

# Commentary: The Dabigatran Dilemma

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In October 2010 the FDA approved dabigatran (Pradaxa<sup>®</sup>; Boehringer Ingelheim Pharmaceuticals, Inc.) as the first oral direct thrombin inhibitor (DTI) for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF). The introduction of this medication marks the first available alternative to coumarin (warfarin), the only oral anticoagulant available in the United States. Warfarin has long been the “gold” standard in the long term prevention of thromboembolism in patients with AF. While warfarin has been proven to reduce the incidence of stroke and death in patients with AF, it comes with a high incidence of major bleeding (3.6% per year). The most notable burden for patients is the requirements for continuous laboratory monitoring and adjustment based on drug and dietary interactions, resulting in a high treatment non-adherence rate.

A major marketing effort to both practitioners and patients regarding dabigatran centers on the patient lifestyle benefit in comparison to treatment with warfarin, the difference being no need for continuous laboratory monitoring and no dietary constraints. With this potential, some practitioners have rushed to include dabigatran on their formularies and transition outpatients to this new medication. However, as with many new therapies, dabigatran comes with limited knowledge of the full extent of its safety profile. In fact, a post-marketing Risk Evaluation and Mitigation Strategy (REMS) regarding evaluating patient understanding of the potential risks associated with dabigatran is required by the FDA. While recommended as a Class I alternative to warfarin by the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, the task force commented that patients already under excellent control of their international normalized ratio (INR) with warfarin may have little to gain by switching to dabigatran.<sup>1</sup>

To understand the dilemma, we need to understand how dabigatran works and the difference between efficacy and effectiveness. The RE-LY trial compared dabigatran 150mg and 110mg versus warfarin in the prevention of stroke in patients with atrial fibrillation. While the lower dose showed less major hemorrhagic bleeding compared to warfarin with similar rates of stroke and embolisms, the FDA approved the 150mg dose as being superior in reducing the rate of stroke and embolisms but with similar rates of major bleeding<sup>2</sup>. RE-LY, a randomized non-inferiority trial, was clear in showing the efficacy of dabigatran in prevention of stroke. However, the effectiveness (tolerability, efficacy and ease of use) remains to be seen.

Dabigatran’s mechanism of inhibiting thrombin, a protein that catalyzes the production of fibrin, is a unique method for an oral agent that prevents clotting. Other medications in this class of DTI are available as intravenous forms for anticoagulant therapy in the acute setting (e.g., lepirudin and argatroban). This mechanism, however, presents some unique problems that may prove to limit the effectiveness of this agent. One of the promoted benefits is the lack of laboratory tests, such as INR, required to monitor its effects; however, this presents several dilemmas. Although a surrogate marker of clinical impact, laboratory tests do help practitioners in delivering the right dose for each patient. This is critically true of an agent that can cause serious bleeding, requires dosage adjustment for patients with creatinine clearances of 30ml/minute or less, and has a relatively long half-life of 12-17 hours. With no method to assess clotting times, a bleeding episode can occur in a relatively unchecked manner. This potential can be magnified in elderly

patients with their natural decline in renal function. This can also be a disadvantage if patients present to the emergency room with signs of bleeding and there is no way to determine degree or magnitude of the problem. Other challenges include use of this agent in patients undergoing emergency surgeries and other acute situations when there is presently no reversal agent available (compared to warfarin where reversal options exist).

There is also the problem of ease of use with dabigatran dosed twice daily compared to the once daily dosing of warfarin; thus, compliance and how to manage a patient who forgets a dose will be issues. The dyspepsia associated with dabigatran (reported in about 1 out of 10 treated patients) will reduce treatment adherence. Effectiveness is hard to measure with any new medication because clinical trials are not necessarily conducted under real life practicalities.

Warfarin is far from a perfect solution, with many drug and food interactions and dosing adjustments required based on laboratory testing. Although it is the current standard of care for millions of patients with atrial fibrillation because of its proven reduction in stroke and embolic events, its widely known adverse safety profile also makes non-compliance high.

While the RE-LY study pointed out an improvement in bleeding episodes with dabigatran compared to warfarin, there was no difference in major bleeding between these two agents. Thus, the relative reversibility of warfarin may outweigh the patient lifestyle benefit promoted by dabigatran. Additionally, the FDA in 2010 added new labeling instructions to warfarin to include genotypic dosing.<sup>3</sup> This type of pharmacogenetic based dosing has been shown to improve accuracy and safety in therapeutic dosing compared to empiric dosing. This will potentially allow for improved treatment adherence and patient outcomes.<sup>4</sup>

Several questions remain unanswered at this time. Will dabigatran's study outcomes translate into overall morbidity and mortality reductions in outpatient conditions? Given national concerns over healthcare costs, will a drug that costs 8 times the direct cost of warfarin, but avoids lab monitoring, be a cost effective alternative? Will the new and expanding list of drug interactions reported with dabigatran create an unexpected safety risk to patients in practice? And finally, will the risk of not having a reliable lab test for what is considered a high risk drug be a disadvantage? Only time will tell. Caution should be used in considering this alternative.

## REFERENCES

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