Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*

ABSTRACT

BACKGROUND

The use of warfarin reduces the rate of ischemic stroke in patients with atrial fibrillation but requires frequent monitoring and dose adjustment. Rivaroxaban, an oral factor Xa inhibitor, may provide more consistent and predictable anticoagulation than warfarin.

METHODS

In a double-blind trial, we randomly assigned 14,264 patients with nonvalvular atrial fibrillation who were at increased risk for stroke to receive either rivaroxaban (at a daily dose of 20 mg) or dose-adjusted warfarin. The per-protocol, as-treated primary analysis was designed to determine whether rivaroxaban was noninferior to warfarin for the primary end point of stroke or systemic embolism.

RESULTS

In the primary analysis, the primary end point occurred in 188 patients in the rivaroxaban group (1.7% per year) and in 241 in the warfarin group (2.2% per year) (hazard ratio in the rivaroxaban group, 0.79; 95% confidence interval [CI], 0.66 to 0.96; P<0.001 for noninferiority). In the intention-to-treat analysis, the primary end point occurred in 269 patients in the rivaroxaban group (2.1% per year) and in 306 patients in the warfarin group (2.4% per year) (hazard ratio, 0.88; 95% CI, 0.74 to 1.03; P<0.001 for noninferiority; P=0.12 for superiority). Major and nonmajor clinically relevant bleeding occurred in 1475 patients in the rivaroxaban group (14.9% per year) and in 1449 in the warfarin group (14.5% per year) (hazard ratio, 1.03; 95% CI, 0.96 to 1.11; P=0.44), with significant reductions in intracranial hemorrhage (0.5% vs. 0.7%, P=0.02) and fatal bleeding (0.2% vs. 0.5%, P=0.003) in the rivaroxaban group.

CONCLUSIONS

In patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group. (Funded by Johnson & Johnson and Bayer; ROCKET AF ClinicalTrials.gov number, NCT00403767.)

From the Duke Clinical Research Institute (M.R.P., K.W.M., J.G., J.P.P., R.C.B.) and Duke Translational Medicine Institute (R.M.C.), Duke University Medical Center, Durham, NC; Johnson & Johnson Pharmaceutical Research and Development, Raritan (G.P., C.C.N.), and Bayer HealthCare Pharmaceuticals, Montville (J.F.P., S.D.B.) — both in New Jersey; Massachusetts General Hospital and Harvard Medical School — both in Boston (D.E.S.); Ruprecht-Karls-University, Heidelberg (W.H.), and Hospital of the University of Münster, Münster (G.B.) — both in Germany; the Cardiovascular Institute, Mount Sinai Medical Center, New York (J.L.H.); Royal Perth Hospital, Perth, WA, Australia (G.J.H.); and the University of Edinburgh and Royal Infirmary of Edinburgh — both in Edinburgh (K.A.A.F.). Address reprint requests to Dr. Patel at Duke Clinical Research Institute, Duke University Medical Center, Rm. 0311 Terrace Level, 2400 Pratt St., Durham, NC 27705, or at manesh.patel@duke.edu.

*A complete listing of the steering committee members and trial investigators in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) is provided in the Supplementary Appendix, available at NEJM.org.

ATRIAL FIBRILLATION IS ASSOCIATED with an increase in the risk of ischemic stroke by a factor of four to five[1] and accounts for up to 15% of strokes in persons of all ages and 30% in persons over the age of 80 years.[2] The use of vitamin K antagonists is highly effective for stroke prevention in patients with nonvalvular atrial fibrillation and is recommended for persons at increased risk.[3-5] However, food and drug interactions necessitate frequent coagulation monitoring and dose adjustments, requirements that make it difficult for many patients to use such drugs in clinical practice.[6-8]

