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Outcomes After Cardioversion and Atrial Fibrillation Ablation in Patients Treated With Rivaroxaban and Warfarin in the ROCKET AF Trial

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Objectives This study sought to investigate the outcomes following cardioversion or catheter ablation in patients with atrial fibrillation (AF) treated with warfarin or rivaroxaban.

Background There are limited data on outcomes following cardioversion or catheter ablation in AF patients treated with factor Xa inhibitors.

Methods We compared the incidence of electrical cardioversion (ECV), pharmacologic cardioversion (PCV), or AF ablation and subsequent outcomes in patients in a post hoc analysis of the ROCKET AF (Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation) trial.

Results Over a median follow-up of 2.1 years, 143 patients underwent ECV, 142 underwent PCV, and 79 underwent catheter ablation. The overall incidence of ECV, PCV, or AF ablation was 1.45 per 100 patient-years (n = 321; 1.44 [n = 161] in the warfarin arm, 1.46 [n = 160] in the rivaroxaban arm). The crude rates of stroke and death increased in the first 30 days after cardioversion or ablation. After adjustment for baseline differences, the long-term incidence of stroke or systemic embolism (hazard ratio [HR]: 1.38; 95% confidence interval [CI]: 0.61 to 3.11), cardiovascular death (HR: 1.57; 95% CI: 0.69 to 3.55), and death from all causes (HR: 1.75; 95% CI: 0.90 to 3.42) were not different before and after cardioversion or AF ablation. Hospitalization increased after cardioversion or AF ablation (HR: 2.01; 95% CI: 1.51 to 2.68), but there was no evidence of a differential effect by randomized treatment (p value for interaction = 0.58). The incidence of stroke or systemic embolism (1.88% vs. 1.86%) and death (1.88% vs. 3.73%) were similar in the rivaroxaban-treated and warfarin-treated groups.

Conclusions Despite an increase in hospitalization, there were no differences in long-term stroke rates or survival following cardioversion or AF ablation. Outcomes were similar in patients treated with rivaroxaban or warfarin. (An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation [ROCKET AF]; NCT00403767) (J Am Coll Cardiol 2013;61:1998–2006) © 2013 by the American College of Cardiology Foundation

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Patients with atrial fibrillation (AF) often require cardioversion or ablation for symptom control (1). Periprocedural management of oral anticoagulation and stroke prevention is challenging yet important given the increased risk of thrombotic events following restoration of sinus rhythm (2). While clinical trials and guidelines address the management of vitamin K antagonists before and after these procedures, there are limited data regarding the use of novel oral anticoagulants, including factor Xa inhibitors (3). The ROCKET AF (Rivaroxaban Once-daily, oral, direct Factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) study was an international, randomized, double-blind, double-dummy, event-driven noninferiority trial comparing fixed-dose rivaroxaban (20 mg daily; 15 mg daily in patients with creatinine clearance of 30 to 49 ml/min) with dose-adjusted warfarin (target international normalized ratio [INR]: 2.0 to 3.0) for the prevention of stroke or non-central nervous system (CNS) embolism in patients with non-valvular AF at moderate or high risk of stroke (4). In 14,264 patients over a median follow-up of 707 days, once-daily rivaroxaban therapy was shown to be noninferior to dose-adjusted warfarin, with less intracranial and fatal bleeding. The goal of this post-hoc analysis was to describe the incidence, predictors, and outcomes associated with cardioversion and catheter ablation in patients treated with warfarin and rivaroxaban in the ROCKET AF trial.

Abbreviations and Acronyms

AF = atrial fibrillation
CI = confidence interval
CNS = central nervous system
ECV = electrical cardioversion
HR = hazard ratio
PCV = pharmacologic cardioversion
TIA = transient ischemic attack

Methods

The rationale and design of the ROCKET AF study have been published previously (NCT00403767) (5). Briefly, the ROCKET AF study was a multicenter, international, double-blind, double-dummy, randomized trial comparing fixed-dose rivaroxaban with adjusted-dose warfarin for prevention of all strokes (ischemic or hemorrhagic) or systemic embolism. The study was funded by Johnson & Johnson Pharmaceutical Research and Development (Raritan, New Jersey) and Bayer HealthCare AG (Leverkusen, Germany). The Duke Clinical Research Institute (Durham, North Carolina) coordinated the trial and performed the statistical analyses for the manuscript independent of the sponsors. An international executive committee designed the study and took responsibility for the accuracy and completeness of the analyses. All appropriate national regulatory authorities and ethics committees at participating centers approved the study.

Definitions, endpoints, and baseline variables. Patients were evaluated at a minimum of every 4 weeks throughout the trial for study drug management, ascertainment of adverse events, and surveillance for the primary endpoints and other clinical events. Procedures to treat AF were captured in case report form. Sites were instructed to record all AF ablations (surgical or catheter-based), electrical cardioversions (ECV), and pharmacologic cardioversions (PCV), including the dates of the procedures. PCV included both intravenous and oral administration of antiarrhythmic medications for the purpose of cardioversion. The use of transesophageal echocardiography was not captured in the case report form.

