Journal of the American College of Cardiology Vol. 61, No. 6, 2013

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.09.057

Outcomes of Discontinuing Rivaroxaban Compared With Warfarin in Patients With Nonvalvular Atrial Fibrillation

Analysis From the ROCKET AF Trial (Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation)

Manesh R. Patel, MD,* Anne S. Hellkamp, MS,* Yuliya Lokhnygina, PhD,* Jonathan P. Piccini, MD,* Zhongxin Zhang, PhD,† Surya Mohanty, PhD,† Daniel E. Singer, MD,‡ Werner Hacke, MD, PhD,§ Günter Breithardt, MD,‖ Jonathan L. Halperin, MD,¶ Graeme J. Hankey, MD,# Richard C. Becker, MD,* Christopher C. Nessel, MD,† Scott D. Berkowitz, MD,** Robert M. Califf, MD,†† Keith A. A. Fox, MB, ChB,‡‡ Kenneth W. Mahaffey, MD*

Durham, North Carolina; Raritan, and Montville, New Jersey; Boston, Massachusetts; Heidelberg, and Münster, Germany; New York, New York; Perth, Australia; and Edinburgh, United Kingdom

Objectives The purpose of this study was to understand the possible risk of discontinuation in the context of clinical care.

Background Rivaroxaban is noninferior to warfarin for preventing stroke in atrial fibrillation patients. Concerns exist regarding possible increased risk of stroke and non–central nervous system (CNS) thromboembolic events early after discontinuation of rivaroxaban.

Methods We undertook a post-hoc analysis of data from 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, n = 14,624) for stroke or non-CNS embolism within 30 days after temporary interruptions of 3 days or more, early permanent study drug discontinuation, and end-of-study transition to open-label therapy.

Results Stroke and non-CNS embolism occurred at similar rates after temporary interruptions (rivaroxaban: n = 9, warfarin: n = 8, 6.20 vs. 5.05/100 patient-years, hazard ratio [HR]: 1.28, 95% confidence interval [CI]: 0.49 to 3.31, p = 0.62) and after early permanent discontinuation (rivaroxaban: n = 42, warfarin: n = 36, 25.60 vs. 23.28/100 patient-years, HR: 1.10, 95% CI: 0.71 to 1.72, p = 0.66). Patients transitioning to open-label therapy at the end of the study had more strokes with rivaroxaban (n = 22) versus warfarin (n = 6, 6.42 vs. 1.73/100 patient-years, HR: 3.72, 95% CI: 1.51 to 9.16, p = 0.0044) and took longer to reach a therapeutic international normalized ratio with rivaroxaban versus warfarin. All thrombotic events within 30 days of any study drug cessation (including stroke, non-CNS embolism, myocardial infarction, and vascular death) were similar between groups (HR: 1.02, 95% CI: 0.83 to 1.26, p = 0.85).

Conclusions In atrial fibrillation patients who temporarily or permanently discontinued anticoagulation, the risk of stroke or non-CNS embolism was similar with rivaroxaban or warfarin. An increased risk of stroke and non-CNS embolism was observed in rivaroxaban-treated patients compared with warfarin-treated patients after the end of the study, underscoring the importance of therapeutic anticoagulation coverage during such a transition. (J Am Coll Cardiol 2013;61:651–8) © 2013 by the American College of Cardiology Foundation

From the *Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina; †Johnson & Johnson Pharmaceutical Research & Development, Raritan, New Jersey; ‡Clinical Epidemiology Unit, General Medicine Division, Massachusetts General Hospital, and Harvard Medical School, Boston, Massachusetts; §Department of Neurology, Ruprecht-Karls-University, Heidelberg, Germany; ‖Department of Cardiology and Angiology, Hospital of the University of Münster, Münster, Germany; ¶The Cardiovascular Institute, Mount Sinai Medical Center, New York, New York; #Department of Neurology, Royal Perth Hospital,

JACC Vol. 61, No. 6, 2013
February 12, 2013:651–8

Abbreviations and Acronyms

AF = atrial fibrillation
CI = confidence interval
CNS = central nervous system
EOS = end of study
HR = hazard ratio
INR = international normalized ratio
MI = myocardial infarction

Patients with atrial fibrillation (AF) are at increased risk for ischemic stroke, a risk that is reduced significantly with warfarin (1). Unfortunately, nearly one-quarter of patients started on warfarin discontinue therapy within the first year, either because of the challenges of monitoring, intolerability, or adverse bleeding events (2,3). The limitations of warfarin illustrate the need for alternative therapeutic options.

See page 659

Rivaroxaban is an oral direct factor Xa inhibitor with consistent and predictable anticoagulation effects. In the double-blind 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), rivaroxaban was found to be noninferior to warfarin for the prevention of stroke and systemic embolism in patients with moderate- to high-risk nonvalvular AF (4). The ROCKET AF findings resulted in rivaroxaban being approved as an alternative to warfarin for stroke prevention. However, concerns regarding a potential increased risk of events after discontinuation led the United States Food and Drug Administration to require a boxed warning on the package insert stating "discontinuing rivaroxaban places patients at an increased risk of thrombotic events," and "an increased risk of stroke was observed following rivaroxaban discontinuation in clinical trials in atrial fibrillation patients" (5).

