Efficacy And Safety Of Dabigatran Etxilate Utilization With Concomitant Dual Antiplatelet Therapy In Atrial Fibrillation

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Abstract
The necessity to add two antiplatelet agents to an oral anticoagulant (OAC) often arises in patients with atrial fibrillation (AF) in routine clinical practice. The majority of AF patients have an indication for continuous OAC, and coronary artery disease co-exists in 25% of these patients. The increasing use of drug-eluting stents to minimize intrastent restenosis necessitates long-term dual antiplatelet therapy with Aspirin plus Clopidogrel to reduce the risk of early and late stent thrombosis. Combined aspirin–clopidogrel therapy, however, is less effective in preventing stroke compared with OAC alone in AF patients, and OAC alone is insufficient to prevent stent thrombosis. The management of AF patients presenting with an acute coronary syndrome poses similar management complexities. Since AF and coronary artery disease with stent placement are common, it is relatively frequent to treat patients with both these conditions, where triple antithrombotic therapy with Aspirin, Clopidogrel and an OAC would be needed. Dabigatran etexilate, an oral direct thrombin inhibitor, has shown that compared with Warfarin given at a dose of 150 mg twice daily significantly reduces stroke with less intracranial bleeding, and at a dose of 110 mg twice daily has similar efficacy with less bleeding. Although, Dabigatran maintained its overall favorable profile compared with Warfarin in patients on dual antiplatelet therapy, we should always bear in mind for the sake of our AF patients that combining dual antiplatelet therapy with chronic anticoagulation with Dabigatran, as well as with Warfarin, significantly increases bleeding risk. This triple therapy association should be evaluated in the individual patient after carefully balancing bleeding versus thrombotic risk.

Introduction
Atrial fibrillation (AF) is the most common sustained arrhythmia encountered by clinicians. AF has a prevalence of approximately 1% and a lifetime risk of approximately 25% after the age of 40.1,2 The annual risk of stroke ranges from 2%-18% depending on other risk factors.3 The prevalence of AF increases with age, and the elderly are the fastest growing subset of the population. It has been estimated that there will be 12 million patients with AF in the United States within the next several decades.4,5 Many fundamental aspects of AF 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. 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 AF may present in a wide variety of clinical conditions. The optimal management strategy for an individual patient with AF depends on the patient’s underlying condition.
Atrial fibrillation shares strong epidemiological associations with other cardiovascular diseases such as heart failure and coronary artery disease.10-12 Coronary heart disease (CHD) is a complex clinical state characterized by a variety of substrate patterns interacting with triggers that may initiate AF. Cumulative effects in a complex disease imply integration of the pathophysiologic context from structural disease development, namely atherosclerosis, to a specific outcome expression, that is, AF. Coronary artery disease coexists in 20% to 30% of patients with AF, and it follows that many will require percutaneous coronary intervention (PCI) at some stage.13-15 Balancing the risk of bleeding and thromboembolism is crucial in the management of patients with AF, and this is never more apparent than when such AF patients require PCI. Therefore, we encountered many patients with the coexistence of these two diseases in our daily clinical practice. This raises the challenge of choosing the best adequate therapy for this complicated scenario.
Antithrombotic therapy reduces the risk of stroke in patients with AF, and Warfarin has been shown to have a relative risk reduction of approximately 60% compared with control and to be
Features of the ideal Anticoagulant drug for AF associated to ACS

Table 1: Features of the ideal Anticoagulant drug for AF associated to ACS

<table>
<thead>
<tr>
<th>Feature Description</th>
<th>Reason for desirability</th>
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<td>4. Predictable pharmacodynamics.</td>
<td>Ensures predictable effects.</td>
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<tr>
<td>5. Minimal food and drug interactions.</td>
<td>Decreases interference with other medications.</td>
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<tr>
<td>7. Antidote.</td>
<td>Provides a means to reverse effects quickly.</td>
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<tr>
<td>8. No necessity for dose adjustments.</td>
<td>Simplifies dosing regimen.</td>
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<td>10. No necessity for regular monitoring.</td>
<td>Minimizes need for frequent medical visits.</td>
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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 open-label 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. 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.

Results and Outcome of the RE-LY Trial

The primary study outcome was stroke or systemic embolism. 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 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 extracranial 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.