The interventions of interest in this analysis were ECV, PCV, and AF ablation as well as the composite of all cardioversions (ECV or PCV), and the composite of all cardioversions and AF ablations (ECV, PCV, or AF ablation) in those patients who were randomized and took one or more doses of the study drug. The primary efficacy endpoint in ROCKET AF was the composite of all strokes (both ischemic and hemorrhagic) and systemic embolism. A full description of the endpoints in ROCKET AF has been published previously (5). Secondary efficacy endpoints included cardiovascular (CV) death, all-cause death, the composite of stroke, systemic embolism, or CV death, and the composite of stroke, systemic embolism, or all-cause death. We also analyzed all hospitalizations. The safety endpoint was major or non-major clinically relevant bleeding. All suspected primary endpoint events and causes of death were adjudicated by an independent clinical endpoint committee. Rates of cardioversion or AF ablation among all ROCKET patients in the safety on-treatment population are presented as events per 100 patient-years of follow-up and total number of events. Rates of endpoints among patients with cardioversion or AF ablation are presented as

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Table 1 Baseline Characteristics According to Cardioversion (Electrical and Pharmacologic) or Catheter Ablation and Randomized Treatment

Characteristic	ECV, PCV, or Ablation		No ECV, PCV, or Ablation	
	Rivaroxaban (n = 160)	Warfarin (n = 161)	Rivaroxaban (n = 6,901)	Warfarin (n = 6,921)
Age, yrs	68.5 (61.5, 75)	71 (62, 76)	73 (65, 78)	73 (65, 78)
Male	66 (41.3)	59 (36.6)	2,725 (39.5)	2,740 (39.6)
Race				
White	146 (91.3)	157 (97.5)	5,710 (82.7)	5,752 (83.1)
Black	3 (1.9)	1 (0.6)	91 (1.3)	84 (1.2)
Asian	4 (2.5)	2 (1.2)	890 (12.9)	885 (12.8)
Other	7 (4.4)	1 (0.6)	210 (3.0)	200 (2.9)
Hispanic or Latino	12 (7.5)	12 (7.5)	1,149 (16.6)	1,155 (16.7)
Region				
Western Europe	34 (21.3)	32 (19.9)	1,006 (14.6)	1,017 (14.7)
Asia/Pacific Islands	4 (2.5)	4 (2.5)	1,048 (15.2)	1,048 (15.1)
Eastern Europe	65 (40.6)	74 (46.0)	2,631 (38.1)	2,630 (38.0)
Latin America	4 (2.5)	6 (3.7)	935 (13.5)	932 (13.5)
North America	53 (33.1)	45 (28.0)	1,281 (18.6)	1,294 (18.7)
$CHADS_2$ score	3 (3, 4)	3 (3, 4)	3 (3, 4)	3 (3, 4)
BMI (kg/m^2)	29.4 (26.6, 32.9)	28.4 (26.1, 32.8)	28.3 (25.1, 32.1)	28.1 (25.1, 31.8)
Heart rate (beats/min)	70.5 (62, 86)	72 (64, 82.5)	76 (68, 85)	76 (67, 86)
Systolic BP (mm Hg)	130 (120, 140)	130 (120, 140)	130 (120, 140)	130 (120, 140)
Diastolic BP (mm Hg)	80 (72, 83)	80 (70.5, 83)	80 (70, 85)	80 (70, 85)
Type of AF				
Persistent	79 (49.4)	75 (46.6)	5,660 (82.0)	5,648 (81.6)
Paroxysmal	76 (47.5)	81 (50.3)	1,152 (16.7)	1,178 (17.0)
New	5 (3.1)	5 (3.1)	89 (1.3)	95 (1.4)
LBBB	13 (8.2)	13 (8.2)	462 (6.7)	477 (6.9)
History of stroke or TIA	82 (51.3)	87 (54.0)	3,640 (52.7)	3,605 (52.1)
History of hypertension	148 (92.5)	146 (90.7)	6,224 (90.2)	6,283 (90.8)
History of CHF	91 (56.9)	98 (60.9)	4,337 (62.9)	4,311 (62.3)
History of diabetes	64 (40.0)	61 (37.9)	2,778 (40.3)	2,732 (39.5)
History of COPD	16 (10.0)	15 (9.3)	728 (10.6)	718 (10.4)
History of GI bleeding	9 (5.6)	8 (5.0)	216 (3.1)	263 (3.8)
History of liver disease	11 (6.9)	8 (5.0)	358 (5.2)	363 (5.2)
Vascular disease indicator for CHA_2DS_2VASC	40 (25.0)	45 (28.0)	1,532 (22.2)	1,669 (24.1)
History of sleep apnea	14 (8.8)	12 (7.5)	307 (4.4)	312 (4.5)
History of cigarette smoking	68 (42.5)	60 (37.3)	2,371 (34.4)	2,250 (32.5)
Alcohol consumption in last 12 months				
None	100 (62.5)	96 (59.6)	4,448 (64.5)	4,494 (64.9)
Light	54 (33.8)	60 (37.3)	2,098 (30.4)	2,080 (30.1)
Moderate	6 (3.8)	4 (2.5)	300 (4.3)	299 (4.3)
Heavy	0 (0)	1 (0.6)	55 (0.8)	47 (0.7)
Aspirin	47 (29.4)	41 (25.5)	1,983 (28.7)	2,027 (29.3)
Thienopyridine	7 (4.4)	4 (2.5)	104 (1.5)	123 (1.8)
VKA	102 (63.8)	115 (71.4)	4,299 (62.3)	4,322 (62.4)
ACE inhibitor/ARB	127 (79.4)	120 (74.5)	5,160 (74.8)	5,121 (74.0)
Beta blocker	123 (76.9)	120 (74.5)	4,438 (64.3)	4,503 (65.1)
Amiodarone	35 (21.9)	27 (16.8)	538 (7.8)	542 (7.8)
Digoxin	33 (20.6)	36 (22.4)	2,689 (39.0)	2,702 (39.0)
Sotalol	19 (11.9)	18 (11.2)	127 (1.8)	123 (1.8)
Lipid lowering	83 (51.9)	93 (57.8)	2,936 (42.5)	2,951 (42.6)
CCB	55 (34.4)	48 (29.8)	1,946 (28.2)	1,884 (27.2)
Other antiarrhythmic drugs	12 (7.5)	15 (9.3)	156 (2.3)	126 (1.8)
Anemia (Hb <13 in men; Hb <12 in women)	24 (15.2)	16 (10.5)	944 (14.0)	980 (14.4)
Platelets ($\times 10^9$/l)	219 (182, 262)	209 (178, 254)	221 (184, 265)	222 (184, 265)