In an effort to understand the possible risk of discontinuation in the context of clinical care, we evaluated patients who had a temporary interruption or an early permanent study drug discontinuation and all patients who completed the ROCKET AF and transitioned to open-label therapy for the primary event of stroke and non–central nervous system (CNS) embolism and other thrombotic events, including myocardial infarction (MI) and death, up to 30 days after discontinuation.

Methods

The design and results of the ROCKET AF have been reported previously (4,6). Briefly, the ROCKET AF was a multicenter, randomized, double-blind, double-dummy, event-driven trial comparing fixed-dose rivaroxaban (20 mg daily or 15 mg daily in patients with creatinine clearance of 30 to 49 ml/min) with adjusted-dose warfarin (target international normalized ratio [INR]: 2.0 to 3.0) for prevention of all stroke (ischemic or hemorrhagic) or systemic embolism (6). To be enrolled in the study, patients were required to have nonvalvular AF and an elevated risk of stroke as defined by a history of stroke, transient ischemic attack, or systemic embolism or at least 2 of the following risk factors: heart failure or left ventricular ejection fraction of 35% or less, hypertension, age 75 years or older, or diabetes mellitus ($CHADS_2$ score [$CHADS_2$ is a mnemonic device in which 1 point is assigned for each of the following risk factors: C = Congestive heart failure, H = Hypertension, A = age ≥75 yrs, D = diabetes, and S2 = 2 points for prior Stroke or TIA]: ≥2). Of note for temporary interruptions, investigators were instructed to stop the warfarin or placebo tablets 4 days before elective procedures and the rivaroxaban or placebo tablets 2 days before elective procedures.

To understand the risk of discontinuation of rivaroxaban compared with warfarin, we evaluated 3 clinically relevant situations during the ROCKET AF (Fig. 1). The first was patients with temporary interruptions, defined as any interruption of more than 3 days. These temporary interruption patients were evaluated for clinical events that occurred from 3 days after study drug interruption to 3 days after resumption of study drug. Multiple patients may have had several temporary interruptions. The second was patients with early permanent study drug discontinuation who were

Perth, Australia; **Bayer HealthCare Pharmaceuticals, Montville, New Jersey; ††Duke Translational Medicine Institute, Duke University Medical Center, Durham, North Carolina; and the ‡‡University of Edinburgh and Royal Infirmary of Edinburgh, Edinburgh, United Kingdom. The ROCKET AF study was sponsored by Johnson & Johnson Pharmaceutical Research & Development, Raritan, New Jersey, and Bayer HealthCare AG, Leverkusen, Germany. Dr. Patel is on the advisory board of and consulting to Baxter, Bayer Healthcare, Otsuka, CSI, Volcano, and Jansen, and receiving research grants from Astra Zeneca and Johnson & Johnson. Dr. Lokhnygina is a consultant to Johnson & Johnson and Bayer. Dr. Piccini reports that his institution receiving a research grant from Janssen Pharmaceuticals and consulting to Janssen Pharmaceuticals, Forest Research Laboratories, Medtronic, and Titan Pharmaceuticals. Dr. Mohanty is an employee of Johnson & Johnson. Dr. Singer is a consultant to Johnson & Johnson, Bayer Healthcare, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Inc., Pfizer, and CSL Behring; has received research support from Johnson & Johnson; and participating in the executive committee of a trial sponsored by Johnson & Johnson. Dr. Hacke has received honoraria, consulting to, and speaking to Boehringer Ingelheim, Bayer, and Photothera and receiving an unrestricted grant from BI. Dr. Breithardt is a member of scientific advisory boards of Bayer Health Care, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, Otsuka Pharma, Sanofi-Aventis, and MSD and receiving fees for lectures at symposia organized by Boehringer Ingelheim, Bayer Health Care, Bristol-Myers Squibb, and Sanofi-Aventis. Dr. Halperin is a consultant to Johnson & Johnson and Bayer Healthcare. Dr. Hankey is a member of the executive committee of the ROCKET AF I study, receiving honoraria from Duke, and receiving clinical research support from the study sponsors, Bayer Pharmaceuticals and Johnson & Johnson. Dr. Becker has received research support and acting as a scientific advisor to Bayer, and Johnson & Johnson. Dr. Nessel is an employee of Johnson & Johnson. Dr. Berkowitz is an employee of Bayer HealthCare Pharmaceuticals. Dr. Califf has received research grants and consulting from Bayer and Johnson & Johnson. Dr. Fox has received research grants from Bayer, Johnson & Johnson, and Lilly; receiving hononaria and being a speaker for Bayer, Johnson & Johnson, Sanofi Aventis, and Astra Zeneca; and receiving a travel grant from Boehringer. Dr. Mahaffey has relationships with AstraZeneca, Bayer, Boehringer Ingleheim, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, Glaxo Smith Kline, Johnson & Johnson, Merck, Novartis, Pfizer, Polymedix, Pozen, Regado Biotechnologies, Sanofi, Schering-Plough, and The Medicines Company; has received consulting fees and research grants from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers-Squibb, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, and Sanofi; and consulting fees from: Pfizer and Polymedix; and grant support from: Pozen, Regado, Schering-Plough, and The Medicines Company.

Manuscript received June 25, 2012; revised manuscript received September 12, 2012, accepted September 16, 2012.

