were followed for a median of 2 years. Annual risk for systemic embolism or stroke was 1.7% in the warfarin group, 1.5% in the 110-mg group, and 1.1% (significantly lower) in the 150-mg group. The incidence of major bleeding was similar to that of warfarin in the 150-mg dabigatran group and was significantly lower in the 110-mg group. Dyspepsia was almost twice as common with dabigatran, and rates of myocardial infarction (MI) also were higher in both dabigatran groups than in the warfarin group (by about 2 cases per 1000 patients treated annually; [JW Cardiol Sep 1 2009](#)).

In a subgroup analysis of 3623 patients with prior (but not very recent) stroke or transient ischemic attack, rates of stroke or systemic embolism were similar in all treatment groups. However, hemorrhagic stroke was significantly less common with either dose of dabigatran, and incidence of major bleeding was significantly lower in the 110-mg dabigatran group than in the warfarin group (relative risk, 0.66; [JW Gen Med Dec 14 2010](#)).

Concerns about the relative costs of these two agents and associated monitoring were addressed recently in a cost-effectiveness model using data from the trial. Assuming dabigatran costs US\$13 daily (an estimate provided by the manufacturer) and is associated with slightly lower stroke and bleeding risks, the cost per quality-adjusted life-year for dabigatran is ≈\$45,000 — a value many experts consider to be cost-effective ([JW Gen Med Dec 2 2010](#)).

Dabigatran is not the only oral alternative to warfarin being touted right now. At the 2010 American Heart Association meeting, researchers presented results from a large study of rivaroxaban (a direct factor Xa inhibitor) to prevent stroke in patients with atrial fibrillation unrelated to valve disease. In the primary analysis, rivaroxaban was noninferior to warfarin, although not significantly superior to warfarin in the full intent-to-treat analysis. Major bleeding incidence was similar ([ROCKET-AF trial preliminary report](#)).

These data and the FDA's approval of dabigatran give physicians an alternative to warfarin in patients with atrial fibrillation who are at high risk for stroke. Some experts have suggested that in patients with stable INRs who are doing well on warfarin, there is little reason to switch, but the case for dabigatran has been bolstered recently by both the favorable subgroup analysis and the new cost-effectiveness analysis (as of this writing, national chain pharmacies were charging between \$230 and \$280 for a 1-month supply

of dabigatran). Many unanswered questions remain, including how the data on MI risk will develop, and how oral warfarin alternatives will perform for other indications.

— **Kirsten E. Fleischmann, MD, MPH**

Published in [Journal Watch General Medicine](#) December 30, 2010