Continued on the next page

Table 1 Continued

Characteristic	ECV, PCV, or Ablation		No ECV, PCV, or Ablation	
	Rivaroxaban (n = 160)	Warfarin (n = 161)	Rivaroxaban (n = 6,901)	Warfarin (n = 6,921)
CrCl (Cockcroft-Gault), (ml/min/1.73 m^2)	75 (56, 100)	71 (56, 99)	67 (52, 87)	67 (52, 86)
Albumin (g/dl)	4.0 (3.8, 4.2)	4.0 (3.8, 4.2)	4.0 (3.8, 4.2)	4.0 (3.8, 4.2)
SGOT/AST (U/l)	22 (19, 27)	22 (19, 28)	23 (19, 28)	23 (19, 28)
SGPT/ALT (U/l)	21 (17, 30)	24 (17, 34)	21 (16, 28)	21 (16, 28)
Total bilirubin (mg/dl)	0.5 (0.4, 0.7)	0.5 (0.4, 0.8)	0.6 (0.4, 0.8)	0.6 (0.4, 0.8)
Serum glucose (mg/dl)	106 (96.5, 133)	106 (97, 128)	107 (95, 135)	108 (95, 135)

Values are median (25th, 75th percentile) or n (%).

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ALT = alanine aminotransferase; ARB = angiotensin receptor blocker; AST = aspartate aminotransferase; BMI = body mass index; BP = blood pressure; CCB = calcium channel blocker; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CrCl = creatinine clearance; ECV = electrical cardioversion; GI = gastrointestinal; Hb = hemoglobin; LBBB = left bundle branch block; PCV = pharmacologic cardioversion; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvate transaminase; TIA = transient ischemic attack; VKA = vitamin K antagonist.

the number of events during the time period divided by the number of patients at risk.

Statistical analysis. Baseline characteristics were summarized numerically for categorical variables and as median values with 25th and 75th percentiles for continuous variables, according to the occurrence of ECV, PCV, or AF ablation and according to randomized treatment assignment. Event rates per 100 patient-years of follow-up and the total number of events while on treatment during the trial were presented for the following endpoints: 1) ECV; 2) PCV; 3) AF ablation; and 4) any ECV, PCV, or AF ablation. Cumulative incidence plots for ECV/PCV/AF ablation with all-cause death as competing risk were presented. Event rates and cumulative incidence plots were repeated for the cardioversion and ablation endpoints stratified by region or randomized treatment. The relationships between region or treatment and intervention were characterized using hazard ratios (HR) and corresponding 95% confidence intervals (CI) from a Cox proportional hazards model. Region and treatment were the only covariates included in the model, where the reference groups were Western Europe and warfarin, respectively.

Cox proportional hazards models were used to identify factors associated with ECV, PCV, or AF ablation and ECV or PCV during follow-up. Twenty-four covariates recorded at randomization were considered for inclusion in the model for prediction of ECV, PCV, and AF ablation: age, sex, race, ethnicity, region, heart rate, body mass index, systolic blood pressure, diastolic blood pressure, type of AF (persistent, paroxysmal, recent onset), prior stroke or transient ischemic attack (TIA), heart failure, hypertension, diabetes mellitus, coronary artery disease (history of myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting), creatinine clearance, peripheral arterial disease, chronic obstructive pulmonary disease, carotid atherosclerosis, prior gastrointestinal bleeding, liver disease, alcohol use, obstructive sleep apnea, and left bundle branch block. Heart failure was defined as a clinical diagnosis of heart failure or a left ventricular ejection fraction ≤35%. The $CHADS_2$ risk scores were derived from baseline covariates (6). Consistent with the CHA_2DS_2VASC risk stratification scheme, coronary, carotid, and peripheral arterial disease were combined as a single variable termed vascular disease (7). Creatinine clearance was calculated using the Cockcroft-Gault formula (8,9). We tested the proportional hazards assumption and the global tests of proportional hazards were not significant. In the multivariable model, covariates were selected stepwise (alpha = 0.05 to enter and retain). Associations are reported as HRs with 95% CIs.