Rivaroxaban is a direct factor Xa inhibitor that may provide more consistent and predictable anticoagulation than warfarin.[9,10] It has been reported to prevent venous thromboembolism more effectively than enoxaparin in patients undergoing orthopedic surgery[11,12] and was noninferior to enoxaparin followed by warfarin in a study involving patients with established venous thrombosis.[13] This trial was designed to compare once-daily oral rivaroxaban with dose-adjusted warfarin for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation who were at moderate-to-high risk for stroke.[14]

METHODS

STUDY DESIGN AND OVERSIGHT

The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) was a multicenter, randomized, double-blind, double-dummy, event-driven trial that was conducted at 1178 participating sites in 45 countries.[14] The study was supported by Johnson & Johnson Pharmaceutical Research and Development and Bayer HealthCare. The Duke Clinical Research Institute coordinated the trial, managed the database, and performed the primary analyses independently of the sponsors. Pertinent national regulatory authorities and ethics committees at participating centers approved the protocol, which is available with the full text of this article at NEJM.org. The members of an international executive committee designed the trial, were responsible for overseeing the study's conduct, retained the ability to independently analyze and present the data, made the decision to submit the manuscript for publication, and take responsibility for the accuracy and completeness of the data and all analyses. The first academic author wrote the initial draft of the manuscript.

STUDY PARTICIPANTS

We recruited patients with nonvalvular atrial fibrillation, as documented on electrocardiography, who were at moderate-to-high risk for stroke. Elevated risk was indicated by a history of stroke, transient ischemic attack, or systemic embolism or at least two of the following risk factors: heart failure or a left ventricular ejection fraction of 35% or less, hypertension, an age of 75 years or more, or the presence of diabetes mellitus (i.e., a $CHADS_2$ score of 2 or more, on a scale ranging from 1 to 6, with higher scores indicating a greater risk of stroke). According to the protocol, the proportion of patients who had not had a previous ischemic stroke, transient ischemic attack, or systemic embolism and who had no more than two risk factors was limited to 10% of the cohort for each region; the remainder of patients were required to have had either previous thromboembolism or three or more risk factors. Complete inclusion and exclusion criteria are provided in the Supplementary Appendix, available at NEJM.org. All patients provided written informed consent.

STUDY TREATMENT

Patients were randomly assigned to receive fixed-dose rivaroxaban (20 mg daily or 15 mg daily in patients with a creatinine clearance of 30 to 49 ml per minute) or adjusted-dose warfarin (target international normalized ratio [INR], 2.0 to 3.0). Patients in each group also received a placebo tablet in order to maintain blinding. Randomization was performed with the use of a central 24-hour, computerized, automated voice-response system. A point-of-care device was used to generate encrypted values that were sent to an independent study monitor, who provided sites with either real INR values (for patients in the warfarin group in order to adjust the dose) or sham values (for patients in the rivaroxaban group receiving placebo warfarin) during the course of the trial. Sham INR results were generated by means of a validated algorithm reflecting the distribution of values in warfarin-treated patients with characteristics similar to those in the study population.[15]

It was intended that patients would continue to take the assigned therapy throughout the course of the trial, unless discontinuation was considered to be clinically indicated. Follow-up

procedures and restrictions on concomitant medications are summarized in the Supplementary Appendix.

OUTCOMES

The primary efficacy end point was the composite of stroke (ischemic or hemorrhagic) and systemic embolism. Brain imaging was recommended to distinguish hemorrhagic from ischemic stroke. In the presence of atherosclerotic peripheral arterial disease, the diagnosis of embolism required angiographic demonstration of abrupt arterial occlusion.

Secondary efficacy end points included a composite of stroke, systemic embolism, or death from cardiovascular causes; a composite of stroke, systemic embolism, death from cardiovascular causes, or myocardial infarction; and individual components of the composite end points. The principal safety end point was a composite of major and nonmajor clinically relevant bleeding events. Bleeding events involving the central nervous system that met the definition of stroke were adjudicated as hemorrhagic strokes and included in both the primary efficacy and safety end points. Other overt bleeding episodes that did not meet the criteria for major or clinically relevant nonmajor bleeding were classified as minor episodes.