In summary, the RE-LY trial (Randomized Evaluation of Long-term anticoagulant therapy) showed that compared with Warfarin the oral direct thrombin inhibitor, Dabigatran etexilate given at a dose of 150 mg twice daily reduces stroke with less intracranial bleeding, and Dabigatran 110 mg twice daily has similar efficacy with less bleeding.

The Necessity for Triple Therapy

The necessity to add two antiplatelet agents to an OAC often arises in patients with AF in routine clinical practice. About 70–80% of all patients in AF have an indication for continuous OAC, and coronary artery disease co-exists in 20–30% of these patients. With an estimated prevalence of AF in 1–2% of the population, one to two million anticoagulated patients in Europe are candidates for coronary revascularization, often in the form of percutaneous coronary interventions (PCI), usually including stents.
Management of AF Patients Presenting with ACS

Acute coronary syndrome (ACS) patients presenting with acute ST-elevation myocardial infarction are increasingly managed with primary PCI with additional combined antithrombotic therapy regimes. The increasing use of drug-eluting stents (DES) to minimize intrastent restenosis necessitates long-term dual antiplatelet therapy with Aspirin plus Clopidogrel to reduce the risk of early and late stent thrombosis. Combined aspirin–clopidogrel therapy, however, is less effective in preventing stoke compared with OAC alone in patients with AF,18 and OAC alone is insufficient to prevent stent thrombosis after PCI.21–24 The management of AF patients presenting with an ACS poses similar management complexities. Those presenting with non–ST-elevation acute myocardial infarction are also managed with combined antithrombotic therapy, and frequently an early invasive revascularization strategy is recommended by guidelines and more commonly used.

Dual Antiplatelet Therapy in ACS Patients Undergoing PCI

Antiplatelet therapy is a key component of management to prevent recurrent ischemic events and stent thrombosis after ACS and/or PCI. Aspirin has been long known to significantly reduce cardiovascular events after ACS.25,26 Over the past decade, DAPT has also been studied extensively in the ACS setting and found to improve outcomes significantly compared with aspirin alone, with studies focusing on Ticlopidine, and later on Clopidogrel as the second antiplatelet agent.25 Recently, newer antiplatelet agents have been evaluated as part of DAPT in the setting of ACS.

Prasugrel and Ticagrelor generally achieve higher degrees of platelet inhibition than Clopidogrel and do not appear to be affected by CYP2C19 polymorphisms. It should be mentioned that no reliable clinical data are available in AF patients on the combined use of an OAC with the new P2Y12 antagonists (Prasugrel or Ticagrelor) either alone or with aspirin. Both medications have been associated with reductions in cardiovascular events in patients with ACS, although with increases in the rates of spontaneous bleeding. Current guidelines for ACS and/or PCI broadly recommend the use of aspirin–clopidogrel combination therapy after ACS. According to current guidelines, all patients with a recent coronary artery stent placement should receive double antiplatelet therapy with a combination of Aspirin plus Clopidogrel to reduce the likelihood of acute and subacute stent thrombosis.29 The length of treatment depends on the type of the stent, with drug-eluting stents requiring at least 6–12 months of both antiplatelet drugs.

Triple Antithrombotic Therapy in AF Patients Associated with ACS

AF increases the overall risk of stroke five-fold, and is associated with particularly severe strokes.27–29 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.30–32 Therefore, AF carries a high risk for thromboembolic events and any patient with at least two moderate risk factors, and probably even one, should be on oral anticoagulation. Since AF and coronary artery disease with stent placement are common, it is not infrequent to treat patients with both these conditions, where triple antithrombotic therapy with Aspirin, Clopidogrel and OAC would be needed. Although triple oral antithrombotic therapy (TOAT) may be necessary to prevent both ischemic and thromboembolic events in patients with both AF and coronary heart disease, the potential for increased bleeding has raised concerns regarding the overall utility of TOAT. The difficulty lies in balancing thromboembolic risk versus bleeding risk in the individual patient.