To investigate the associations among ECV/PCV/AF ablation and the long-term outcomes, Cox regression models were fitted with ECV/PCV/AF ablation as a time-dependent variable. All models were adjusted for sex, age, diastolic blood pressure, and chronic obstructive pulmonary disease. Additionally, efficacy models were adjusted for prior stroke or TIA, estimated glomerular filtration rate, vascular disease, type of AF, heart rate, congestive heart failure, body mass index, region, alcohol use, diabetes, and creatinine; the bleeding model additionally was adjusted for gastrointestinal bleeding, aspirin, and anemia. Models assume there are no time-dependent covariates that could be associated with both ECV/PCV/AF ablation and outcomes. Only the first intervention per patient was included. HR estimates with 95% CIs were presented. For the endpoints of hospitalization and major or non-major clinically relevant bleeding, differences in association by randomized treatment were investigated by including terms for treatment (rivaroxaban or warfarin), the intervention of interest (ECV/PCV/AF ablation) as a time-dependent variable, and the interaction in the model. Separate HR estimates and 95% CIs were presented for each treatment only if the interaction term was significant at the 0.05 level. For other efficacy endpoints, the interaction of treatment and ECV/PCV/AF was not investigated because of the low event counts. Events in the 30 days following cardioversion or ablation were summarized but were not modeled due to the small number of events. All analyses were performed using SAS version 9.2 software (SAS Institute, Inc., Cary, North Carolina).

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Results

Patient characteristics. Among the 14,264 patients randomized in ROCKET AF, follow-up was complete in 99.9% of patients (32 patients were lost to follow-up). The median patient age at randomization was 73 years, the median $CHADS_2$ score was 3.0, 52% had prior stroke or TIA, and 81% had persistent AF. As shown in Table 1, patients who underwent cardioversion or AF ablation were younger (median age: 69), more often white, and more commonly had paroxysmal AF, a higher prevalence of sleep apnea, and were more frequently taking amiodarone or another antiarrhythmic agent. Patient characteristics were similar among patients who did and did not undergo cardioversion or ablation in the 2 treatment arms (rivaroxaban vs. warfarin).

Incidence and predictors of cardioversion and catheter ablation. Over a median follow-up of 2.1 years (1.6 [25th percentile], 2.4 [75th percentile]) years, 321 patients had a total of 460 on randomized treatment cardioversion or AF ablation procedures. A total of 143 patients underwent 181 ECV procedures (119 had only 1, 14 had 2, 7 had 3, 2 had 4, and 1 patient had 5 procedures), 142 patients underwent 194 PCV procedures (113 with 1, 20 with 2, 3 with 3, 2 with 4, 3 with 5, and 1 with 9), and 79 patients underwent 85 AF ablation procedures. Among the patients undergoing AF ablation, only 6 (7.6%) underwent repeat ablation. During the trial, the overall incidence of ECV, PCV, or AF ablation was 1.45 per 100 patient-years (n = 321). As shown in Figure 1 and Table 2, the rate of ECV, PCV, or AF ablation was 1.44 per 100 patient-years (n = 161) in the warfarin arm and 1.46 per 100 patient-years in the rivaroxaban arm (n = 160). On the day of ECV, PCV, or AF ablation, 256 of 321 patients (80%) were taking randomized treatment, including 39 of 79 (49%) AF ablation patients, 120 of 143 (84%) ECV patients, and 129 of 142 (91%) PCV patients. Only 24 patients (rivaroxaban n = 12, warfarin n = 12) received low-molecular-weight heparin within 24 h of ECV, PCV, or ablation. The composite rates of ECV, PCV, or AF ablation were greatest in North America and Western Europe (Fig. 2). The rates of ECV and AF

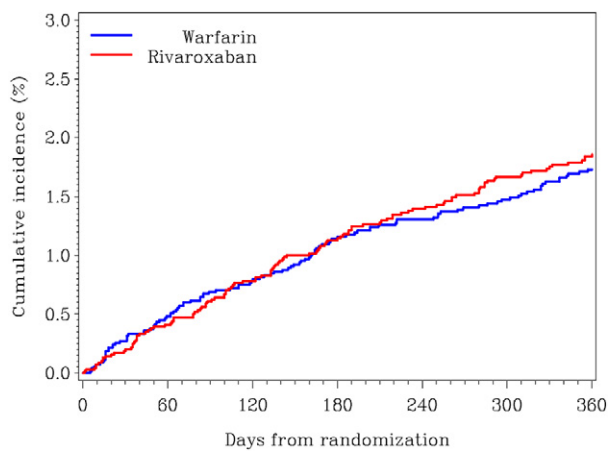

Figure 1 Cumulative Incidence of Electrical Cardioversion, Pharmacologic Cardioversion, or Catheter Ablation According to Treatment Assignment

Electrical cardioversion, pharmacologic cardioversion, or catheter ablation by randomized treatment (warfarin or rivaroxaban).

