

Warfarin and dabigatran: an historical handover?

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It was in the early 1943 that Karl Paul Link first lectured on the anticoagulant properties of dicumarol. Since then, warfarin and other vitamin K antagonists have been used for prevention and treatment of thrombosis for almost 70 years. Because atrial fibrillation (AF) is the most common heart rhythm disorder [1], and its presence increases the chance of stroke by five-fold [2], AF patients constitute the vast majority of patients with indications for anticoagulation therapy. However, anticoagulant therapy is often a source of frustration to both patients and physicians. Although it has been shown to reduce the incidence of stroke by 61%, only half of eligible patients receive appropriate treatment [3]. While on warfarin, patients are required to complete an international normalized ratio (INR) monthly check and, if they are above or below the recommended range, have to go back the following week. Nonetheless, despite the frequent check up and the institution of anticoagulation centers, patients on warfarin are <60% of the time in the therapeutic INR range [4]. In addition, many elderly patients, which represent the vast majority of patients with indications to anticoagulation therapy, often present with limited mobility and autonomy and therefore have additional difficulties for attending hospital-located monitoring facilities. Moreover, since warfarin effects are affected by factors such as food and drug-drug interactions, patients are also equipped with a long list of “things to avoid while on warfarin”, which is commonly a life-long therapy. Therefore, fairly enough, when implementing such a treatment, patients tend to be very reluctant and regard it as a kind of a “punishment”, especially the asymptomatic ones, in whom AF diagnosis was based on an accidental electrocardiogram (ECG) finding.

Although researchers have been looking for replacing warfarin for several decades, until recently no drug presented as a suitable substitute. However, after a long quiescence period, we are perhaps witnessing an historical event. Indeed, as reported in the 2010 European Society of Cardiology guidelines for the management of patients with AF, dabigatran received guidance for use as an alternative to warfarin [5]. Moreover, in the more recently published, 2011 American College of Cardiology/American Heart Association homologue guidelines, dabigatran obtained a “Class I, Level of Evidence B” insertion as an alternative to warfarin for AF patients [1].

Dabigatran is a “classmate” of ximelagatran, the first direct thrombin inhibitor which, despite showing clinical efficacy for prevention of thromboembolic events, led to fatal hepatotoxicity and therefore was withdrawn from clinical use. The first credentials for safety and efficacy issues arose from phase III clinical studies that compared dabigatran to enoxaparin or

warfarin in patients undergoing orthopedic surgery [6]. However, the conclusive results are based on the RE-LY trial, which assessed the two-year outcomes of some 18,113 AF patients receiving dabigatran (110 or 150 mg twice daily) or warfarin. In this study, the rate of the primary outcome (systemic embolism) was lower with dabigatran at a dosage of 150 mg twice daily. Importantly, although gastro intestinal bleeding in elderly patients slightly increased, a 70% reduction in intracerebral bleeding was observed in patients receiving both doses of dabigatran as compared to warfarin. Moreover, continuous monitoring revealed no significant increase in hepatic enzymes associated with dabigatran. Nonetheless, there was a very small but statistically significant increase in the risk of myocardial infarction with dabigatran (reaching statistical significance in the 110 mg regime), which may temper some of the enthusiasm for the use of this drug. Another important issue with dabigatran is the lack of an antidote for reversal of anticoagulation, although, in extreme cases, can be controlled by fresh plasma infusion.

Dabigatran etexilate is an oral pro-drug rapidly converted by serum esterases to dabigatran, a competitive direct thrombin inhibitor. It reaches peak plasma concentrations within 1–2 hours after administration and has a half-life of 12–17 hours. It necessitates twice-daily administration, does not interact with CYP450 system and is excreted by kidneys. There are, however, other “attention” labels to its use. Dabigatran is a substrate of p-glycoprotein, a protein involved in active transportation of drugs through membranes. Therefore, drugs that strongly inhibit (amiodarone, verapamil, and quinidine) or induce (rifamicin, pantoprazole) p-glycoprotein activity should be used with caution or avoided. Nonetheless, contrary to expectancies, such interactions did not reveal relevant in the RE-LY study.

From a practical point of view, besides evaluating the above-mentioned medical conditions, when considering a switch from warfarin to dabigatran we should ask whether patients have plain access to anticoagulation centers, can fully comply with the twice-daily dosing, or prefer one to another treatment. On the other hand, cost issues will also have a great impact in determining treatment choices. However, a preliminary cost-effective study that based the estimates on the United Kingdom prices of dabigatran showed promising results [7].

In conclusion, provided the brand new, guideline-recommended dabigatran fulfill current promises, we may be witnessing an historical warfarin-to-dabigatran handover. •

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