Anticoagulant Options — Why the FDA Approved a Higher but Not a Lower Dose of Dabigatran

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On October 19, 2010, the Food and Drug Administration (FDA) approved dabigatran for the reduction of the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Approval was based on a multicenter, active-control trial, the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY), in which patients were randomly assigned to receive 150 mg of dabigatran, 110 mg of dabigatran, or warfarin. Dabigatran was given twice daily; warfarin was titrated to achieve an international normalized ratio (INR) of 2.0 to 3.0. Assignment to warfarin or dabigatran treatment was unblinded; assignment to a specific dabigatran dose was double-blind. RE-LY was a noninferiority study, attempting to rule out a hazard ratio of more than 1.38 for the primary end point, stroke or systemic embolism.

These results are shown in the top line of the table. Both dabigatran regimens were noninferior to warfarin, but the 150-mg regimen was significantly superior to warfarin and to the 110-mg regimen. With respect to major bleeding episodes (bleeding leading to a reduction in hemoglobin of ≥2 g per deciliter or necessitating a transfusion of ≥2 units of blood or packed cells or symptomatic bleeding in a critical area or organ), 110 mg of dabigatran was superior to warfarin, whereas 150 mg was similar to warfarin. Thus, 150 mg reduced the risk of stroke and systemic embolism more than 110 mg did but also caused more bleeding. Both regimens would have been considered safe and effective if studied alone in comparison with warfarin, although the noninferiority finding for the 110-mg dose is somewhat less compelling. But given the clear differences between the two doses, the FDA’s critical regulatory decision was whether to approve both strengths or only the higher strength. In the end, we approved only the higher dose.

There were certainly reasons why we might have approved both doses. First, both met evidentiary standards for safety and effectiveness, the higher dose showing clear superiority but even the lower dose proving noninferior to standard anticoagulant therapy. Second, patients and doctors value choices that allow treatment to be individualized. For patients for whom there is reason for heightened concern about bleeding, the lower dose might have seemed desirable, even at the cost of increased risk of stroke. Moreover, many patients now refuse to take warfarin because of fear of bleeding. Whether or not it would be a rational choice, 110 mg of dabigatran might have provided an attractive option for such patients — an option clearly preferable to no treatment at all.

On the other hand, nonfatal and extracranial bleeding episodes are clearly less clinically significant than strokes for most patients, and users of a lower dose would be more likely to have strokes, most likely embolic ones. The FDA review team therefore sought to identify, within RE-LY, a patient population for whom the benefit–risk assessment of 110 mg of dabigatran suggested superiority to the 150 mg dose. Our analyses focused on elderly patients, patients with impaired renal function, and patients with previous bleeding episodes. Since such patients would be exposed to higher dabigatran concentrations or would have a greater predisposition to bleeding episodes — or both — the lower dose might offer an advantage.

Older patients were of particular interest, because atrial fibrillation is largely a disease of the elderly and the risks of stroke and bleeding increase with advancing age. Among the 40% of patients in RE-LY who were 75 years of age or older (n = 7238), the rate of stroke or systemic embolism was lower with 150 mg of dabigatran (1.4 per 100 patient-years) than with 110 mg (1.9 per 100 patient-years), but the rate of major bleeding was higher (5.1 vs. 4.4 per 100 patient-years). If stroke or systemic embolism and major hemorrhage were considered equally undesirable, these rates would indicate similar benefit–risk assessments for the two doses. Most people would agree, however, that the irreversible effects of strokes and systemic emboli have greater clinical significance than nonfatal bleeding. Any benefit–risk assessment in which strokes and systemic emboli are given more weight than
nonfatal bleeding events would find the higher dose more favorable in elderly patients.

Since dabigatran is cleared primarily by the kidneys, patients with impaired renal function could potentially benefit from a lower dose. Patients with severe renal impairment were excluded from RE-LY, but we examined patients (n = 3343) with moderate renal impairment (creatinine clearance >30 to 50 ml per minute), whose dabigatran concentrations were two to three times as high as those in patients with normal renal function. In this population, the rate of stroke or systemic embolism with 150 mg of dabigatran (1.3 per 100 patient-years) was approximately half that with 110 mg (2.4 per 100 patient-years), and the rate of bleeding was no greater (5.3 vs. 5.7 major bleeding episodes per 100 patient-years). Thus, even in a population exposed to relatively high concentrations of dabigatran, the 150-mg dose had a superior benefit–risk profile.

We also considered patients who were at higher risk for bleeding because of previous hemorrhage. In RE-LY, 57% of patients who had a major bleeding event during the study either resumed taking or had no interruption in their study medication, continuing to take the same dose. The percentages of these patients who had an additional major hemorrhage were similar: 16%, 14%, and 12% in the 110-mg dabigatran, 150-mg dabigatran, and warfarin groups, respectively. These findings, although exploratory, do not support the strategy of transitioning patients to the lower dose if they have a bleeding episode while receiving the higher dose.

We were thus unable to find any population for whom the availability of a lower dose would improve dabigatran's benefit–risk profile, and it appeared clear that most, if not all, patients should receive the higher dose. For patients with severe renal impairment, in whom exposure is increased by a factor of six, we reduced the dose to 75 mg. As with most dose adjustments related to renal impairment, this decision was based not on efficacy and safety data, but on pharmacokinetic and pharmacodynamic modeling.

Warfarin is widely known to be underutilized in patients with atrial fibrillation, at a cost of unnecessary strokes and disability. Fear of bleeding accounts for some of the underuse, but the difficulties of warfarin use (e.g., the need for repeated INR monitoring and dietary restrictions) also play a role. For patients who don't take warfarin because of difficulty maintaining an INR in the therapeutic range, dabigatran at either strength would provide an acceptable therapy for stroke reduction. Some patients who currently reject warfarin for fear of bleeding might have been willing to use dabigatran at the 110-mg dose, with its lower bleeding risk. Nevertheless, we concluded that encouraging the “play it safe” option for patients and physicians represented an undesirable stim-
Hospitals’ Race to Employ Physicians — The Logic behind a Money-Losing Proposition

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U.S. hospitals have begun responding to the implementation of health care reform by accelerating their hiring of physicians. More than half of practicing U.S. physicians are now employed by hospitals or integrated delivery systems, a trend fueled by the intended creation of accountable care organizations (ACOs) and the prospect of more risk-based payment approaches. Whether physicians, hospitals, or payers end up leading ACOs will depend on local market factors, competitive behaviors, and first-mover advantage, but employment decisions made by physicians today will have long-term repercussions for the practice and management of medicine.1

In the 1990s, hospitals acquired many physician practices of which they subsequently divested themselves. After the current cycle of physician-practice acquisitions, it will be harder to revert to private practice if relationships sour, since new payment structures and care models will make it increasingly difficult for traditional private practices to remain profitable. Many clinicians are unaware that hospitals lose money on their employed physicians, though hiring them may be a wise long-term investment. Understanding the economics of these decisions will help physicians to anticipate the evolution of their employment situations and see why hospitals are making increasingly aggressive plans to acquire physician practices.

Hospitals lose $150,000 to $250,000 per year over the first 3 years of employing a physician — owing in part to a slow ramp-up period as physicians establish themselves or transition their practices and adapt to management changes. The losses decrease by approximately 50% after 3 years but do persist thereafter. New primary care physicians (PCPs) contribute nearly $150,000 less to hospitals than their more-established counterparts; among specialists, the difference is $200,000. For hospitals to break even, newly hired PCPs must generate at least 30% more.