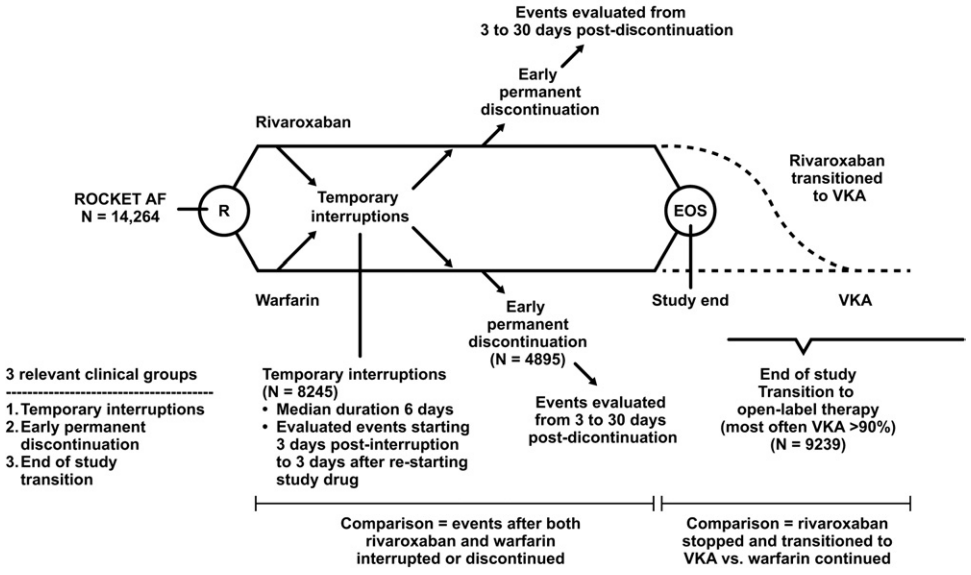

Figure 1 **Study Flow Diagram**

ROCKET AF study flow with relevant populations for analysis of interruption or discontinuation. EOS = end of study; VKA = vitamin K antagonist.

analyzed for clinical events from 3 to 30 days after discontinuation. The third was patients completing the study, defined as receiving the study drug at site notification of study end. These end-of-study patients underwent blinded transition to open-label therapy, most commonly warfarin. Patients also were followed up for events from 3 to 30 days after the end of the study.

Outcomes and outcomes assessments. In the ROCKET AF, a double-blind design was chosen to reduce bias in cointerventions and to ensure adequate assessment and reporting of clinical events both during administration of study drug and after all study drug discontinuations. The protocol required that all randomized patients be seen at 1, 2, and 4 weeks and monthly thereafter for the duration of the study for measurement of INR, surveillance for primary end point events, transient ischemic attack, MI, medical or surgical procedures, adverse events, and vital status. Study coordinators conducted a pill count at each visit. Personnel at sites were trained explicitly not to record a drug interruption for dose titration or any inadvertently missed dose or accidental interruption that was shorter than 3 days.

The primary efficacy end point was the composite of all stroke (both ischemic and hemorrhagic) and systemic embolism. Stroke was defined as a sudden focal neurologic deficit of presumed cerebrovascular cause that persisted beyond 24 h and was not the result of another identifiable cause. An event matching this definition but lasting fewer than 24 h was considered to be a transient ischemic attack. Non-CNS systemic embolism was defined as abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of another likely mechanism (e.g., atherosclerosis, instrumentation, or trauma). In the presence of atherosclerotic peripheral arterial disease, a diagnosis of embolism required angiographic demonstration of abrupt arterial occlusion. The major secondary efficacy end point included stroke, non-CNS embolism, MI, and vascular death.

The principal safety end point was the composite of major and nonmajor clinically relevant bleeding events. Major bleeding was defined as clinically overt bleeding associated with any of the following: fatal outcome, involvement of a critical anatomic site (intracranial, spinal, ocular, pericardial, articular, retroperitoneal, or intramuscular with compartment syndrome), fall in hemoglobin concentration of 2 g/dl or more, transfusion of 2 units or more of whole blood or packed red blood cells, or permanent disability. An independent clinical end point committee adjudicated all suspected stroke, systemic embolism, MI, vascular death, and bleeding events based on the pre-specified end point definitions.

The study was supported by grants from Johnson & Johnson Pharmaceutical Research & Development, Raritan, New Jersey, and Bayer HealthCare AG, Leverkusen, Germany. The Duke Clinical Research Institute, Durham, North Carolina, coordinated the trial, managed the database, and performed the primary analyses for this study, independent of the sponsors. All appropriate national regulatory authorities and ethics committees at participating centers approved the study. An international executive committee, which included nonvoting representatives from the sponsors, designed the trial and was responsible for

JACC Vol. 61, No. 6, 2013
February 12, 2013:651–8

oversight of study conduct and reporting of results and takes responsibility for the accuracy and completeness of this post hoc analysis of clinical events after discontinuations.