An independent clinical end-point committee applied protocol definitions to adjudicate all suspected cases of stroke, systemic embolism, myocardial infarction, death, and bleeding events that contributed to the prespecified end points. Detailed definitions of the end-point events are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The primary hypothesis was that rivaroxaban would be noninferior to warfarin for the prevention of stroke or systemic embolism. The primary analysis was prespecified to be performed in the per-protocol population, which included all patients who received at least one dose of a study drug, did not have a major protocol violation, and were followed for events while receiving a study drug or within 2 days after discontinuation (group A in Fig. 1 in the Supplementary Appendix).[16-19]

For the primary analysis, we determined that a minimum of 363 events would provide a power of 95% to calculate a noninferiority margin of 1.46 with a one-sided alpha level of 0.025. However, 405 events were selected as the prespecified

target to ensure a robust statistical result. On the basis of a projected event rate of 2.3% per 100 patient-years in the warfarin group and a projected 14% rate of annual attrition, it was estimated that approximately 14,000 patients would need to be randomly assigned to a study group.

If noninferiority was achieved in the primary analysis, a closed testing procedure was to be conducted for superiority in the safety population during treatment, which included patients who received at least one dose of a study drug and were followed for events, regardless of adherence to the protocol, while they were receiving the assigned study drug or within 2 days after discontinuation (group B in Fig. 1 in the Supplementary Appendix). Key secondary efficacy end points were also tested for superiority in the as-treated safety population.[20] Testing for noninferiority and superiority was also performed in the intention-to-treat population, which included all patients who underwent randomization and were followed for events during treatment or after premature discontinuation (group C in Fig. 1 in the Supplementary Appendix).

In addition, we performed post hoc analyses of events in the intention-to-treat population and events occurring during the end-of-study transition to open-label treatment with conventional anticoagulant agents. In the warfarin group, we used the method of Rosendaal et al.[21] to calculate the overall time that INR values fell within the therapeutic range. Comparative analyses of treatment efficacy were performed according to quartiles of time that INR values fell within the therapeutic range at the participating clinical sites.

Event rates per 100 patient-years are presented as proportions of patients per year. Hazard ratios, confidence intervals, and P values were calculated with the use of Cox proportional-hazards models with treatment as the only covariate. Testing for noninferiority was based on a one-sided significance level of 0.025; testing for superiority was based on a two-sided significance level of 0.05.

RESULTS

RECRUITMENT AND FOLLOW-UP

From December 18, 2006, through June 17, 2009, a total of 14,264 patients underwent randomization (Fig. 1 in the Supplementary Appendix). The study was terminated on May 28, 2010. The proportions of patients who permanently stopped

Table 1. Characteristics of the Intention-to-Treat Population at Baseline.

Characteristic	Rivaroxaban (N = 7131)	Warfarin (N = 7133)
Age — yr		
Median	73	73
Interquartile range	65–78	65–78
Female sex — no. (%)	2831 (39.7)	2832 (39.7)
Body-mass index*		
Median	28.3	28.1
Interquartile range	25.2–32.1	25.1–31.8
Blood pressure — mm Hg		
Systolic		
Median	130	130
Interquartile range	120–140	120–140
Diastolic		
Median	80	80
Interquartile range	70–85	70–85
Type of atrial fibrillation — no. (%)		
Persistent	5786 (81.1)	5762 (80.8)
Paroxysmal	1245 (17.5)	1269 (17.8)
Newly diagnosed or new onset	100 (1.4)	102 (1.4)
Previous medication use — no. (%)		
Aspirin	2586 (36.3)	2619 (36.7)
Vitamin K antagonist	4443 (62.3)	4461 (62.5)
CHADS$_2$ risk of stroke†		
Mean score (±SD)	3.48±0.94	3.46±0.95
Score — no. (%)		
2	925 (13.0)	934 (13.1)
3	3058 (42.9)	3158 (44.3)
4	2092 (29.3)	1999 (28.0)
5	932 (13.1)	881 (12.4)
6‡	123 (1.7)	159 (2.2)
Coexisting condition — no. (%)		
Previous stroke, systemic embolism, or transient ischemic attack	3916 (54.9)	3895 (54.6)
Congestive heart failure	4467 (62.6)	4441 (62.3)
Hypertension	6436 (90.3)	6474 (90.8)
Diabetes mellitus	2878 (40.4)	2817 (39.5)
Previous myocardial infarction‡	1182 (16.6)	1286 (18.0)
Peripheral vascular disease	401 (5.6)	438 (6.1)
Chronic obstructive pulmonary disease	754 (10.6)	743 (10.4)
Creatinine clearance — ml/min§		
Median	67	67
Interquartile range	52–88	52–86