The Efficacy and Safety of Triple Therapy

In order to obtain a better understanding of the efficacy and safety of adding one or two antiplatelet agents to Dabigatran, post-hoc analyses from trials such as the RE-LY trial, and data from a Phase II trial in ACS patients will be considered. Dans AL et al report on the efficacy and safety of two doses of Dabigatran in combination with antiplatelet therapies.33 Since it was a sub-study, the utilization of antiplatelet agents was not randomized or stratified. At the beginning of the study 40% of the patients were using an antiplatelet agent and only one out of five used it continuously throughout the study. Most of these patients were taking Aspirin, while the use of Clopidogrel only was 1.9%, and the utilization of dual antiplatelet therapy was 4.5%. Other P2Y12 inhibitors such as Ticagrelor or Prasugrel were not used. It was demonstrated that any antiplatelet utilization increased the risk of major or minor extracranial bleeding. Intracranial hemorrhage was not more frequent, although numbers were relatively low. Overall, antiplatelet therapy doubled the risk of bleeding, but the magnitude of risk increased with the number of antiplatelet agents used. The addition of a single antiplatelet agent, in most cases Aspirin, significantly increased the risk of major bleeding with 60%, while the risk of major bleeding was 2.3 times higher after adding Clopidogrel on top of Aspirin. The non-inferiority of the 110 mg bid Dabigatran dose in terms of efficacy was preserved with concomitant antiplatelet therapy.33 The lower risk of major and minor bleeding complications, including intracranial hemorrhage, as observed in the overall trial, was also maintained in patients on concomitant antiplatelet. Considering the 150 mg bid Dabigatran’s dose, its superior efficacy when compared with warfarin tended to diminish to some extent in patients also taking antiplatelet agents. In contrast, the risk of major and minor bleeding complications remained similar to Warfarin, but the risk of intracranial hemorrhage was still lower with this dose of Dabigatran.33 Therefore, Dabigatran maintained its overall favorable profile compared with Warfarin in patients on antiplatelet therapy. The 2 doses of Dabigatran etexilate were shown to be effective and safe for the prevention of stroke or systemic embolism in AF patients even in the long-term follow-up.34 This favorable outcome of Dabigatran compared to Warfarin is also observed in different ethnicities.35

The first randomized evaluation of treatment with Dabigatran in patients with a recent non-ST or ST-elevation myocardial infarction in which all patients were required to be on dual antiplatelet therapy with both Aspirin and Clopidogrel was the RE-DEEM trial.36 In this double-blind, placebo-controlled, dose-escalation trial, 1861 patients in 161 centers were enrolled after an ST-elevation or non-ST-elevation myocardial infarction and randomized to twice daily treatment with Dabigatran 50 mg, 75 mg, 110 mg, 150 mg, or placebo. Primary outcome was the composite of major or clinically relevant minor bleeding during the 6-month treatment period. The addition of Dabigatran was associated with a dose-dependent increase in major or clinically relevant minor bleeding. Specifically at 6 months of treatment with Dabigatran from 50 to 150 mg twice daily was associated with a dose-related two to four times increased risk of bleeding in post-myocardial infarction patients receiving dual antiplatelet therapy, although the absolute incidence of major bleeding events was low. Dabigatran significantly reduced coagulation activity...
and may have the potential to reduce cardiovascular events when added to dual antiplatelet treatment in the doses 110–150 mg twice daily. However, considering the uncertainties regarding several aspects of treatment, such as, level of anticoagulation, risk/benefit ratio of dual vs. single antiplatelet therapy on top of Dabigatran, and optimal duration of combination therapy makes it necessary to personalize the triple therapy taking into account the individual thrombotic and bleeding risk of each patient.

Conclusions:
Concomitant antiplatelet drug therapy on top of Dabigatran appeared to increase the risk for major bleeding in AF patients and CHD without affecting the advantages of Dabigatran over Warfarin. It seems that in patients requiring Aspirin 80–100 mg, Dabigatran 110 mg might be a safer alternative to Warfarin. The data available does not provide solid guidance on the optimal duration of antiplatelet therapy on top of Dabigatran. The duration of triple therapy largely depends on the clinical context, and this association should be evaluated in the individual patient after carefully balancing bleeding versus thrombotic risk. Although, Dabigatran maintained its overall favorable profile compared with Warfarin in patients on antiplatelet therapy, we should always bear in mind for the sake of our AF patients that combining dual or single antiplatelet therapy with chronic anticoagulation with Dabigatran, as well as with Warfarin, significantly increases bleeding risk.

References:


