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Apixaban in patients with atrial fibrillation and prior coronary artery disease: Insights from the ARISTOTLE trial☆,☆☆

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ABSTRACT

Background: A substantial portion of patients with atrial fibrillation (AF) also have coronary artery disease (CAD) and are at risk for coronary events. Warfarin is known to reduce these events, but increase the risk of bleeding. We assessed the effects of apixaban compared with warfarin in AF patients with and without prior CAD.

Methods and results: In ARISTOTLE, 18,201 patients with AF were randomized to apixaban or warfarin. History of CAD was defined as documented CAD, prior myocardial infarction, and/or history of coronary revascularization. We analyzed baseline characteristics and clinical outcomes of patients with and without prior CAD and compared outcomes by randomized treatment using Cox models. A total of 6639 (36.5%) patients had prior CAD. These patients were more often male, more likely to have prior stroke, diabetes, and hypertension, and more often received aspirin at baseline (42.2% vs. 24.5%). The effects of apixaban were similar among patients with and without prior CAD on reducing stroke or systemic embolism and death from any cause (hazard ratio [HR] 0.95, 95% confidence interval [CI] 0.71–1.27, *P* for interaction = 0.12; HR 0.96, 95% CI 0.81–1.13, *P* for interaction = 0.28). Rates of myocardial infarction were numerically lower with apixaban than warfarin among patients with and without prior CAD. The effect of apixaban on reducing major bleeding and intracranial hemorrhage was consistent in patients with and without CAD.

Conclusions: In patients with AF, apixaban more often prevented stroke or systemic embolism and death and caused less bleeding than warfarin, regardless of the presence of prior CAD. Given the common occurrence of AF and CAD and the higher rates of cardiovascular events and death, our results indicate that apixaban may be a better treatment option than warfarin for these high-risk patients.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice and is associated with significant morbidity and mortality [1–5]. Patients with AF have reduced quality of life, a higher risk of developing heart failure, cognitive impairment, and approximately one-third have a history of coronary artery disease (CAD) [6]. The estimated prevalence of AF in a large international cohort is 12.5% in patients with CAD [7]. In addition, patients with both AF and CAD are at an increased risk for ischemic events and cardiovascular death [7].

Oral anticoagulation with warfarin, a vitamin K antagonist, is known to reduce stroke in patients with AF [8] and also to reduce stroke and mortality in patients with AF following myocardial infarction (MI) [9,10]. Recently, 3 pivotal trials have demonstrated benefits of the new oral anticoagulants dabigatran [11,12], rivaroxaban [13,14], and apixaban [15,16] compared with warfarin in patients with AF and an increased risk of stroke. A recent subgroup analysis of the RE-LY study showed that the beneficial effects of dabigatran over warfarin were similar in AF patients with and without prior CAD [17], although there

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was a higher rate of MI with dabigatran compared with warfarin in the trial [12]. In contrast, there was no difference in the rate of MI when comparing apixaban with warfarin in the ARISTOTLE trial or with aspirin in the AVERROES trial [18]. When comparing the 5 mg twice daily dose of apixaban with placebo in patients on antiplatelet agents after an acute coronary syndrome in the prematurely terminated APPRAISE-2 trial, there was no significant reduction in ischemic events [19]. This finding is in contrast to the reduction with low doses of rivaroxaban in the ATLAS-2 trial [20]. However, in both trials there was a 2–3 times increase in major bleeding when adding the factor Xa inhibitors to antiplatelet treatment in patients with CAD. Thus, the usefulness of novel oral anticoagulants in patients with AF and CAD needs further definition.

In the ARISTOTLE [16] trial, 18,201 patients with AF and at least 1 additional risk factor for stroke were randomized to apixaban or dose-adjusted warfarin. In the apixaban group there was a 21% relative reduction in the rate of the primary outcome (stroke or systemic embolism), 31% in major bleeding, and 11% in death from any cause. In this pre-specified subgroup analysis, we evaluated the treatment effects of apixaban compared with warfarin in patients with and without prior CAD.

2. Methods

2.1. Study population

The design and results of the ARISTOTLE trial have been reported [15,16]. Briefly, 18,201 patients with AF or atrial flutter were randomly assigned to receive apixaban or dose-adjusted warfarin. The dose of apixaban (or matching placebo) was 5 mg twice daily or 2.5 mg twice daily for patients with 2 or more of the following factors: age ≥80 years, body weight ≤60 kg, and serum creatinine ≥1.5 mg/dL (133 μmol/L). Patients were enrolled in 39 countries between 2006 and 2010. The median duration of follow-up was 1.8 years. Patients taking concomitant aspirin (≤165 mg/day) were eligible, but patients taking dual antiplatelet therapy with aspirin plus clopidogrel were not.

The ARISTOTLE trial complied with the Declaration of Helsinki. All patients enrolled provided written informed consent, and the trial was approved by the institutional review boards and ethics committees of participating sites.

2.2. Coronary artery disease

CAD was defined as documented CAD, history of MI, and/or history of coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery) at randomization. Classification was used as recorded on the case report form (CRF), and no attempt to adjudicate these classifications was undertaken. Patients with missing data on the above-mentioned CRF check box were excluded.

