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Efficacy and Safety of Apixaban in Patients After Cardioversion for Atrial Fibrillation

Insights From the ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation)

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Objectives The aim of this study was to determine the risk of major clinical and thromboembolic events after cardioversion for atrial fibrillation in subjects treated with apixaban, an oral factor Xa inhibitor, compared with warfarin.

Background In patients with atrial fibrillation, thromboembolic events may occur after cardioversion. This risk is lowered with vitamin K antagonists and dabigatran.

Methods Using data from the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, we conducted a post-hoc analysis of patients undergoing cardioversion.

Results A total of 743 cardioversions were performed in 540 patients: 265 first cardioversions in patients assigned to apixaban and 275 in those assigned to warfarin. The mean time to the first cardioversion for patients assigned to warfarin and apixaban was 243 ± 231 days and 251 ± 248 days, respectively; 75% of the cardioversions occurred by 1 year. Baseline characteristics were similar between groups. In patients undergoing cardioversion, no stroke or systemic emboli occurred in the 30-day follow-up period. Myocardial infarction occurred in 1 patient (0.2%) receiving warfarin and 1 patient receiving apixaban (0.3%). Major bleeding occurred in 1 patient (0.2%) receiving warfarin and 1 patient receiving apixaban (0.3%). Death occurred in 2 patients (0.5%) receiving warfarin and 2 patients receiving apixaban (0.6%).

Conclusions Major cardiovascular events after cardioversion of atrial fibrillation are rare and comparable between warfarin and apixaban. (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation [ARISTOTLE]; NCT00412984) (J Am Coll Cardiol 2014;63:1082–7) © 2014 by the American College of Cardiology Foundation

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Patients with atrial fibrillation (AF) who undergo cardioversion are at risk for thromboembolic events (1–3), and vitamin K antagonists appear to lower this risk (4–7). Anticoagulation with an international normalized ratio of 2.0 to 3.0 is currently recommended for 3 weeks before elective cardioversion and is to be continued for a minimum of 4 weeks after cardioversion (8). Dabigatran, a direct thrombin inhibitor, appears to have efficacy comparable to that of warfarin in selected patients after cardioversion (9).

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The factor Xa inhibitor apixaban, when compared with warfarin, has been shown to reduce the risk of stroke and systemic emboli in patients with AF and risk factors for stroke in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial (10). The effectiveness of apixaban for prevention of stroke in patients undergoing cardioversion is unknown. The aim of the present analysis was to compare the baseline characteristics of patients undergoing cardioversion with those not undergoing cardioversion, describe the duration of anticoagulation before cardioversion, and examine the rate of major clinical events, including stroke, systemic embolism, myocardial infarction (MI), major bleeding, and death, in these patients.

Methods

Study population. The design and results of the ARISTOTLE trial have been previously reported (10,11). In brief, patients eligible for this trial had AF documented by electrocardiography at the time of enrollment or, if not in AF at the time of enrollment, had AF documented on 2 occasions at least 2 weeks apart within the 12 months before enrollment. Documentation of AF was by electrocardiogram or rhythm strip, Holter monitor, or intracardiac recording and lasted longer than 1 min. In addition, at least 1 of the following risk factors for stroke was required: age ≥75 years; previous stroke, transient ischemic attack, or systemic embolism; symptomatic heart failure within the previous 3 months or left ventricular ejection fraction ≤40%; and diabetes or hypertension requiring pharmacological therapy. Key exclusion criteria were AF due to a reversible cause, moderate or severe mitral stenosis, conditions other than AF that required anticoagulation (e.g., a prosthetic heart valve), stroke within the previous 7 days, a need for aspirin >165 mg/day or for both aspirin and clopidogrel, and renal insufficiency with a creatinine level >2.5 mg/dl or a creatinine clearance <25 ml/min.

Abbreviations and Acronyms

AF = atrial fibrillation

MI = myocardial infarction

Randomization. Patients were randomized to receive either warfarin or apixaban. Warfarin was adjusted to achieve a target international normalized ratio of 2.0 to 3.0. Apixaban was administered at dosages of 5 mg twice daily or 2.5 mg twice daily in patients who had 2 or more of the following criteria: age ≥80 years, body weight ≤60 kg, or serum creatinine level ≥1.5 mg/dl.

Clinical outcomes. The primary efficacy outcome of the study was stroke, defined as the abrupt onset of a nontraumatic, focal neurological deficit lasting at least 24 h, or systemic embolism, defined as symptoms consistent with acute loss of blood to a noncerebral artery confirmed by autopsy, angiography, vascular imaging, or some other objective testing. Secondary endpoints included MI and death. MI was defined as symptoms with biomarker elevation at least 2 times greater than normal (creatine kinase, creatine kinase-myocardial band, or troponin) or with new Q waves in ≥2 contiguous leads. Death was classified as cardiovascular (stroke, systemic embolism, MI, sudden death, heart failure, or indeterminate) or noncardiovascular. The primary safety outcome was major bleeding as defined by the International Society of Thrombosis and Haemostasis (12). All primary and secondary outcomes were adjudicated by a clinical events committee blinded to treatment assignment.

Cardioversion. For this post-hoc analysis, all patients who underwent cardioversion for AF in the ARISTOTLE trial were identified by a case report form completed at the center of enrollment. During the study, investigators were asked to continue randomized therapy before and after the procedure but had the option to suspend study medication for open-label warfarin during cardioversion. The number of patients undergoing cardioversion on assigned study medication was determined. The duration of anticoagulant therapy before and after cardioversion was assessed, and major clinical events, including stroke or systemic emboli,

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