* The body-mass index is the weight in kilograms divided by the square of the height in meters.
† The CHADS$_2$ score for the risk of stroke ranges from 1 to 6, with higher scores indicating an increased risk. Three patients (one in the rivaroxaban group and two in the warfarin group) had a CHADS$_2$ score of 1.
‡ P<0.05 for the between-group comparison.
§ Creatinine clearance was calculated with the use of the Cockcroft–Gault formula.

their assigned therapy before an end-point event and before the termination date were 23.7% in the rivaroxaban group and 22.2% in the warfarin group. The median duration of treatment exposure was 590 days; the median follow-up period was 707 days. Only 32 patients were lost to follow-up. Because of violations in Good Clinical Practice guidelines at one site that made the data unreliable, 93 patients (50 in the rivaroxaban group and 43 in the warfarin group) were excluded from all efficacy analyses before unblinding. An additional issue with data quality was raised at another trial site, but this issue was resolved without the exclusion of the patients from the analysis (for details, see the Supplementary Appendix).

PATIENT CHARACTERISTICS AND TREATMENTS

Key clinical characteristics of the patients who underwent randomization are shown in Table 1. The median age was 73 years (a quarter of the patients were 78 years of age or older), and 39.7% of the patients were women. The patients had substantial rates of coexisting illnesses: 90.5% had hypertension, 62.5% had heart failure, and 40.0% had diabetes; 54.8% of the patients had had a previous stroke, systemic embolism, or transient ischemic attack. The mean and median CHADS$_2$ scores were 3.5 and 3.0, respectively. Data on medication use at baseline are provided in Table 1 in the Supplementary Appendix. Previous use of vitamin K antagonists was reported by 62.4% of patients. At some time during the study, 34.9% of patients in the rivaroxaban group and 36.2% of those in the warfarin group took aspirin concurrently with the assigned study drug. Among patients in the warfarin group, INR values were within the therapeutic range (2.0 to 3.0) a mean of 55% of the time (median, 58%; interquartile range, 43 to 71).

PRIMARY OUTCOME

In the per-protocol population (the patients included in the primary efficacy analysis), stroke or systemic embolism occurred in 188 patients in the rivaroxaban group (1.7% per year) and in 241 patients in the warfarin group (2.2% per year) (hazard ratio in the rivaroxaban group, 0.79; 95% confidence interval [CI], 0.66 to 0.96; P<0.001 for noninferiority) (Table 2 and Fig. 1A). In the as-treated safety population, primary events occurred in 189 patients in the rivaroxaban group (1.7% per year) and in 243 patients in the warfarin