2.3. Study outcomes

The primary efficacy outcome was stroke or systemic embolism. The key secondary efficacy outcome was death from any cause. Additional outcomes were MI and coronary revascularization.

The primary safety outcome was major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH) criteria [21]. A clinical event committee, whose members were not aware of study group assignments, adjudicated the primary and secondary efficacy and safety outcomes on the basis of pre-specified criteria.

2.4. Statistical analysis

Baseline characteristics of patients with and without history of CAD are presented as medians with 25th and 75th percentiles for continuous variables and frequencies and percentages for categorical variables. Both groups are compared using Wilcoxon tests for continuous variables and chi-square tests for categorical variables. Events during follow-up are summarized as event rates per 100 patient-years of follow-up. Hazard ratios (HRs) along with 95% confidence intervals (CIs) comparing randomized treatments are derived from Cox regression models. The interaction between randomized treatment and CAD status was tested in a Cox model that included the main effects for treatment and CAD and their interaction. The probability of primary efficacy and safety endpoints are presented as Kaplan–Meier curves. The proportional hazard assumption was tested using methods based on cumulative sums of martingale residuals [22]. The proportional hazard assumption was valid for all the endpoints presented except for death from any cause in patients with prior CAD. Results for that endpoint represent an average HR and should be interpreted cautiously.

Although it is recommended in the guidelines to avoid aspirin with warfarin for patients with AF and stable coronary disease, it is unknown whether novel oral anticoagulants alone are sufficient for patients with AF and chronic CAD. We performed an exploratory analysis to determine whether the treatment effect of apixaban versus warfarin in patients with CAD was consistent among patients taking and not taking aspirin at baseline, including the effect on MI.

In all analyses, a P value <0.05 was considered statistically significant. All statistical analyses were performed with SAS software version 9.22 (SAS Institute, Inc., Cary, NC, USA).

3. Results

3.1. Baseline characteristics

Of the 18,201 patients included in the ARISTOTLE study, excluding the 17 with missing data on CAD, 6639 (36.5%) had prior CAD. Of those, 2585 (38.9%) had prior MI, 1206 (18.2%) had prior CABG, and 1651 (24.9%) had prior PCI. Of patients with a history of PCI, 694 had a bare-metal stent and 388 received a drug-eluting stent. Baseline characteristics are shown in Table 1. Patients with prior CAD were more often male, and more commonly had prior peripheral arterial disease (PAD) and paroxysmal AF. Prior stroke, transient ischemic attack, or systemic embolism, and heart failure, reduced left ventricular ejection fraction (LVEF), diabetes, and hypertension were also more prevalent in patients with prior CAD. Accordingly, patients with prior CAD had higher $CHADS_2$ scores, with a score of 3 or more in 36.7% compared with 26.5% in those without prior CAD.

3.2. Medications

At baseline, patients with prior CAD were more likely to be on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, and statins compared with patients with no CAD (Table 1). Aspirin use at randomization was 42.2% in patients with prior CAD compared with 24.5% in those without prior CAD.

During the follow-up period and in the group of patients with prior CAD, study drug discontinuation rates, excluding discontinuation due to death, per 100 patient-years of follow-up were 14.4 for apixaban and 15.2 for warfarin ($P = 0.32$). For patients without prior CAD, the rates were 11.4 in the apixaban group and 13.1 in the warfarin group ($P = 0.0008$).

In the warfarin group, the median time in the target range of the international normalized ratio was 65.2% in patients with prior CAD and 66.4% in patients without prior CAD ($P = 0.0013$).

3.3. Outcomes

3.3.1. Prior CAD versus no CAD

Compared with patients without a history of CAD, patients with prior CAD were more likely to die from any cause (4.30 vs. 3.39% per 100 patient-years, $P < 0.0001$) (Table 2). The rate of stroke or systemic embolism was similar (1.51 vs. 1.39% per 100 patient-years, $P = 0.3666$). In the prior CAD subgroup, the rate of MI was 3-fold higher than in patients without prior CAD (0.97 vs. 0.34% per 100 patient-years; $P < 0.0001$).

Patients with and without prior CAD had similar rates of ISTH major bleeding (2.72 vs. 2.54% per 100 patient-years, respectively; $P = 0.3638$). There were, however, numerically fewer intracranial hemorrhages in patients with prior CAD compared with patients without prior CAD.

3.3.2. Apixaban versus warfarin according to CAD status

The absolute reductions in stroke or systemic embolism with apixaban were 0.48 per 100 patient-years in patients without prior CAD and 0.08 in patients with prior CAD. Treatment with apixaban was associated with a reduced rate of stroke or systemic embolism, death from any cause, and MI in both patients with prior CAD and those without prior CAD (P for interaction = 0.12, 0.28, and 0.45, respectively). Coronary revascularization including PCI and CABG during follow-up was 2- to 3-fold more common in patients with prior CAD. However, the treatment effect of apixaban on revascularization