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Dabigatran, a direct thrombin inhibitor, in atrial fibrillation: Is it already time for a change in oral anticoagulation therapy?

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Introduction

Atrial fibrillation (AF) is a common arrhythmia, and its prevalence increases with aging and the severity of heart disease. AF affects more than 2 million people in the US, and more than 4 million in Europe. It is expected that the age adjusted prevalence in US will excede 10 million people by the year 2050.[1-5] In the last decade, we were able to see the light shed by several trials that dealt with AF mechanisms and the appropriate management of AF patients. Clinical studies have focused mainly on the electrophysiological properties of the substrate in the atrial muscle during sinus rhythm and on the atrial electrical responses elicited by premature stimulation method.[6-9] However, many fundamental aspects of this arrhythmia have been poorly understood until quite recently, and there are several features on the mechanisms of AF that makes it difficult to manage it properly. Increasing awareness of AF as a disease with possible fatal complications rather than as an acceptable alternative to sinus rhythm has led to search for clear arguments to support a certain strategy as a golden standard.

There is no atrial contraction during AF, a situation that renders the pooled blood inside the atrium susceptible to develop thrombus formation particularly in the left atrium. AF increases the overall risk of stroke five-fold, and is associated with particularly severe strokes .[10-12] About 76% of AF patients have a moderate to high risk of embolic complications, and they have also a significant risk factor for stroke recurrence.[13-15] It looks very clear that all the difficulties we have to face in finding proper answer to its therapeutic management. Vitamin K antagonist drugs, such as warfarin and acenocumarol, reduce the risk of AF-related stroke by about 70%.[4, 16] They are the only oral antico agulants currently recommended for the prevention of stroke in patients with a moderate to high risk of stroke[15] These pharmacological agents produce their anticoagulant effect by preventing the g-carboxylation of the vitamin K-dependent coagulation factors prothrombin and Factors VII, IX, and X.[17] Despite the good clinical results obtained with these oral anticoagulants that are far from being ideal [Table 1], there are some inconvenient factors which make their conventional use difficult to implement and follow. There is a consistent suboptimal utilization of oral anticoagulation therapy. Warfarin is prescribed to only two thirds of appropriate candidates despite guidelines recommendations.[18] The narrow therapeutic window in the anticoagulation process makes it neccessary to monitor closely the prothrombin time. Insufficient

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Table 1	Characteristics of an ideal anticoagulant for long-term use in AF

1. Oral administration.
2. Predictable pharmacokinetics.
3. Predictable pharmacodynamics.
4. Low propensity for food and drug interactions.
5. Administration of fixed doses.
6. Wide therapeutic window.
7. No necessity for regular monitoring.

anticoagulation may result in embolic complications, while over-anticoagulation increases the risk of bleeding.[19] There are also other disadvantages related to the unpredictable pharmacokinetics and pharmacodynamics of these oral anticoagulants, which are affected by genetic factors, drug to drug interactions, and consumption of foods containing vitamin K. Therefore, it is paramount that a regular coagulation monitoring and dose adjustment is necessary to ensure adequate anticoagulation. This fact leads to high rates of discontinuation of therapy, and many patients remaining on therapy have also inadequate anticoagulation. Another important issue is the concern about real-world effectiveness which was found to be around 35%.[18] It is clear to see that there is a great need of new oral anticoagulants for stroke prevention in patients with AF. Connolly et al[20] reported recently in the New England Journal of Medicine, the clinical findings with a new oral anticoagulant, dabigatran, which was compared to warfarin in a large, multicenter, randomized trial with AF patients. Dabigatran etexilate is an oral thrombin inhibitor prodrug, that after conversion to its active form, dabigatran competitively inhibits thrombin. Since the conversion is carried out by a serum esterase that is independent of cytochrome P-450, dabigatran should be less susceptible to dietary and drug interactions and to genetic polymorphisms that affect warfarin. In addition, neither anticoagulation monitoring nor dose adjustments are necessary with dabigatran.

The RE-LY trial design and outcome

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) was a large, multicenter, randomized trial designed to compare two fixed doses of dabigatran (110 mg and 150 mg), each administered in a blinded manner, with openlabel use of warfarin in AF patients who were at increased risk for stroke. Patients recruited from 951 clinical centers in 44 countries were eligible if they had documented AF on electrocardiography performed at screening or within 6 months beforehand and at least one of the following characteristics: previous stroke or transient ischemic attack, a left ventricular ejection fraction of less than 40%, New York Heart Association class II or higher heart-failure symptoms within 6 months before screening, and an age of at least 75 years or an age of 65 to 74 years plus diabetes mellitus, hypertension, or coronary artery disease. Exclusion criteria are detailed in [Table 2]. Dabigatran was administered, in a blinded fashion, in capsules containing either 110 mg or 150 mg of the drug, to be taken twice daily. Warfarin was administered, in an unblinded fashion, in tablets of 1, 3, or 5 mg and was adjusted locally to an international normalized ratio (INR) of 2.0 to 3.0, with the INR measured at least monthly.