Table 2 Incidence of ECV, PCV, and AF Ablation

Endpoint	Events per 100 Patient Yrs (Total Events)	HR (95% CI)	p Value
ECV			
Overall	0.64 (143)		
Randomized treatment			
Warfarin	0.60 (67)	1.00	—
Rivaroxaban	0.69 (76)	1.15 (0.83–1.60)	0.398
Region			<0.001
Western Europe	1.23 (39)	1.00	—
Asia/Pacific islands	0.09 (3)	0.07 (0.02–0.24)	<0.001
Eastern Europe	0.41 (35)	0.34 (0.21–0.53)	<0.001
Latin America	0.14 (4)	0.11 (0.04–0.32)	<0.001
North America	1.42 (62)	1.20 (0.81–1.80)	0.365
PCV			
Overall	0.64 (142)		
Randomized treatment			
Warfarin	0.63 (71)	1.00	—
Rivaroxaban	0.64 (71)	1.01 (0.73–1.41)	0.936
Region			<0.001
Western Europe	0.72 (23)	1.00	—
Asia/Pacific islands	0.09 (3)	0.13 (0.04–0.43)	<0.001
Eastern Europe	1.05 (90)	1.50 (0.95–2.37)	0.083
Latin America	0.07 (2)	0.10 (0.02–0.40)	0.001
North America	0.54 (24)	0.81 (0.45–1.43)	0.459
Ablation			
Overall	0.35 (79)		
Randomized treatment			
Warfarin	0.38 (43)	1.00	—
Rivaroxaban	0.32 (36)	0.85 (0.55–1.33)	0.476
Region			<0.001
Western Europe	0.50 (16)	1.00	—
Asia/Pacific islands	0.06 (2)	0.12 (0.03–0.53)	0.005
Eastern Europe	0.24 (21)	0.49 (0.25–0.94)	0.031
Latin America	0.14 (4)	0.28 (0.09–0.85)	0.024
North America	0.81 (36)	1.68 (0.93–3.03)	0.084
Cardioversion or ablation			
Overall	1.45 (321)		
Randomized treatment			
Warfarin	1.44 (161)	1.00	—
Rivaroxaban	1.46 (160)	1.01 (0.81–1.26)	0.934
Region			<0.001
Western Europe	2.10 (66)	1.00	—
Asia/Pacific islands	0.24 (8)	0.12 (0.06–0.24)	<0.001
Eastern Europe	1.64 (139)	0.80 (0.59–1.07)	0.126
Latin America	0.35 (10)	0.17 (0.09–0.32)	<0.001
North America	2.25 (98)	1.13 (0.83–1.55)	0.439

AF = atrial fibrillation; CI = confidence interval; ECV = electrical cardioversion; HR = hazard ratio; PCV = pharmacologic cardioversion; yrs = years.

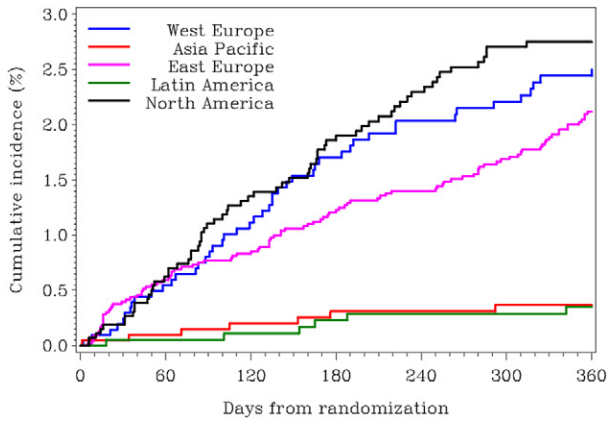

Figure 2 Cumulative Incidence of Electrical Cardioversion, Pharmacologic Cardioversion, or Catheter Ablation by Region

Electrical cardioversion, pharmacologic cardioversion, or catheter ablation by region.

ablations were highest in North America, and PCV was most frequent in Eastern Europe (Table 2).

In the multivariable model analysis, heart rate ≥80 beats/min, diastolic blood pressure <75 mm Hg, paroxysmal AF, and new-onset AF were associated with a higher probability of ECV, PCV, or AF ablation (Table 3).

Table 3 Multivariable Model of Factors Associated With the Utilization of ECV, PCV, or AF Ablation

Factor	HR	95% CI	p Value
Age, HR for 10-year increase	0.77	0.69–0.87	<0.001
Region			
Asia/Pacific Islands	0.13	0.06–0.27	<0.001
Eastern Europe	0.68	0.50–0.92	
Latin America	0.21	0.11–0.41	
North America	1.11	0.80–1.53	
Western Europe	1.00	—	
Systolic BP, HR for 10-mm Hg increase	0.86	0.78–0.94	<0.001
Heart rate, HR for 10-beats/min increase			
Linear spline ≤80	0.82	0.72–0.93	0.001
Linear spline ≥80	1.19	1.07–1.32	
Diastolic BP, HR for 10 mm Hg increase			
Linear spline ≤75	1.70	1.24–2.35	0.004
Linear spline ≥75	0.84	0.67–1.06	
Type of AF			
Persistent	1.00	—	<0.001
Paroxysmal	2.72	2.14–3.47	
New	3.19	1.66–6.11	
Sotalol	3.63	2.49–5.27	<0.001
Amiodarone	2.65	1.96–3.60	<0.001
Other antiarrhythmic drugs	2.85	1.87–4.34	<0.001
Digoxin	0.62	0.47–0.82	<0.001
Calcium channel blocker	1.38	1.08–1.76	0.009
Thienopyridine	2.02	1.10–3.71	0.024
Beta blocker	1.31	1.00–1.71	0.046

AF = atrial fibrillation; BP = blood pressure; CI = confidence interval; ECV = electrical cardioversion; HR = hazard ratio; PCV = pharmacologic cardioversion.

