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Review

New oral anticoagulants and dual antiplatelet therapy: Focus on apixaban

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ABSTRACT

The combination of AF and coronary artery disease not only is a common clinical setting, it is also a complex setting to deal with anticoagulation and antiplatelet therapy, and it is associated with significantly higher mortality rates. Unfortunately, there are no sufficient data available to optimally guide clinical practice in such settings. This review focuses specifically on newer oral anticoagulants (NOACs) associated with dual antiplatelet therapy (DAPT) in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI). There are no randomized studies comparing vitamin K antagonists and NOACs in patients with AF undergoing PCI either for acute coronary syndromes or for stable patients, i.e. those patients who have an indication to receive DAPT. Moreover, new antiplatelet agents such as ticagrelor and prasugrel have entered the market for acute coronary syndromes. So far, there are no large-scale randomized studies published evaluating these newer antiplatelet agents in patients with AF receiving either vitamin K antagonists or NOACs, adding to the uncertainty on how to use these antithrombotics in combination when both coronary artery disease (unstable or stable patients) and AF converge in a given patient. The lack of large outcome trials and the large number of possible combinations are reflected in the wide variety of practices in the real world. To date, given the lack of data, watchfulness when using NOACs as component of DAPT or triple oral antithrombotic therapy is warranted.

1. Introduction

The recent introduction of newer oral anticoagulants (NOACs) into the clinical arena, including the direct factor IIa inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban and edoxaban, has resulted in a paradigm shift that, for the first time in 60 years, has challenged the supremacy of warfarin for stroke prophylaxis in atrial fibrillation (AF) [1–4].

In this review, we aim at summarizing the pharmacology, efficacy and safety of NOACs with special reference to the most common clinical scenarios of everyday medical practice, that are patients presenting with both AF and acute coronary syndromes and/or undergoing percutaneous coronary intervention (PCI) with stenting.

2. Pharmacology

Dabigatran, rivaroxaban, apixaban and edoxaban are metabolized primarily by the cytochrome P4503A enzyme (rivaroxaban and apixaban) and/or efflux transporter P-glycoprotein (dabigatran and edoxaban), which contributes to their predictable pharmacokinetic responses [5–9]. As a result, practitioners should be aware of potential interactions between NOACs and strong CYP3A or P-glycoprotein inhibitors or inducers. Concomitant medications that inhibit platelet function, such as aspirin, oral P2Y12 inhibitors (e.g., clopidogrel, prasugrel or ticagrelor) and nonsteroidal anti-inflammatory drugs, may increase the risk of bleeding during treatment with NOACs [10]. For dabigatran, the co-administration of P-glycoprotein inducers, such as rifampin, should be avoided, since it reduces dabigatran's plasma concentration [5]. Close clinical surveillance for bleeding is required if dabigatran is coadministered with strong P-glycoprotein inhibitors, such as amiodarone, verapamil, quinidine, ketoconazole and clarithromycin, due to an increase in its plasma concentration [5]. For rivaroxaban, apixaban and edoxaban, concomitant use of combined strong P-glycoprotein and CYP3A inhibitors, such as antimycotics or protease inhibitors, may

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increase their plasma concentrations and should be avoided [11]. The concomitant use of either a strong P-glycoprotein or strong CYP3A4 inducer, or both, including rifampin, carbamazepine and phenytoin with factor Xa inhibitors, should be avoided or requires vigilance [6–9].

3. Efficacy and safety of NOACs in patients with coronary artery disease

Current guidelines recommend NOACs in preference or as an alternative to warfarin for stroke prophylaxis, but these guidelines do not specify which NOAC should be used for which type of AF patient due to the absence of published randomized controlled clinical trials directly comparing these agents [12–15]. It is unlikely that such head-to-head trials will be undertaken, as they would require in excess of 50,000 patients simply to show non-inferiority [16]. However, there are some network meta-analyses that have indirectly compared dabigatran, rivaroxaban and apixaban vs. warfarin [17–19]. The results showed that: i) dabigatran 150 mg and apixaban are significantly superior to dabigatran 110 mg and rivaroxaban but not significantly different from each other regarding the primary efficacy endpoint, which was any stroke or systemic thromboembolism; ii) apixaban and dabigatran 110 mg (that is not available in North America) are superior to rivaroxaban and dabigatran 150 mg but are not significantly different from each other regarding the primary safety endpoint, which was major bleeding, assessed by the International Society on Thrombosis and Hemostasis criteria, for all trials except the ROCKET-AF (*Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation*) [2]. Noteworthy, published meta-analyses indicate that myocardial infarction occurs less frequently on either rivaroxaban or apixaban (not different from each other) compared to both doses of dabigatran [17–19].