Statistical analysis. To evaluate the effect of interruption or discontinuation of therapy, this post hoc analysis was conducted in all ROCKET AF patients who received 1 dose of study drug and were followed up for events after temporary interruptions of 3 days or more, permanent discontinuations, and after the end-of-study transition. Hazard ratios (HRs) for rivaroxaban and warfarin, 95% confidence intervals (CIs), and p values were determined based on Cox proportional hazards models with treatment as the only covariate. For analysis of outcomes after early permanent discontinuation or study completion, only patients with at least 3 days of follow-up after ending study drug treatment are included. Testing for superiority used a 2-sided significance level of 0.05.

Results

In the ROCKET AF, 14,264 patients underwent randomization. As previously noted, because of violations in Good Clinical Practice making the data unreliable, 93 patients (50 in the rivaroxaban group and 43 in the warfarin group) were excluded from the analysis. An additional 28 patients never received study drug. After excluding these patients, 14,143 patients took at least 1 dose of study drug and were eligible for the analysis of discontinuation. During the 590 days of median treatment exposure, 8,245 temporary interruptions occurred (3,734 in the rivaroxaban group and 4,511 in the warfarin group). Early permanent discontinuation occurred in 4,895 (2,470 in the rivaroxaban group and 2,425 in the warfarin group). Completion of the study without an investigator-suspected primary end point event, death, or early permanent discontinuation occurred in 9,239 patients (4,587 in the rivaroxaban group and 4,652 in the warfarin group).

Patient characteristics. Key clinical characteristics of patients who received study drug and had any type of discontinuation (n = 8,261 [rivaroxaban: 4,021, warfarin: 4,240]) compared with patients who did not have any discontinuation (n = 5,882 [rivaroxaban: 3,040, warfarin: 2,842]) are shown in Table 1. In general, patients in both groups were similar with regard to age (median age: 73 years), sex (more than 60% male), and risk factors for stroke. Patients

Table 1 Baseline Characteristics by Discontinuation Status and Randomized Treatment

		Any Discontinuation		No Discontinuation		
	All Patients (n = 14,143)	Rivaroxaban (n = 4,021)	Warfarin (n = 4,240)	Rivaroxaban (n = 3,040)	Warfarin (n = 2,842)	p Value*
Age, yrs	73 (65, 78)	74 (66, 79)	73 (66, 78)	72 (64, 77)	71 (64, 77)	<0.0001
Male	8,553 (60.5)	2,503 (62.2)	2,549 (60.1)	1,767 (58.1)	1,734 (61.0)	0.050
BMI, kg/m^2	28.2 (25.1, 32.0)	28.2 (25.2, 32.0)	28.0 (25.1, 31.7)	28.4 (25.1, 32.2)	28.1 (25.1, 31.9)	0.28
Blood pressure, mm Hg						
Systolic	130 (120, 140)	130 (120, 140)	130 (120, 140)	130 (120, 140)	130 (120, 140)	0.017
Diastolic	80 (70, 85)	80 (70, 85)	80 (70, 85)	80 (72, 86)	80 (72, 86)	<0.0001
Type of atrial fibrillation						0.23
Persistent	11,462 (81.0)	3,244 (80.7)	3,412 (80.5)	2,495 (82.1)	2,311 (81.3)	
Paroxysmal	2,487 (17.6)	726 (18.1)	764 (18.0)	502 (16.5)	495 (17.4)	
Newly diagnosed or new onset	194 (1.4)	51 (1.3)	64 (1.5)	43 (1.4)	36 (1.3)	
Previous medication use						
Aspirin at baseline	4,098 (29.0)	1,251 (31.1)	1,291 (30.4)	779 (25.6)	777 (27.3)	<0.0001
Vitamin K antagonist	8,834 (62.5)	2,490 (61.9)	2,617 (61.7)	1,910 (62.8)	1,817 (63.9)	0.062
$CHADS_2$ score						<0.0001
1	3 (<0.1)	1 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)	
2	1,853 (13.1)	571 (14.2)	602 (14.2)	351 (11.5)	329 (11.6)	
3	6,156 (43.5)	1,726 (42.9)	1,834 (43.3)	1,299 (42.7)	1,297 (45.6)	
4	4,061 (28.7)	1,148 (28.6)	1,156 (27.3)	925 (30.4)	832 (29.3)	
5	1,793 (12.7)	496 (12.3)	545 (12.9)	422 (13.9)	330 (11.6)	
6	277 (2.0)	79 (2.0)	101 (2.4)	43 (1.4)	54 (1.9)	
Coexisting condition						
Previous stroke or TIA	7,414 (52.4)	1,976 (49.1)	2,088 (49.2)	1,746 (57.4)	1,604 (56.4)	<0.0001
Congestive heart failure	8,837 (62.5)	2,529 (62.9)	2,675 (63.1)	1,899 (62.5)	1,734 (61.0)	0.14
Hypertension	12,801 (90.5)	3,636 (90.4)	3,890 (91.7)	2,736 (90.0)	2,539 (89.3)	0.0044
Diabetes	5,635 (39.8)	1,661 (41.3)	1,734 (40.9)	1,181 (38.8)	1,059 (37.3)	0.0003
COPD	1,477 (10.4)	476 (11.8)	532 (12.6)	268 (8.8)	201 (7.1)	<0.0001
CrCl, ml/min†	67 (52, 87)	66 (51, 86)	65 (50, 84)	70 (54, 90)	70 (55, 90)	<0.0001

Values are median (25th, 75th) or n (%). *For aggregate evaluation of any discontinuation vs. no discontinuation. †Creatinine clearance was calculated using the Cockcroft-Gault formula.