Table 4 Multivariable Model of Factors Associated With ECV or PCV

Factor	HR	95% CI	p Value
Age, HR for 10-year increase	0.79	0.69–0.90	<0.001
Region			
Asia/Pacific Islands	0.12	0.05–0.27	<0.001
Eastern Europe	0.75	0.54–1.05	
Latin America	0.16	0.07–0.37	
North America	1.09	0.76–1.55	
Western Europe	1.00	—	
Heart rate, HR for 10-beats/min increase			
Linear spline ≤80	0.81	0.71–0.94	0.003
Linear spline ≥80	1.18	1.06–1.32	
Systolic BP, HR for 10-mm Hg increase	0.85	0.77–0.93	<0.001
Diastolic BP, HR for 10-mm Hg increase	1.15	0.98–1.34	0.088
Type of AF			
Persistent	1.00	—	<0.001
Paroxysmal	3.05	2.34–3.98	
New	3.15	1.52–6.52	
Sotalol	3.53	2.34–5.33	<0.001
Amiodarone	2.41	1.73–3.35	<0.001
Other antiarrhythmic drugs	2.98	1.93–4.61	<0.001
Digoxin	0.57	0.42–0.78	<0.001
Calcium channel blocker	1.43	1.10–1.86	0.007

AF = atrial fibrillation; BP = blood pressure; CI = confidence interval; HR = hazard ratio. ECV = electrical cardioversion; PCV = pharmacologic cardioversion.

Similarly, sotalol, amiodarone, other antiarrhythmic therapy, calcium channel blockade, beta-blockade, and thienopyridine use were all associated with a higher probability of ECV, PCV, or catheter ablation. Conversely, global region (outside North America or Western Europe), older age, increasing systolic blood pressure, heart rate <80 beats/min, and digoxin use were associated with lower rates of ECV, PCV, or AF ablation. As illustrated in Table 4, predictors of cardioversion alone (ECV or PCV) following multivariable adjustment were similar.

30-day outcomes following cardioversion or AF ablation. As shown in Table 5, there were no stroke or systemic embolism events before intervention in those patients who underwent cardioversion or ablation. The risk of stroke or death in the first 30 days after ECV, PCV, or AF was increased despite the low absolute numbers of events (n = 3 strokes or systemic emboli and n = 4 all-cause deaths). Overall, in the first 30 days after ECV, PCV, or AF ablation, the rate of stroke or systemic emboli was 0.93% and the mortality rate was 1.25%. The rate of major and non-major clinically relevant bleeding in the first 30 days after ECV, PCV, or AF ablation was 2.18% compared with 9.97% at baseline (Table 5).

Long-term outcomes following cardioversion or AF ablation. Longer-term outcomes (>30 days) after ECV, PCV, or AF ablation are also shown in Table 5. When examining the time to first event, the hazards for stroke or systemic embolism, cardiovascular death, all-cause death, the composite of stroke, systemic embolism or cardiovascular death, and the composite of stroke, systemic embolism, or all-cause death were not statistically different before and

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Table 5 Association Between ECV/PCV/AF Ablation and Outcomes

Event	Event Pre-Procedure	Event Post-procedure in Event-Free Patients at Time of Procedure		Event Post-procedure Regardless of Whether an Event Occurred Pre-Procedure		HR (95% CI)*	p Value
		0–30 days	>30 days	0–30 days	>30 days		
Stroke or systemic embolism	0 (0)	3 (0.93)	3 (0.93)	3 (0.93)	3 (0.93)	1.38 (0.61–3.11)	0.4423
CV death	0 (0)	4 (1.25)	2 (0.62)	4 (1.25)	2 (0.62)	1.57 (0.69–3.55)	0.2793
All-cause death	0 (0)	4 (1.25)	5 (1.56)	4 (1.25)	5 (1.56)	1.75 (0.90–3.42)	0.0990
Hospitalization†	121 (37.69)	12 (6.0)	38 (19.0)	22 (6.85)	76 (23.68)	2.01 (1.51–2.68)	<0.0001
Stroke, systemic embolism, or CV death	0 (0)	7 (2.18)	5 (1.56)	7 (2.18)	5 (1.56)	1.53 (0.86–2.72)	0.1507
Stroke, systemic embolism, or all-cause death	0 (0)	7 (2.18)	8 (2.49)	7 (2.18)	8 (2.49)	1.64 (0.98–2.75)	0.0605
Major or NMCR bleeding†	32 (9.97)	6 (2.08)	39 (13.49)	7 (2.18)	44 (13.71)	1.51 (1.12–2.05)	0.0072

Event rates are shown as number of events (%). As these are raw percentages, they cannot be compared directly. *Hazard ratios (HR) and confidence intervals (CI) come from Cox proportional hazards regression models that include all patients where cardioversion/ablation is included as a time-dependent covariate. All models are adjusted for sex, age, diastolic blood pressure, and chronic obstructive pulmonary disease. Additionally, efficacy models are adjusted for prior stroke or transient ischemic attack, estimated glomerular filtration rate, vascular disease, type of AF, heart rate, congestive heart failure, body mass index, region, alcohol use, diabetes, and creatinine; the bleeding model additionally adjusts for gastrointestinal bleeding, aspirin, and anemia. †Interaction between electrical cardioversion/pharmacologic cardioversion/atrial fibrillation ablation and treatment = 0.5792 for hospitalization and 0.4590 for major or non-major clinically relevant bleeding.

CV = cardiovascular; NMCR = non-major clinically relevant.

after ECV, PCV, or AF ablation when considering all available follow-up. In the 79 patients who underwent AF ablation, no strokes were observed on treatment; however, 1 patient (n = 1 of 79, 1.3%) suffered a stroke off-treatment (not taking randomized study medication).

