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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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MI, major bleeding, and death, were assessed during the follow-up period. Because strokes or systemic emboli may occur several days to weeks after cardioversion, likely due to restoration of mechanical function of the atria, a 30-day follow-up period was used to capture these events and to preserve a temporal correlation to the procedure.

Statistical analysis. The baseline characteristics of those patients who underwent cardioversion for AF were compared with noncardioverted patients, and baseline characteristics in patients were compared according to randomized treatment. Continuous variables are presented as mean ± SD with between-group comparisons. Student *t* tests were used for normally distributed data and nonparametric (Wilcoxon) tests for other data. Categorical variables are presented as counts and percentages and compared by chi-square tests or Fisher exact tests where appropriate.

Clinical events are reported as the number of first, unique events in the 30 days after cardioversion. The occurrence of 1 event did not preclude the counting of another event except for the inherent competing risk of mortality, after which no event could be observed. The proportion of such events out of the total number of cardioversions is also reported. Hence, a patient with multiple cardioversions could experience multiple MI events and each would be counted, although only the first MI event was counted among multiple MI events after a single cardioversion. Events are unique, meaning that a single event occurring within 30 days of multiple cardioversions would only be counted once. Thus, the results are descriptive of the sample and qualitative comparisons are made but inference is limited.

The investigators had the option to temporarily suspend study medication before cardioversion (likely to place the patient on open-label warfarin). We conducted an intention-to-treat style comparison according to randomized treatment as our primary method of analysis. This was designed to preserve randomization (as much as possible in a post-randomization cohort) and capture potential influences of randomized treatment that might be active before or after the procedure. An on-treatment analysis, including only those patients receiving study medications (apixaban or warfarin) or warfarin at the time of cardioversion, was also performed.

Results

A total of 18,201 patients were enrolled in the ARISTOTLE trial, and 743 cardioversions were performed in 540 patients. At baseline, the principal investigator classified AF as paroxysmal in 2,786 patients and either persistent or permanent in 15,412 patients. A total of 414 patients underwent 1 cardioversion, 87 underwent 2 cardioversions, and 39 underwent ≥3 cardioversions. Seventy-five percent of the procedures occurred during the first year of follow-up. The mean time from study entry to first cardioversion for patients assigned to warfarin was 243 ± 231 days and for patients assigned to apixaban was 251 ± 248 days. The minimum duration of therapy before cardioversion was 4 days for warfarin and 1 day for apixaban. The median time in therapeutic range for patients undergoing cardioversion was 59% (quartile 1: 42%, quartile 3: 73%). At the time of cardioversion, 80% of patients assigned to warfarin and 84% assigned to apixaban were taking the assigned study drug. Open-label warfarin was used in 3.9% of patients assigned to warfarin and in 3.6% of patients assigned to apixaban. The anticoagulation status of the remaining patients was uncertain.

Baseline characteristics. Patients undergoing cardioversion were younger, more likely male, and more likely from North America or Europe than patients who did not undergo cardioversion. Mean weight was higher in patients undergoing cardioversion than those not undergoing cardioversion. Patients undergoing cardioversion were also less likely to have congestive heart failure or a prior stroke or transient ischemic attack, among other differences noted in Table 1. Other baseline demographic variables, including age, sex, geographic location, cardiac risk factors, type of AF at baseline (paroxysmal or persistent/permanent), and $CHADS_2$ (congestive heart failure, hypertension, age, diabetes, and stroke) score (apixaban: 1.8 ± 1.0; warfarin: 1.9 ± 1.1), were similar in patients undergoing cardioversion assigned to either apixaban or warfarin. Cardiac medications were similar between the groups (Table 1).

Transesophageal echocardiogram. Transesophageal echocardiographic data were available in 171 patients (203 cardioversions): 86 patients (97 cardioversions) assigned to apixaban and 85 patients (106 cardioversions) assigned to warfarin. None of the patients had evidence of a left atrial thrombus. Four patients had evidence of spontaneous echo contrast (1 patient assigned to apixaban and 3 patients assigned to warfarin).

Clinical outcomes. In the 30 days after cardioversion for AF, no stroke or systemic emboli occurred (Table 2). The corresponding 95% confidence intervals for the stroke or systemic embolism rates were 0% to 1.0% and 0% to 1.2% for apixaban and warfarin, respectively. One patient assigned to apixaban experienced an MI compared with 1 patient assigned to warfarin. Major bleeding occurred in 1 patient assigned to apixaban and 1 assigned to warfarin.