All of this information may help to inform decision makers until head-to-head comparative studies become available. For instance, the balance between efficacy and safety might influence clinicians to choose dabigatran 150 mg or apixaban when the risk of stroke is high or might prompt the choice of apixaban or dabigatran 110 mg when the risks of major bleeding and/or gastrointestinal bleeding are high. Apixaban may be preferred in patients with prior myocardial infarction/acute coronary syndrome. This is consistent with the results of ARISTOTLE trial (*Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation*) [3], which showed that apixaban has consistent effects versus warfarin in patients with and without coronary artery disease (Fig. 1) [3].

4. Acute coronary syndromes and percutaneous coronary intervention/stenting

The category of AF patients presenting with acute coronary syndrome and/or undergoing PCI with stenting not only represents a common clinical scenario but also is notably challenging to manage in clinical practice owing to the need to balance carefully the risk of bleeding against the risk of thromboembolism.

The use of dual antiplatelet therapy (DAPT) is the mainstay treatment for the secondary prevention of major adverse cardiovascular events (i.e. composite of cardiac death, myocardial infarction, stent thrombosis, or target-vessel revascularization) in patients who have survived acute coronary syndrome and/or have received a stent.

Currently, American guidelines recommend DAPT for 12 months after ACS and after elective stenting with a drug-eluting stent, with the option of a lower duration in case of bare metal stents [20–22]. Conversely, DAPT is less effective in preventing AF-related strokes compared to oral anticoagulation alone, and the latter itself is inadequate to prevent stent thrombosis. Thus, given the high prevalence of AF, acute coronary syndromes and/or PCI with stenting, there are many patients who have indications for both oral anticoagulation and DAPT, leading clinicians to face the dilemma of whether to start the so-called triple oral antithrombotic therapy, defined as the combined use of therapeutic oral anticoagulation and DAPT. Indeed, these patients pose substantial management challenges. The omission of oral anticoagulants could lead to an increased risk of thromboembolic stroke, whereas DAPT is essential to preventing major adverse cardiovascular events. At present, European and American experts recommend triple oral antithrombotic therapy in AF patients with acute coronary syndrome and/or undergoing PCI with stenting [12,13,23]. Specifically, newer guidelines for patients with acute coronary syndrome [22,23] suggest that a period of triple therapy, i.e. oral anticoagulation therapy plus aspirin plus clopidogrel, is needed in patients with AF undergoing PCI with stenting, followed by the combination oral anticoagulation plus a single antiplatelet drug and, after one year, management can be with oral anticoagulation alone (vitamin K antagonist or NOAC) in stable patients [12,13].

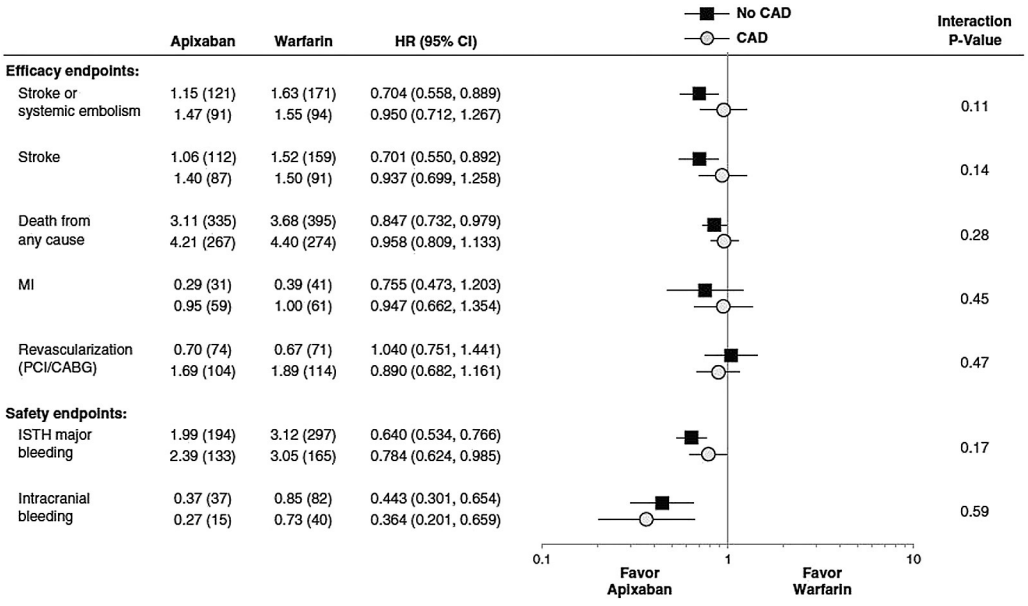

Fig. 1. Apixaban versus warfarin according to coronary artery disease status.
(Modified from Bahit MC et al. Int J Cardiol 2013; 170:215–220)