BMI = body mass index; $CHADS_2$ = C = Congestive heart failure, H = Hypertension, A = age ≥75 yrs, D = diabetes, and S2 = 2 points for prior Stroke or TIA; COPD = chronic obstructive pulmonary disease; CrCl = creatinine clearance; TIA = transient ischemic attack.

Table 2 Transitions to Open-Label Vitamin K Antagonist or Aspirin Within 30 Days After Study Drug Early Study Drug Discontinuation and Study Completion*

	All Patients		Early Discontinuation		Completed	
	Rivaroxaban (n = 7,061)	Warfarin (n = 7,082)	Rivaroxaban (n = 2,470)	Warfarin (n = 2,425)	Rivaroxaban (n = 4,591)	Warfarin (n = 4,657)
Transition to open-label VKA	5,332 (75.5)	5,345 (75.5)	1,095 (44.3)	1,044 (43.1)	4,237 (92.3)	4,301 (92.4)
VKA type						
Warfarin	4,091 (57.9)	4,082 (57.6)	853 (34.5)	822 (33.9)	3,238 (70.5)	3,260 (70.0)
Other VKA	1,241 (17.6)	1,263 (17.8)	242 (9.8)	222 (9.2)	999 (21.8)	1,041 (22.4)
None	1,729 (24.5)	1,737 (24.5)	1,375 (55.7)	1,381 (56.9)	354 (7.7)	356 (7.6)
Aspirin	210 (3.0)	179 (2.5)	128 (5.2)	112 (4.6)	82 (1.8)	67 (1.4)

Values are n (%). *Includes all safety patients (n = 14,143).
VKA = vitamin K antagonist.

discontinuing therapy were more likely to be treated with aspirin at baseline compared with those completing the study (30.8% vs. 26.5%, $p < 0.0001$). Patient characteristics for those undergoing early permanent discontinuation and those completing the study and transitioning to open-label therapy are presented in Online Table 1.

Discontinuation reasons and post-discontinuation therapy. The most common reasons for early permanent study drug discontinuation included adverse events (39%), both nonbleeding and bleeding (Online Table 2). Additionally, investigators were instructed to stop study drug permanently when a primary end point was suspected, which occurred in 12.9% (n = 632) of discontinuations. It should be noted that when these patients did not meet blinded adjudication criteria for stroke or systemic embolism, they were followed up for subsequent evidence of the primary end points (stroke or systemic embolism). These events occurred and met adjudication criteria in 53 patients (rivaroxaban: n = 30, warfarin: n = 23). A substantial number of all discontinuations occurred when patients withdrew consent (27.4%, n = 1,343) or had study drug stopped based on investigator decision (7.4%, n = 364).

The most common reasons for temporary interruption were surgical or invasive procedures (38.2%) and adverse events (40.2%), both bleeding and nonbleeding. Review of procedures performed within 30 days before interruption showed a low rate of cardiovascular procedures such as percutaneous coronary intervention and coronary artery bypass graft surgery (Online Table 3). The median duration for all temporary interruptions was 6 days.

A vitamin K antagonist was used in patients undergoing an early permanent discontinuation in 44.3% of rivaroxaban-treated patients and in 43.1% of warfarin-treated patients. In patients completing the study, a vitamin K antagonist was used in 92.3% of rivaroxaban-treated patients and in 92.4% of warfarin-treated patients (Table 2). As previously noted, more than 60% of warfarin-treated patients completing the study had a therapeutic INR (2.0 to 3.0) at the first protocol-allowed check at 3 days, whereas less than 50% of rivaroxaban-treated patients transitioning to open-label vitamin K antagonist therapy had a therapeutic INR (2.0 to 3.0) at 30 days (Fig. 2) (4).

Stroke or non-CNS embolism outcomes. Stroke and non-CNS embolism occurred at similar rates after temporary interruptions (rivaroxaban: n = 9, warfarin: n = 8, 6.20 vs. 5.05 per 100 patient-years, HR: 1.28, 95% CI: 0.49 to 3.31, p = 0.62) and after early permanent discontinuation (rivaroxaban: n = 42, warfarin: n = 36, 25.60 vs. 23.28 per 100 patient-years, HR: 1.10, 95% CI: 0.71 to 1.72, p = 0.66) (Table 3). When stroke or non-CNS embolisms for any temporary interruption or permanent discontinuation of study drug were evaluated in aggregate up to study completion, the rates also were similar between rivaroxaban- and warfarin-treated patients (rivaroxaban: n = 51, warfarin: n = 44, 16.49 vs. 14.05 events per 100 patient-years, HR: 1.21, 95% CI: 0.81 to 1.81, p = 0.35). Finally, when events occurring after permanent discontinuation for suspected stroke or non-CNS embolism were censored, the rates remained similar between rivaroxaban- and warfarin-treated patients (rivaroxaban: n = 12, warfarin: n = 13, 8.12 vs. 9.14 events per 100 patient-years, HR: 0.86, 95% CI: 0.39 to 1.89, p = 0.71).