Randomized treatment and outcomes following cardioversion or AF ablation. The hazards of hospitalization (HR: 2.01; 95% CI: 1.51 to 2.68, p < 0.0001) and major and non-major clinically relevant bleeding (HR: 1.51; 95% CI: 1.12 to 2.05, p = 0.0072) were greater following ECV, PCV, or AF ablation. Among the hospitalization events, 11% (n = 11) were elective, 22% were urgent (n = 22), and 66% (n = 65) were emergent. Causes for hospitalization included bleeding (11%; n = 11), acute coronary syndrome (1%; n = 1), non-CNS embolism (1%; n = 1), stroke (1%; n = 1), TIA (1%; n = 1), elective admission (11%; n = 11), and other adverse events (73%; n = 72). In order to assess modification of treatment effect according to cardioversion or ablation procedures, interaction tests were performed. Interaction terms for randomized treatment-by-cardioversion or ablation were not significant for either hospitalization (p = 0.5792) or major or non-major clinically relevant bleeding (p = 0.4590). As shown in Table 6, individual event counts were similar between the rivaroxaban- and warfarin-treated patients following ECV, PCV, or AF ablation. After ECV, PCV, or ablation, the rate of stroke or systemic embolism was 1.88% (n = 3) in the rivaroxaban arm and 1.86% (n = 3) in the warfarin arm. In terms of all-cause death, the rate was 1.88% (n = 3) in the rivaroxaban arm versus 3.73% (n = 6) in the warfarin arm. When we restricted this analysis to only those patients who were taking the study drug on the day of the procedure, the results were similar (Table 7).

Table 6 Outcomes After ECV, PCV, or Catheter Ablation According to Randomized Treatment

Endpoint Following ECV, PCV, or Ablation	Rivaroxaban (N = 160)	Warfarin (N = 161)	All (N = 321)
Stroke or systemic embolism	3 (1.88)	3 (1.86)	6 (1.87)
CV death	2 (1.25)	4 (2.48)	6 (1.87)
All-cause death	3 (1.88)	6 (3.73)	9 (2.80)
Hospitalization	50 (31.25)	48 (29.81)	98 (30.53)
Stroke or systemic embolism or CV death	5 (3.13)	7 (4.35)	12 (3.74)
Stroke or systemic embolism or death from any cause	6 (3.75)	9 (5.59)	15 (4.67)
Major or NMCR bleeding	30 (18.75)	21 (13.04)	51 (15.89)

Values are numbers of events following cardioversion or ablation; percentages of patients with cardioversion or ablation in the given treatment group are shown in parentheses.

CV = cardiovascular; ECV = electrical cardioversion; NMCR = non-major clinically relevant; PCV = pharmacologic cardioversion.

Discussion

Restoration of sinus rhythm in patients with symptomatic or hemodynamically significant AF can improve cardiovascular hemodynamics, functional status, and quality of life (10,11). However, all means of restoring sinus rhythm, including cardioversion and AF ablation carry a transient

Table 7 Outcomes after ECV, PCV, or Catheter Ablation Among Those Taking Study Drug on the Day of Procedure

Endpoint Following ECV, PCV, or Ablation	Rivaroxaban (N = 124)	Warfarin (N = 121)	All (N = 245)
Stroke or systemic embolism	2 (1.61)	3 (2.48)	5 (2.04)
CV death	0 (0)	2 (1.65)	2 (0.82)
All-cause death	1 (0.81)	4 (3.31)	5 (2.04)
Hospitalization	40 (32.26)	37 (30.58)	77 (31.43)
Stroke or systemic embolism or CV death	2 (1.61)	5 (4.13)	7 (2.86)
Stroke or systemic embolism or death from any cause	3 (2.42)	7 (5.79)	10 (4.08)
Major or NMCR bleeding	24 (19.35)	17 (14.05)	41 (16.73)

Values are numbers of events following cardioversion or ablation; percentages of patients taking study drug on the day of cardioversion or ablation in the given treatment group are shown in parentheses.

CV = cardiovascular; ECV = electrical cardioversion; NMCR = non-major clinically relevant; PCV = pharmacologic cardioversion.

increase in thrombotic risk (2,12). While there is a wealth of data for cardioversion and AF ablation in patients treated with warfarin, there are limited data and clinical experience regarding restoration of sinus rhythm in patients being treated with direct, oral factor Xa inhibitors such as rivaroxaban. In this study of moderate- to high-risk patients with non-valvular AF, there was no significant difference in long-term outcomes following cardioversion or AF ablation. Additionally, outcomes following ECV, PCV, or AF ablation were similar in those patients treated with rivaroxaban or warfarin.

It is important to recognize that patients who underwent cardioversion or catheter ablation in ROCKET AF were at moderate to high risk of stroke due to the inclusion criteria for the trial. Additionally, by protocol, patients with plans for elective cardioversion or restoration of sinus rhythm during screening were excluded from enrolling in ROCKET AF. Consequently, a significant majority (81%) of patients in the ROCKET AF trial had persistent AF. However, following study entry, patients who required cardioversion due to hemodynamic instability, progressive heart failure, or refractory symptoms despite optimal medical therapy could undergo cardioversion or AF ablation per study protocol. Despite a relatively selected, high-risk population, we found no evidence of increased rates of stroke or systemic embolism or mortality in long-term follow-up among those who underwent procedures for restoration of sinus rhythm. While there is evidence of transient increases in risk after ECV, PCV, and AF ablation, our findings provide reassurance that the risk of stroke is successfully mitigated in the long term with post-procedural oral anticoagulation.