In the 30 days after cardioversion for AF, death occurred in 4 patients: 2 patients assigned to apixaban and 2 patients assigned to warfarin. One patient assigned to apixaban experienced an MI complicated by cardiogenic shock and AF, underwent cardioversion, and died on the same day. Another patient assigned to apixaban experienced a seizure and was intubated and hospitalized. Central nervous system imaging revealed a left frontal hemorrhage. The patient underwent cardioversion but remained in a coma and died 17 days later. One of 2 patients assigned to warfarin experienced syncope and head trauma. The patient was hospitalized and found to have central nervous system bleeding. The patient later developed AF, underwent cardioversion, and died 8 days thereafter. A second patient

Table 1 Baseline Characteristics of Patients in the ARISTOTLE Trial Who Underwent at Least 1 Cardioversion by Treatment Group Compared With Those Who Did Not Undergo Cardioversion

Characteristic	Apixaban (n = 265)	Warfarin (n = 275)	p Value	Patients Who Underwent Cardioversion (n = 540)	Patients Who Did Not Undergo Cardioversion (n = 17,648)	p Value
Age (yrs)	67.1 ± 9.2	67.3 ± 9.4	0.7749	67.2 ± 9.3	69.1 ± 9.7	<0.0001
Age ≥75 yrs	56 (21.1)	72 (26.2)	0.1678	128 (23.7)	5,546 (31.4)	0.0001
Female	72 (27.2)	74 (26.9)	0.9456	146 (27.0)	6,269 (35.5)	<0.0001
Region			0.9539			<0.0001
North America	125 (47.2)	134 (48.7)		249 (48.0)	4,213 (23.9)	
Latin America	9 (3.4)	11 (4.0)		20 (3.7)	3,446 (19.5)	
Europe	122 (46.0)	121 (44.0)		243 (45)	7,098 (40.2)	
Asia Pacific	9 (3.4)	9 (3.3)		18 (3.3)	2,891 (16.4)	
Systolic blood pressure (mm Hg)	131.2 ± 17.1	129.8 ± 18.0	0.3622	130.5 ± 17.6	131.4 ± 16.3	0.2272
Diastolic blood pressure (mm Hg)	79.6 ± 10.5	78.3 ± 10.9	0.2340	78.9 ± 10.7	79.2 ± 10.5	0.5597
Weight (kg)	92.3 ± 20.3	93.4 ± 20.4	0.5226	92.8 ± 20.4	83.8 ± 20.7	<0.0001
Prior myocardial infarction	33 (12.5)	50 (18.2)	0.0624	83 (15.4)	2,499 (14.2)	0.4214
Congestive heart failure	60 (22.6)	64 (23.3)	0.8616	124 (23)	5,408 (30.6)	0.0001
Prior stroke, transient ischemic attack, or systemic embolism	33 (12.5)	43 (15.6)	0.2876	76 (14.1)	3,459 (19.6)	0.0014
Diabetes	69 (26.0)	75 (27.3)	0.7456	144 (26.7)	4,397 (24.9)	0.3542
Hypertension	232 (87.5)	244 (88.7)	0.6715	476 (88.1)	15,429 (87.4)	0.6180
Prior clinically relevant or spontaneous bleeding	49 (18.5)	54 (19.6)	0.7348	103 (19.1)	2,933 (16.6)	0.1327
History of fall within previous year	22 (8.7)	10 (3.8)	0.0212	32(6.2)	720 (4.5)	0.0665
Type of atrial fibrillation			0.3979			<0.0001
Paroxysmal	75 (28.3)	87 (31.6)		162 (30.0)	2,622 (14.9)	
Persistent or permanent	190 (71.7)	188 (68.4)		378 (70.0)	15,023 (85.1)	
Vitamin K antagonist naïve	108 (40.8)	121 (44.0)	0.4456	229 (42.4)	7,566 (42.9)	0.8300
$CHADS_2$ score	1.8 ± 1.0	1.9 ± 1.1	0.1714	1.9 ± 1.0	2.1 ± 1.1	<0.0001
$CHADS_2$ score			0.3137			<0.0001
1	125 (47.2)	119 (43.3)		244 (45.2)	5,938 (33.6)	
2	87 (32.8)	86 (31.3)		173 (32.0)	6,339 (35.9)	
≥3	53 (20.0)	70 (25.5)		123 (22.8)	5,371 (30.4)	
LVEF	52.9 ± 14.1	52.1 ± 14.3	0.4199	52.5 ± 14.2	54.2 ± 13.2	0.0157
LVEF class			0.1947			0.8034
Normal	62 (73.8)	53 (62.4)		115 (68.0)	3,081 (68.2)	
Mild	11 (13.1)	14 (16.5)		25 (14.8)	758 (16.8)	
Moderate	5 (6.0)	13 (15.3)		18 (10.7)	438 (9.7)	
Severe	6 (7.1)	5 (5.9)		11 (6.5)	239 (5.3)	
Medications at time of randomization						
ACE inhibitor or ARB	190 (71.7)	202 (73.5)	0.6473	392 (72.6)	12,433 (71.6)	0.6283
Amiodarone	63 (23.8)	56 (20.4)	0.3392	119 (22.0)	1,929 (11.1)	<0.0001
Beta-blocker	184 (69.4)	193 (70.2)	0.8499	377 (69.8)	11,098 (63.9)	0.0051
Aspirin	83 (31.3)	88 (32.0)	0.8653	171 (31.7)	5,456 (30.9)	0.7100
Clopidogrel	3 (1.1)	5 (1.8)	0.7249	8 (1.5)	330 (1.9)	0.5103
Digoxin	53 (20.0)	56 (20.4)	0.9162	109 (20.2)	5,713 (32.9)	<0.0001
Calcium blocker	85 (32.1)	75 (27.3)	0.2218	160 (29.6)	5,405 (31.1)	0.4541
Lipid-lowering agent	154 (58.1)	152 (55.3)	0.5055	306 (56.7)	7,889 (45.5)	<0.0001
Statins	137 (51.7)	132 (48.0)	0.3902	269 (49.8)	7,201 (41.5)	0.0001
Nonsteroidal anti-inflammatory drug	34 (12.8)	38 (13.8)	0.7356	72 (13.3)	1,447 (8.3)	<0.0001
Gastric antacid drug	64 (24.2)	67 (24.4)	0.9540	131 (24.3)	3,215 (18.5)	0.0008
Maximum number of cardioversions			0.0160			
1	214 (80.8)	200 (72.7)				
2	40 (15.1)	47 (17.1)				
≥3	11 (4.2)	28 (10.2)				

