To Monitor Dabigatran or Not: A Matter of Patient Safety

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In October 2010, the US Food and Drug Administration (FDA)2 approved dabigatran etexilate (Pradaxa), a new oral, direct thrombin inhibitor, for prevention of stroke and thrombosis in patients with nonvalvular atrial fibrillation (AF). This marked a new era in the development of fixed-dose novel oral anticoagulants (NOACs) with the hope of achieving improved safety and clinical outcomes compared with warfarin. The concept of a fixed-dose anticoagulant that requires no monitoring quickly made the transition from concept to practice, helped partially by the FDA’s new approach to innovative therapies. This new approach gave the manufacturer, Boehringer Ingelheim, access to priority reviews and a shorter approval process for its blockbuster drug, dabigatran. Rather than the conventional requirement of at least 2 pivotal trials, only a single large clinical trial was necessary for approval. Fixed-dose dabigatran demonstrated noninferior performance compared with dose-optimized warfarin therapy in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial for prevention of stroke and thrombosis in patients with nonvalvular AF, thus providing the bulk of support for FDA approval.

After approval by the FDA in 2010 and the European Medicines Agency (EMA) a year later, dabigatran’s popularity grew quickly, and by the end of 2013 sales approached $2 billion. However, amid litigation in US courts that centered on claims that dabigatran caused severe and fatal bleeding in patients, an investigation by the British Medical Journal revealed that as far back as 2010 Boehringer Ingelheim had knowledge that adjusting the dose of dabigatran might provide patients with superior efficacy and safety compared with a fixed dose (1, 2). This raised serious concerns about what the manufacturer chose not to disclose as it sought regulatory approval.

The clinical impetus to explore novel anticoagulants originated from the difficulty in managing anticoagulation in patients receiving the standard-of-care treatment, warfarin. Anticoagulation has a complex pharmacokinetic profile resulting from numerous drug and food interactions and, if not well controlled, can result in serious adverse events including major bleeds and thrombotic events. In the case of warfarin, dose adjustments and regular monitoring are imperative to minimize patient risk. Dabigatran was developed to overcome these limitations and provide patients with an alternative to warfarin with more convenience, better efficacy, and a better safety profile. Based on promising results from earlier pilot studies, a much larger study, the RE-LY trial, which included 18113 participants, was undertaken to compare dabigatran with warfarin (3). The primary objective of the RE-LY trial was to determine whether a fixed dose of dabigatran (either 110 or 150 mg twice a day) would be noninferior to warfarin in patients with nonvalvular AF; primary outcomes were stroke or systemic embolism. The major conclusions drawn from the RE-LY trial were that the lower dose of dabigatran (110 mg BID) provided the same level of protection from stroke and systemic embolism as warfarin, but with lower rates of major hemorrhage. The higher dose (150 mg BID) reduced rates of stroke and systemic embolism compared with warfarin, but had similar rates of major hemorrhage. Both doses of dabigatran reduced the occurrence of life-threatening bleeding and intracranial bleeding relative to warfarin. These results demonstrated that a fixed dose of NOACs, in this case dabigatran, could be a suitable replacement for warfarin.

The FDA approved dabigatran at a fixed dose of 150 mg BID from the RE-LY trial. In documents obtained by the British Medical Journal, the FDA expressed concerns that the 110-mg BID dose would be overused, putting the average patient at risk for stroke, and thus did not approve the lower dose. However, the FDA did instruct the manufacturer to introduce a 75-mg BID dose for patients with renal impairment [creatinine clearance (CrCl) 15–30 mL/min]. This dose was not included in the RE-LY trial and had not been tested in randomized trials; rather it was based on pharmacokinetic modeling and use in Europe. In contrast, the EMA approved both the 150 and 110 mg BID dosages and contraindicated dabigatran use in patients with severe renal impairment. In addition, the EMA stipulated that the drug maker had...
to implement an educational program on how to monitor renal function and reduce bleeding risks, provide a published therapeutic range (48–200 ng/mL), and ensure that a validated assay was available that could measure the anticoagulation activity of dabigatran.

Data suggesting patients receiving dabigatran may benefit from drug monitoring were published only recently, on the basis of a substudy of the RE-LY trial that included 9183 patients (4). That study concluded that ischemic stroke and bleeding outcomes correlated with dabigatran plasma concentrations. Importantly, dabigatran demonstrated significant interindividual variability. Considering only the 10th to 90th percentile, steady-state trough concentrations varied approximately 5.2-fold between individuals receiving the 150-mg BID dose. The probability of having a major bleed increased with increasing trough concentrations of dabigatran, and this was amplified in the elderly and those with impaired kidney function—not surprising, considering that dabigatran’s primary route of elimination is through the kidneys. In elderly patients, the study demonstrated that there was not significant loss of efficacy in preventing ischemic stroke or systemic embolic events as steady-state trough concentrations decreased from 300 to 50 ng/mL; however, there was a significant reduction in the probability of having major bleeding (approximately 10% to approximately 3%) (4). The authors concluded that patients with risk factors for higher trough concentrations (old age, reduced CrCl, or low body weight) might benefit from customized dosing. Furthermore, according to the British Medical Journal investigation, Boehringer Ingelheim built a simulation model based on results of the RE-LY substudy suggesting that if plasma drug concentrations were optimized for each patient to a range of 90–140 ng/mL, more than half of the patients would receive a lower dose, which would reduce the risk of bleeding without loss of efficacy (1). In a more troublesome development, documents reviewed by the British Medical Journal indicated that as early as 2010, Boehringer Ingelheim had identified 200 ng/mL as a drug concentration that should not be exceeded owing to risk of bleeding (2). Based on the RE-LY substudy, at least 10% of patients receiving the 150 mg BID dose had plasma drug concentrations >200 ng/mL (4). Considering both the data published in the RE-LY substudy and the information reviewed in the British Medical Journal investigative report, dose optimization and therapeutic drug monitoring would be beneficial for many patients.

Measurement of dabigatran concentrations during the RE-LY trial and subsequent trials was performed using LC-MS/MS, the best available method. Several common coagulation assays including thrombin time (TT), dilute TT (dTT), prothrombin time (PT), dilute PT (dPT), and activated partial thrombin time (aPTT) have also been evaluated to determine if clotting times would correlate with dabigatran concentrations (5). The PT and dPT tests had limited utility because of poor sensitivity and a nonlinear relationship. The TT test had too narrow a measurable range to be useful and suffered from substantial reagent variability. A dose-dependent increase in aPTT is observed up to 200 ng/mL dabigatran. However, owing to a curvilinear response of the aPTT assay at supratherapeutic concentration of dabigatran, the aPTT assay should be used with caution to assess overdose and should not be used as a quantitative measure of plasma drug concentration. As part of the EMA approval process, the Hemoclot DTI assay, a dTT test, fulfilled the EMA’s requirement to have a validated and reliable assay to measure dabigatran (1). Hemoclot DTI is the only functional assay showing good reproducibility, high sensitivity, and linear correlation with LC-MS/MS across a broad range of dabigatran concentrations (down to 50 ng/mL) (5). However, it is currently available in the US for research use only. LC-MS/MS assays are advantageous, as they can be used to monitor multiple NOACs, can directly measure the drug concentration, have a low limit of quantification, and are less likely to suffer from reagent variability.

Regardless of the ability to accurately measure dabigatran concentrations, there is a lack of prospective data to demonstrate if targeting a specific therapeutic range can translate into superior outcomes. Without such data to offer guidance, it is difficult to implement therapeutic drug monitoring for dabigatran. The FDA maintains that titration of dabigatran dose to target a specific therapeutic concentration range is unnecessary, but this does not preclude laboratories from having the capability to measure dabigatran and other NOACs. When patients receiving NOACs present to the hospital, accurate quantitative assessment of these drugs can improve management of acute bleeding events and emergent invasive procedures and provide periprocedural assessment of anticoagulation status. Furthermore, measuring concentrations may be essential in patients who present with acute kidney failure.

Despite the problems and questions uncovered by the British Medical Journal investigation and recent litigation, both the FDA and Boehringer Ingelheim maintain that dabigatran is a safe and effective replacement for warfarin in patients with nonvalvular AF. Additional data collected by the FDA postapproval corroborate that dabigatran is safer than warfarin. However, it is important to recognize that some patients will likely achieve superior benefits for the risk when doses are optimized to achieve specific trough dabigatran concentrations. Prospective studies are required to better define the ideal therapeutic concentration and confirm whether targeting these therapeutic concentrations results in superior outcomes—a small, but invaluable, measure considering the consequences of ill-applied anticoagulation.
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References