In contrast to the above findings, we observed increased rates of hospitalization following cardioversion or AF ablation. Increased hospitalization has been observed in other studies of rhythm management, including the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial (13). In the AFFIRM trial, cardioversion was associated with a 6-fold increase in cardiac hospitalization (39.3% vs. 5.8%) compared with the 2-fold increase observed in the ROCKET AF study. Most of the hospitalizations following cardioversion or AF ablation were for non-cardiovascular causes, and most were emergent. The potential reasons for an increased rate of hospitalization are many and include the confounding associated with a post-randomization variable. For example, patients who become ill and require restoration of sinus rhythm may very well have an increased risk of hospitalization independent of the procedure. Future studies should investigate the causes for hospitalization after cardioversion or AF ablation, and how the risk of admission/readmission may be modified or avoided.

While professional society guidelines recommend restoration of sinus rhythm in patients with AF complicated by hemodynamic impairment or in patients with impaired quality of life despite adequate rate control (1,10), the use of cardioversion and AF ablation in clinical practice is variable (14). In this study of more than 14,000 patients across 45 countries, we found significant regional variation in the use of cardioversion and AF ablation. These regional differences likely reflect differences in standard local practice, as well as differing perspectives regarding the risks and benefits of restoring and maintaining sinus rhythm. Additionally, these differences may also reflect availability. In the United States, decreased availability of cardioversion during weekend admissions has been associated with increased length of stay and cost (15). Similar to the variation in the use of rhythm-control therapies, recent data from the international RE-LY AF (Randomized Evaluation of Long-term anticoagulant therapy) registry also demonstrate significant international variation in oral anticoagulation, stroke rates, and mortality in patients with AF (16). Future studies should investigate the reasons behind variation and whether treatment differences are linked to differential outcomes.

Several retrospective, observational studies have suggested that the risk of stroke after catheter ablation of AF is low (12) and that long-term anticoagulation, even in moderate to high-risk patients, may not be necessary (17). However, in contrast to these studies, we found that the long-term risk of stroke or systemic embolism following restoration of sinus rhythm was substantial (1.86 events per 100 patient-years) despite anticoagulant therapy.

While these data represent the first reported experience with cardioversion or AF ablation in patients treated with oral factor Xa inhibition, there are published data regarding cardioversion in patients treated with oral direct thrombin inhibition. An analysis of outcomes following cardioversion in the RE-LY trial demonstrated no difference in stroke or systemic embolism or major bleeding at 30 days in patients treated with dabigatran 150 mg twice daily versus dose-adjusted warfarin (3). Due to differences in trial design (including higher baseline risks of the patients and higher proportion with persistent AF in ROCKET AF) as well as differences in blinding, cardioversion and AF ablation were less frequent in ROCKET AF. However, consistent with the findings from RE-LY, we found no evidence of an increased risk of stroke or systemic embolism in patients treated with a novel oral anticoagulant in ROCKET AF (rivaroxaban) compared with warfarin. When comparing the rates of stroke or systemic embolism at 30 days, 0.3% of the dabigatran 150 mg-treated patients and 0.6% of the warfarin-treated patients in the RE-LY trial experienced a stroke after cardioversion compared with 0.9% in the moderate- to high-risk population in ROCKET AF.

Study limitations. First, this analysis was a post hoc analysis of prospectively collected clinical trial data. Furthermore, given the post-randomization nature of cardioversion or AF ablation, we cannot completely exclude the possibility that confounding influenced the comparisons. Second, given the trial design, cardioversion and AF ablation were relatively uncommon events. Therefore, our sample size and power to detect small differences in outcomes were limited. Finally, cardioversion procedures are often guided by trans-

esophageal echocardiography; however, data on the use and findings of transesophageal echocardiography were not collected. On the other hand, these data represent the first international experience of long term outcomes following restoration of sinus rhythm in patients treated with an anti-Xa inhibitor.

Clinical implications. First, treated patients receiving oral anticoagulation do not appear to be at excessive risk of stroke or systemic embolism in the long term following cardioversion or AF ablation. Therefore, clinicians should follow guideline recommendations and ensure adequate anticoagulation in moderate- to high-risk patients. Therapeutic anticoagulation is required before and after cardioversion, regardless of vitamin K antagonism or the use of factor Xa inhibition. While we found no evidence of differential outcomes according to treatment with rivaroxaban or warfarin, these questions will ultimately require testing in dedicated clinical trials of novel oral anticoagulation surrounding cardioversion and catheter ablation. Caution should be exercised when using raw event rates to draw clinical inferences about post-randomization management strategies.

Conclusions

There are limited data and clinical experience regarding restoration of sinus rhythm in patients being treated with direct, oral factor Xa inhibitors. In this study of moderate- to high-risk patients with non-valvular AF, there was significant regional variation in the use of procedures for the restoration and maintenance of sinus rhythm. In the overall trial population, despite an increase in hospitalization, there was no significant difference in long-term stroke rates or survival following cardioversion or AF ablation. Finally, outcomes following ECV, PCV, or AF ablation were similar in those patients treated with rivaroxaban or warfarin.

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Key Words: atrial fibrillation ■ cardioversion ■ catheter ablation ■ stroke ■ rivaroxaban ■ warfarin.