Significantly more strokes occurred in rivaroxaban-treated patients (n = 22) compared with warfarin-treated patients (n = 6) after the end-of-study transition from blinded study drug to open-label warfarin (6.42 vs. 1.73 per 100 patient-years, HR: 3.72, 95% CI: 1.51 to 9.16, p = 0.0044). When all discontinuations and interruptions before study end were added to events after the end-of-study transition, there were significantly more primary events with rivaroxaban (n = 73) compared with warfarin (n = 50, HR: 11.20 vs. 7.57 per 100 patient-years, HR: 1.50, 95% CI: 1.05 to 2.15, p = 0.026) (Table 3).

Aggregate thrombotic outcome events. When all thrombotic events (the major secondary efficacy end point of the trial)—defined as stroke, non-CNS embolism, MI, and vascular death—were evaluated, there were similar rates after temporary interruptions (14 with rivaroxaban and 17 with warfarin, 9.66 vs. 10.75 per 100 patient-years, HR: 0.95, 95% CI: 0.47 to 1.94, p = 0.89) and early permanent discontinuations (131 with rivaroxaban and 147 with warfarin, 80.01 vs. 95.28 per 100 patient-years, HR: 0.84, 95% CI: 0.67 to 1.01, p = 0.16) (Table 3). After the end of the study, there were significantly more thrombotic events with

JACC Vol. 61, No. 6, 2013
February 12, 2013:651–8

Table 3 Stroke or Non–Central Nervous System Embolism Rates and Stroke, Non–Central Nervous System Embolism, Myocardial Infarction, or Vascular Death During Post–Study-Drug Discontinuation Risk Period*

	Events per 100 Patient-Yrs (Total Events)			
	Rivaroxaban	Warfarin	Rivaroxaban: Warfarin HR (95% CI)	p Value
Stroke or non-CNS embolism rates				
All discontinuations and interruptions (before end of study)	16.49 (51)	14.05 (44)	1.21 (0.81–1.81)	0.35
Temporary interruptions	6.20 (9)	5.05 (8)	1.28 (0.49–3.31)	0.62
Permanent discontinuations	25.60 (42)	23.28 (36)	1.10 (0.71–1.72)	0.66
After end of study	6.42 (22)	1.73 (6)	3.72 (1.51–9.16)	0.0044
All discontinuations and interruptions (before end of study) + after end of study events	11.20 (73)	7.57 (50)	1.50 (1.05–2.15)	0.026
Stroke, non-CNS embolism, MI, or vascular death				
All discontinuations and interruptions (before end of study)	46.97 (145)	52.50 (164)	0.92 (0.74–1.15)	0.47
Temporary interruptions	9.66 (14)	10.75 (17)	0.95 (0.47–1.94)	0.89
Permanent discontinuations	80.01 (131)	95.28 (147)	0.84 (0.67–1.07)	0.16
After end of study	9.05 (31)	4.03 (14)	2.24 (1.19–4.22)	0.012
All discontinuations and interruptions (before end of study) + after end of study events	27.02 (176)	26.97 (178)	1.02 (0.83–1.26)	0.85

*Risk period for temporary interruptions is 3 days post-stop to 3 days post-resumption; for permanent discontinuations and end of study is 3–30 days post-stop; for permanent discontinuations and end of study, only patients with ≥3 days follow-up post-stop are included (N=13,650).
CI = confidence interval; CNS = central nervous system; HR = hazard ratio; MI = myocardial infarction.

rivaroxaban (n = 31) compared with warfarin (n = 14, 9.05 vs. 4.03 per 100 patient-years, HR: 2.24, 95% CI: 1.19 to 4.22, p = 0.012). When all discontinuations and interruptions before the study end and end-of-study events were evaluated in aggregate, there was no significant difference between rivaroxaban and warfarin (HR: 1.02, 95% CI: 0.83 to 1.36, p = 0.85).

Major bleeding. The rates of major bleeding were similar after temporary interruptions (24 with rivaroxaban and 27 with warfarin, 16.66 vs. 17.20 per 100 patient-years, HR: 1.02, 95% CI: 0.59 to 1.77, p = 0.94) and after early permanent discontinuation (21 with rivaroxaban and 33 with warfarin, 12.71 vs. 21.29 per 100 patient-years, HR: 0.60, 95% CI: 0.35 to 1.04, p = 0.067) (Table 4). Significantly more major bleeding events were observed after the end of the study during the transition period in rivaroxaban-treated subjects compared with warfarin-treated subjects (25 with rivaroxaban and 7 with warfarin, 7.29 vs. 2.01 per 100 patient-years, HR: 3.62, 95% CI: 1.56 to 8.36, p < 0.0026). Again, there was no significant difference when all discontinuations and interruptions before completion and end-of-study major bleeds were evaluated in aggregate (70 with rivaroxaban and 67 with warfarin, 10.74 vs. 10.16 per 100 patient-years, HR: 1.07, 95% CI: 0.77 to 1.50, p = 0.67).