The primary study outcome was stroke or systemicembolism. The primary safety outcome was major hemorrhage. Secondary outcomes were stroke, systemic embolism, and death. Other outcomes were myocardial infarction, pulmonary embolism, transient ischemic attack, and hospitalization. The primary net clinical benefit outcome was the composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major hemorrhage. A total of 18,113 patients were enrolled. The three treatment groups were well balanced with respect to baseline characteristics. The mean age of the patients was 71 years, and 64% were men. Half the patients had received long-term therapy with vitamin K antagonists. The mean CHADS2 score was 2.1. The rate of the primary outcome was significantly lower with

Table 2	Exclusion criteria in the RE-LY trial

1. Presence of a severe heart-valve disorder.
2. Stroke within 14 days.
3. Severe stroke within 6 months before screening.
4. A condition that increased the risk of hemorrhage.
5. Creatinine clearance of less than 30 ml per minute.
6. Active liver disease.
7. Pregnancy.

dabigatran at a dose of 150 mg twice daily (1.11% per year) than with either dabigatran at a dose of 110 mg twice daily (1.53% per year) or warfarin (1.69% per year). Both doses of dabigatran were noninferior to warfarin (p<0.001), and the higher dose of dabigatran was even superior to warfarin (p<0.001). The rate of non-hemorrhagic stroke was also significantly lower with 150 mg of dabigatran (0.92% per year) than with either 110 mg of dabigatran (1.34% per year) or warfarin (1.20% per year). The rates per year of hemorrhagic stroke with the 110-mg and 150-mg dabigatran doses (0.12% and 0.10%) were significantly lower than that with warfarin (0.38%). The rate of extracra nial hemorrhage was similar in all three groups: 2.51% with 110 mg of dabigatran, 2.84% with 150 mg of dabigatran, and 2.67% with warfarin.

Other interesting outcomes are as follows: there was no significant difference in the rates of death from any cause, and they were 4.13% per year with warfarin, as compared with 3.75% per year with 110 mg of dabigatran and 3.64% per year with 150 mg of dabigatran. The rate of myocardial infarction was 0.53% per year with warfarin and was higher with dabigatran: 0.72% per year in the 110-mg group (relative risk, 1.35; 95% CI, 0.98 to 1.87; P = 0.07) and 0.74% per year in the 150-mg group (relative risk, 1.38, 95% CI, 1.00 to 1.91; P = 0.048). The rate of major bleeding was 3.36% per year in the warfarin group, as compared with 2.71% per year in the group that received 110 mg of dabigatran (relative risk with dabigatran, 0.80; 95% CI, 0.69 to 0.93; P = 0.003) and 3.11% per year in the group that received 150 mg of dabigatran. The only adverse effect that was significantly more common with dabigatran than with warfarin was dyspepsia. Hepatotoxicity was investigated in detail in this trial. Elevations in the serum aspartate aminotransferase or alanine aminotransferase level of more than 3 times the upper limit of the normal range did not occur more frequently with dabigatran, at either dose, than with warfarin. Patients requiring hospitalization for a liver disorder was equivalent in the three treatment groups. However, the follow-up period in this trial was only a median of 2.0 years, so the hepatic risks of long-term use are unclear. The hepatotoxicity and safety of the long-term use of dabigatran is being investigated in a follow-up study.

A finding that needs our full attention and should be addressed in a long-term follow-up is the fact that the rate of myocardial infarction was higher with both doses of dabigatran than with warfarin. Therefore, it seems that warfarin provides better protection against coronary ischemic events than dabigatran. Although warfarin was shown to reduce the risk of myocardial infarction,[21] when it was compared to another direct thrombin inhibitor (Ximelagatran) in AF patients, the rates of myocardial infarction were similar.[22] The explanation for this finding of higher rates of myocardial infarction with dabigatran remains therefore uncertain.

Is it time for a change in oral anticoagulation therapy of AF?

A new oral anticoagulant for AF patients which would have similar efficacy and safety as warfarin, in addition to obviate the need for permanent monitoring of blood tests and dosing would incline the scales toward the utilization of the new oral anticoagulant. However, Dabigatran showed more than just similar efficacy compared to warfarin. Both dabigatran doses were noninferior to warfarin with respect to the primary efficacy outcome of stroke or systemic embolism. In addition, the 150-mg dose of dabigatran was superior to warfarin with respect to stroke or systemic embolism, and the 110-mg dose was superior to warfarin with respect to major bleeding. Furthermore, there is no necessity for anticoagulation monitoring neither dose adjustments with dabigatran.

The RE-LY trial is the first large, multicenter, randomized trial that investigated this new oral anticoagulant agent, dabigatran, in AF patients. Therefore, despite the excellent results in efficacy and safety of dabigatran and the superiority shown over warfarin in embolic complications, a class IIB indication can only be given to the use of dabigatran in AF patients at this moment. Results of longterm follow-up and from more trials are needed in order to give dabigatran a class IA indication.

Nevertheless, we have to keep in mind certain issues with the use of dabigatran in AF patients. There was a higher rate of myocardial infarction in AF patients treated with dabigatran. Also, this

direct thrombin inhibitor is not without important drug interactions. It is known that P-glycoprotein inhibitors, such as verapamil, amiodarone, and quinidine, raise dabigatran serum concentrations considerably. This interaction may have contributed to the trend toward greater efficacy of dabigatran in the subgroup of patients taking amiodarone in the RE-LY trial, but it could elevate the risk of hemorrhage in such patients. These issues should be addressed in detail in the long-term follow-up study which is underway.

Coumarins were discovered more than 60 years ago, and for more than 50 years, they have been the sole anticoagulant drugs available to clinicians, and are currently the only oral anticoagulants available.[23] Several new anticoagulants have been introduced, and many more are under clinical development. Dabigatran given at a dose of 150 mg twice daily prevented more strokes than warfarin, and dabigatran at a dose of 110 mg twice daily caused fewer hemorrhagic complications than warfarin. Indeed, dabigatran showed statistical significant superiority compared to warfarin. It is hard to say good-bye to a good friend after more than 50 years of friendship. However, with dabigatran, a new friend around, it may be already time for a change in oral anticoagulant therapy for atrial fibrillation.

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