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; $CHADS_2$ = congestive heart failure, hypertension, age, diabetes, and stroke; LVEF = left ventricular ejection fraction.

Table 2 Clinical Outcomes After Any Cardioversion, Within 30 Days, in Patients Assigned to Either Warfarin or Apixaban

Outcomes	Warfarin (n = 412)	Apixaban (n = 331)	Total (n = 743)
Stroke or systemic embolism	0	0	0
Myocardial infarction	1 (0.2)	1 (0.3)	2 (0.2)
Major bleeding	1 (0.2)	1 (0.3)	2 (0.2)
Death	2 (0.5)	2 (0.6)	4 (0.5)

Values are n (%).

assigned to warfarin had elective cardioversion for dyspnea. After cardioversion, hypotension occurred with subsequent liver and renal failure. The patient died in the hospital 8 days later.

Because investigators had the opportunity to interrupt study medication and convert to open-label warfarin for a cardioversion procedure, a second analysis, an on-treatment evaluation including only patients on study medication during the cardioversion, was performed. A total of 451 patients were included in this analysis. The baseline characteristics and results of the on-treatment analysis are shown in Online Table 1. The event rates of this analysis confirm a low rate of clinical events that did not differ between the apixaban- and warfarin-treated patients (Online Table 2).

Discussion

The results of this analysis show that clinical events occurring after cardioversion of AF are comparable between warfarin and apixaban. Of note was that neither stroke nor systemic embolism was observed. Based on annualized event rates for the larger trial population of 1.27% and 1.6% for apixaban and warfarin, respectively, a stroke or systemic embolism rate after 30 days would be expected to be 0.35% for apixaban and 0.55% for warfarin, so the fact that neither occurred is reasonable.