Discussion

This analysis of clinical events occurring after temporary interruptions, early permanent discontinuations, or end-of-study transition from study drug during the ROCKET AF provides several critical insights for clinicians considering the use of anticoagulants in AF patients at moderate to high risk of stroke. The most important finding in this analysis is that there were no significant differences between rivaroxaban and warfarin in the rates of stroke or non-CNS embolism after temporary interruption or early permanent discontinuation, when both blinded therapies were stopped. After the end of the study and after mandatory withdrawal of blinded study drug, when patients treated with rivaroxaban frequently were transitioned to open-label vitamin K

Table 4 Discontinuation Events: Major Bleeding Occurring During Post–Study-Drug Discontinuation Risk Period*

	Events per 100 Patient-Yrs (Total Events)			
	Rivaroxaban	Warfarin	Rivaroxaban: Warfarin HR (95% CI)	p Value
All discontinuations and interruptions (before end of study)	14.55 (45)	19.23 (60)	0.79 (0.54–1.16)	0.23
Temporary interruptions	16.66 (24)	17.20 (27)	1.02 (0.59–1.77)	0.94
Permanent discontinuations	12.71 (21)	21.29 (33)	0.60 (0.35–1.04)	0.067
After end of study	7.29 (25)	2.01 (7)	3.62 (1.56–8.36)	0.0026
All discontinuations and interruptions (before end of study) + after end-of-study events	10.74 (70)	10.16 (67)	1.07 (0.77–1.50)	0.67

*Risk period for temporary interruptions is 3 days after stopping to 3 days after resumption. That for permanent discontinuations and end of study is 3 to 30 days after stopping. That for permanent discontinuations and end of study, only patients with 3 days or more of follow-up after stopping are included (n = 13,650).
Abbreviations as in Table 3.

antagonists and patients treated with warfarin were continued on vitamin K antagonist prophylaxis, there were significantly more strokes and non-CNS embolism events in patients who had received rivaroxaban compared with those who had received warfarin. Finally, when all thrombotic events that included stroke, non-CNS embolism, MI, and vascular death were evaluated for interruptions and discontinuation both during and after the study, there was no significant difference between rivaroxaban and warfarin.

Review of the events after withdrawal of therapy, both during and after the trial, provides important implications regarding the existing box warning and provides lessons for the current clinical use of rivaroxaban and warfarin. Consistent with the moderate- to high-risk elderly population enrolled in the ROCKET AF, temporary interruptions were frequent in both groups. Surgical and invasive procedures were the most common reasons for temporary interruptions, and the median duration of a temporary interruption was 6 days. Although there were few strokes (9 with rivaroxaban and 8 with warfarin), given the large number of short interruptions in a trial of this size, the rate of stroke and systemic embolism observed provides an important observation for physicians and patients considering interruption. The rate of stroke and systemic embolism observed was similar between therapies and likely represents the intrinsic stroke rate for patients at moderate to high risk who are without therapeutic anticoagulation. Stated another way, even with short temporary interruptions, the protection from anticoagulant therapy for AF is lost and the baseline patient risk becomes evident when observed over several thousand interruptions. These findings draw attention to the potential value of adequate anticoagulation coverage during interruptions, an aim of ongoing studies (7), and the importance of minimizing interruptions.

Patients undergoing early permanent study drug discontinuation had high rates of both stroke and systemic embolism and all thrombotic events within 30 days of cessation of therapy. To understand the high observed event rates, it is important to recognize that this group represents a unique set of patients during the conduct of the clinical trial. These patients often had adverse events (both bleeding and nonbleeding) before permanent study discontinuation and were deemed high risk by study investigators for continued anticoagulation, as evidenced by less than 50% receiving vitamin K antagonists within the first 30 days after permanent discontinuation of study drug. These findings underscore the complex interplay between bleeding and thrombosis and the difficulty in managing moderate- to high-risk AF patients unable to tolerate anticoagulation therapy. Additionally, most of the events in patients undergoing permanent discontinuation (n = 53) occurred in patients whose local physician or investigator suspected a stroke or non-CNS embolism. This finding highlights patients with transient ischemic attacks and possible stuttering neurologic clinical events that led to permanent discontinuation and recurrent events within 30 days, as might have been expected. This is consistent with the findings of prior studies in patients with suspected stroke, which indicated that the interruption of anticoagulation increases the risk of subsequent thrombotic events (8,9). Hence, these findings draw attention to the importance of anticoagulation coverage and decisions for patients having adverse events, specifically patients with suspected embolic events. Despite all of these complexities, we found that patients with early permanent study drug discontinuation had similar rates of stroke, systemic embolism, and all thrombotic events when treated with rivaroxaban compared with those treated with warfarin.

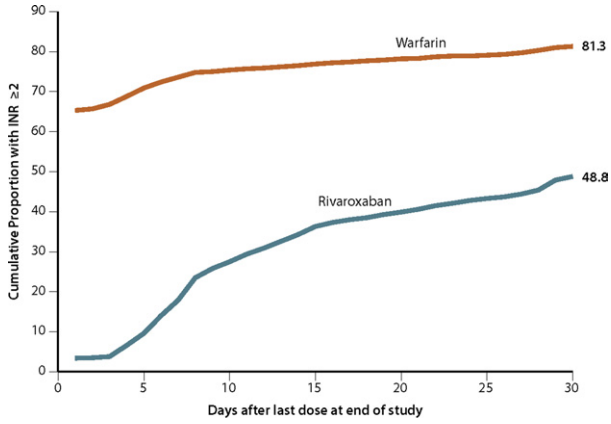

Figure 2 **Time to Therapeutic International Normalized Ratio**

Cumulative proportion of patients with international normalized ratio (INR) of 2 or more after the end of the study for those treated with warfarin and rivaroxaban during the ROCKET AF study.