The association of stroke with cardioversion of AF has been recognized for more than 50 years. Case-controlled studies, which suggested a reduction in stroke with warfarin after cardioversion, coupled with the assumption that it may take weeks for a newly-formed thrombus to become firmly adherent to the atrial wall and not dislodge with atrial contraction, resulted in the early recommendation that adequate anticoagulation be administered for 3 weeks before cardioversion (13). In addition, because atrial contractility often takes weeks for complete recovery after cardioversion (14) and observing the occurrence of stroke several days after cardioversion (15), anticoagulation was subsequently recommended for 4 weeks after cardioversion. This protocol has an established safety record (16).

It may take 2 or more months to achieve adequate anticoagulation for cardioversion with warfarin (17). Because effective anticoagulation is achieved more quickly with new oral anticoagulants than with warfarin, a hypothetical advantage is that the new anticoagulants may shorten the pre-treatment time needed for adequate anticoagulation before cardioversion. However, the minimum duration of therapy required to assure a low risk of an embolic event remains unknown. In the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial, which included 18,113 patients, 1,319 cardioversions were performed over a 24-month follow-up period. Although the duration of anticoagulation before cardioversion was not reported, it was recommended that patients assigned to dabigatran receive at least 3 weeks of therapy before cardioversion. In the ARISTOTLE trial, which included 18,201 patients, fewer patients underwent cardioversion and cardioversion usually occurred after months of therapy. In both studies, approximately 25% of patients underwent transesophageal echocardiography. Although the combined findings of these 2 analyses indicate a low risk of stroke or systemic emboli after cardioversion, they do not define the optimal duration of pre-cardioversion anticoagulation therapy with new anticoagulants. Until additional data are reported, elective cardioversion of AF could be performed with a low risk of stroke or systemic emboli in patients treated on a long-term basis with new oral anticoagulants. Although this analysis suggests that a strategy of treatment with apixaban for at least several weeks before and after cardioversion appears to be effective, these remaining uncertainties underscore the need for more data on the safest approaches toward cardioversion in patients receiving apixaban.

Death related to cardioversion is believed to be rare. In the largest, most recently reported survey of cardioversion, the Euro Heart Survey reported only 4 deaths in 1,801 patients around the time of cardioversion (18). In the RE-LY trial, 7 of 1,270 patients (1,983 cardioversions) died in the first 30 days of follow-up (9). A Danish study reported 6 deaths in 385 procedures within 10 days of cardioversion (19). The occurrence of 4 deaths in our study during the first month after cardioversion, all in patients with serious comorbid conditions, is consistent with these studies. Death occurred in seriously ill patients with comorbid conditions. Death was equally likely in the apixaban and warfarin groups, lessening the chance that death was related to either therapy.

Study limitations. This analysis was a post-hoc, non-randomized comparison between apixaban and warfarin, and important differences may have existed between the groups that were not detected by our data. The number of patients undergoing cardioversion was small, and therefore statistical power to evaluate rare endpoints is excessively low. The results are descriptive of the sample. Although qualitative comparisons are made, these must be interpreted with caution because chance is likely to explain discrepancies. It is uncertain why cardioversion was performed more frequently in patients assigned to warfarin than apixaban, and this could have been due to chance. The international normalized ratio at the time of cardioversion was not known. Post-cardioversion electrocardiograms were not provided, so the success of cardioversion was not obtained and data were

not collected on the type of cardioversion (electric or pharmacological) performed. Incomplete transesophageal echocardiographic information represents another limitation. Only 80% of patients assigned to warfarin and 84% of patients assigned to apixaban were taking the assigned study drug on the date of cardioversion. Finally, the sample was derived from a case report form indicating that cardioversion had been performed. This was initiated by the local investigator. Electrocardiograms before cardioversion were not reviewed centrally. Although it is possible that some cardioversions were performed for cardiac rhythms other than AF, it is likely that these numbers were small and unlikely to have any bearing on the results.

Conclusions

Despite these limitations, this analysis showed that stroke or systemic embolism is uncommon in the first 30 days after cardioversion of AF and rates are comparable between apixaban and warfarin. Additional data will be helpful to firmly establish the efficacy and safety of apixaban in patients undergoing cardioversion.

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Key Words: atrial fibrillation ■ cardioversion ■ factor Xa inhibitor ■ thromboembolic events ■ vitamin K antagonist.

APPENDIX

For supplemental tables, please see the online version of this article.