Patients completing the study and transitioning to open-label prophylaxis, most often vitamin K antagonists, represent 2 distinct populations. The patients who transitioned from rivaroxaban to warfarin had a period of transition consistent with prolonged time to a therapeutic INR (Fig. 2). In this sense, these patients were similar to those with temporary interruptions, where anticoagulation coverage was not present. In fact, the observation of similar stroke rates (approximately 6 per 100 patient-years) between these 2 groups highlights this similar and likely intrinsic risk for moderate- to high-risk AF patients. Unlike the rivaroxaban patients who had poor coverage through the transition, the warfarin group continued to receive vitamin K antagonist prophylaxis and had no uncovered period, as evidenced by the time to a therapeutic INR (3 days), the first time investigators were permitted to check an unblinded INR at the end of the study. This observed event rate of fewer than 2 per 100 patient-years is consistent with the rate that may be expected in patients completing the study and is similar to the on-treatment event rate in the overall trial.

In aggregate, these data have several implications. Regarding the existing box warning, there is in fact a numerically increased thrombotic risk with discontinuation of

rivaroxaban. This risk with discontinuation of rivaroxaban was statistically similar when compared with discontinuation of warfarin. The hazard seen during the post-clinical trial transition from rivaroxaban to warfarin drives the excess strokes seen after all interruptions and discontinuations. Further research is needed to understand how to manage these patients best. Additionally, from a study methodology perspective, post-study transition events and therapy post-discontinuation should be collected and reported for clinical trials evaluating anticoagulants to help inform these decisions.

Several findings should inform current clinical practice. First, both clinicians and patients should be aware of the significant risk of stroke, non-CNS embolism, and thrombotic events when anticoagulation, including rivaroxaban or warfarin, is stopped on either a temporary or permanent basis. For the temporary interruptions, these findings support careful assessment of continued anticoagulation coverage in these moderate- to high-risk AF patients, where the intrinsic stroke or non-CNS embolism rate may be approximately 6 per 100 patient-years (10). Whether bridging anticoagulation will produce net clinical benefit is unclear, but it seems wise to minimize the period of discontinuation. Additionally, these findings argue for careful attention in ensuring timely anticoagulation coverage if patients are transitioned from rivaroxaban to warfarin. It should be noted that there is not a known mechanism for a prothrombotic state during this transition. This may not be a common occurrence in clinical practice, but should be considered carefully if needed.

This study is limited by the observational nature of the analysis. Additionally, there may be unmeasured confounders that are associated with discontinuation. However, the blinded nature of the study should provide reassurance regarding decisions to discontinue therapies. Finally, although the current analysis is limited by the lack of detailed information regarding medical therapy after discontinuation, available data on the use of vitamin K antagonists demonstrate high rates of use for patients completing the study.

Conclusions

In moderate- to high-risk AF patients temporarily interrupting or permanently discontinuing anticoagulation, the risk of stroke or systemic embolism was similar when they were treated with rivaroxaban or warfarin. After the end-of-study transition to warfarin, an increased risk of stroke and systemic embolism was observed for patients being treated with rivaroxaban compared with those treated with warfarin, underscoring the importance of expeditious anticoagulation coverage during the transition from one antithrombotic therapy to another.

Acknowledgment

The authors thank Elizabeth Cook, Duke Clinical Research Institute, for providing editorial support.

Reprints requests and correspondence: Dr. Manesh R. Patel, Department of Medicine, Duke Clinical Research Institute, Duke University Medical Center, Room 0311 Terrace Level, 2400 Pratt Street, Durham, North Carolina 27705. E-mail: manesh.patel@duke.edu.

REFERENCES

1. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. Ann Intern Med 1999;131:492–501.
2. Fang MC, Go AS, Chang Y, et al. Warfarin discontinuation after starting warfarin for atrial fibrillation. Circ Cardiovasc Qual Outcomes 2010;3:624–31.
3. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. Circulation 2007;115:2689–96.
4. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883–91.
5. United States Food and Drug Administration. XARELTO (Rivaroxaban) tablets. Risk Evaluation and Mitigation Strategy (REMS). Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM295405.pdf?utm_source=fdaSearch&utm_medium=website&utm_term=Rivaroxaban box warning&utm_content=1. Accessed April 4, 2012.
6. Rivaroxaban-Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation: rationale and design of the ROCKET AF study. Am Heart J 2010;159:340–7.
7. Effectiveness of Bridging Anticoagulation for Surgery (the BRIDGE Study). ClinicalTrials.gov. Available at: http://clinicaltrials.gov/ct2/show/NCT00786474?term=bridge+trial&rank=30. Accessed April 4, 2012.
8. Kim YD, Lee JH, Jung YH, et al. Effect of warfarin withdrawal on thrombolytic treatment in patients with ischaemic stroke. Eur J Neurol 2011;18:1165–70.
9. García Rodríguez LA, Cea Soriano L, Hill C, Johansson S. Increased risk of stroke after discontinuation of acetylsalicylic acid: a UK primary care study. Neurology 2011;76:740–6.
10. Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e326S–350S.

Key Words: atrial fibrillation ■ factor Xa ■ rivaroxaban ■ stroke ■ warfarin.

APPENDIX

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