Table 2. Primary End Point of Stroke or Systemic Embolism.*

Study Population	Rivaroxaban			Warfarin			Hazard Ratio (95% CI)†	P Value	
	No. of Patients	No. of Events	Event Rate	No. of Patients	No. of Events	Event Rate		Noninferiority	Superiority
			no./100 patient-yr			*no./100 patient-yr*			
Per-protocol, as-treated population‡	6958	188	1.7	7004	241	2.2	0.79 (0.66–0.96)	<0.001	
Safety, as-treated population	7061	189	1.7	7082	243	2.2	0.79 (0.65–0.95)		0.02
Intention-to-treat population§	7081	269	2.1	7090	306	2.4	0.88 (0.75–1.03)	<0.001	0.12
During treatment		188	1.7		240	2.2	0.79 (0.66–0.96)		0.02
After discontinuation		81	4.7		66	4.3	1.10 (0.79–1.52)		0.58

* The median follow-up period was 590 days for the per-protocol, as-treated population during treatment; 590 days for the safety, as-treated population during treatment; and 707 days for the intention-to-treat population.
† Hazard ratios are for the rivaroxaban group as compared with the warfarin group.
‡ The primary analysis was performed in the as-treated, per-protocol population during treatment.
§ Follow-up in the intention-to-treat population continued until notification of study termination.

group (2.2% per year) (hazard ratio, 0.79; 95% CI, 0.65 to 0.95; P=0.01 for superiority). Among all randomized patients in the intention-to-treat analysis, primary events occurred in 269 patients in the rivaroxaban group (2.1% per year) and in 306 patients in the warfarin group (2.4% per year) (hazard ratio, 0.88; 95% CI, 0.74 to 1.03; P<0.001 for noninferiority; P=0.12 for superiority) (Fig. 1B).

During treatment in the intention-to-treat population, patients in the rivaroxaban group had a lower rate of stroke or systemic embolism (188 events, 1.7% per year) than those in the warfarin group (240 events, 2.2% per year) (P=0.02) (Table 2 and Fig. 2). Among patients who stopped taking the assigned study drug before the end of the study, during a median of 117 days of follow-up after discontinuation, primary events occurred in 81 patients in the rivaroxaban group (4.7% per year) and in 66 patients in the warfarin group (4.3% per year) (P=0.58). (Details regarding the time to events in patients who completed the study and were switched to standard medical therapy are provided in Fig. 2 in the Supplementary Appendix.)

BLEEDING OUTCOMES

Major and clinically relevant nonmajor bleeding occurred in 1475 patients in the rivaroxaban group and in 1449 patients in the warfarin group (14.9% and 14.5% per year, respectively; hazard ratio in the rivaroxaban group, 1.03; 95% CI, 0.96 to 1.11; P=0.44) (Table 3). Rates of major bleeding were

similar in the rivaroxaban and warfarin groups (3.6% and 3.4%, respectively; P=0.58). Decreases in hemoglobin levels of 2 g per deciliter or more and transfusions were more common among patients in the rivaroxaban group, whereas fatal bleeding and bleeding at critical anatomical sites were less frequent. Rates of intracranial hemorrhage were significantly lower in the rivaroxaban group than in the warfarin group (0.5% vs. 0.7% per year; hazard ratio, 0.67; 95% CI, 0.47 to 0.93; P=0.02). Major bleeding from a gastrointestinal site was more common in the rivaroxaban group, with 224 bleeding events (3.2%), as compared with 154 events in the warfarin group (2.2%, P<0.001) (Table 2 in the Supplementary Appendix). (Data on nonhemorrhagic adverse events are provided in Table 3 in the Supplementary Appendix.)

SECONDARY EFFICACY OUTCOMES

The rates of secondary efficacy outcomes in the as-treated safety population are presented in Table 4 in the Supplementary Appendix. During treatment, myocardial infarction occurred in 101 patients in the rivaroxaban group and in 126 patients in the warfarin group (0.9% and 1.1% per year, respectively; hazard ratio in the rivaroxaban group, 0.81; 95% CI, 0.63 to 1.06; P=0.12). In the same analysis population, there were 208 deaths in the rivaroxaban group and 250 deaths in the warfarin group (1.9% and 2.2% per year, respectively; hazard ratio, 0.85; 95% CI, 0.70 to 1.02;
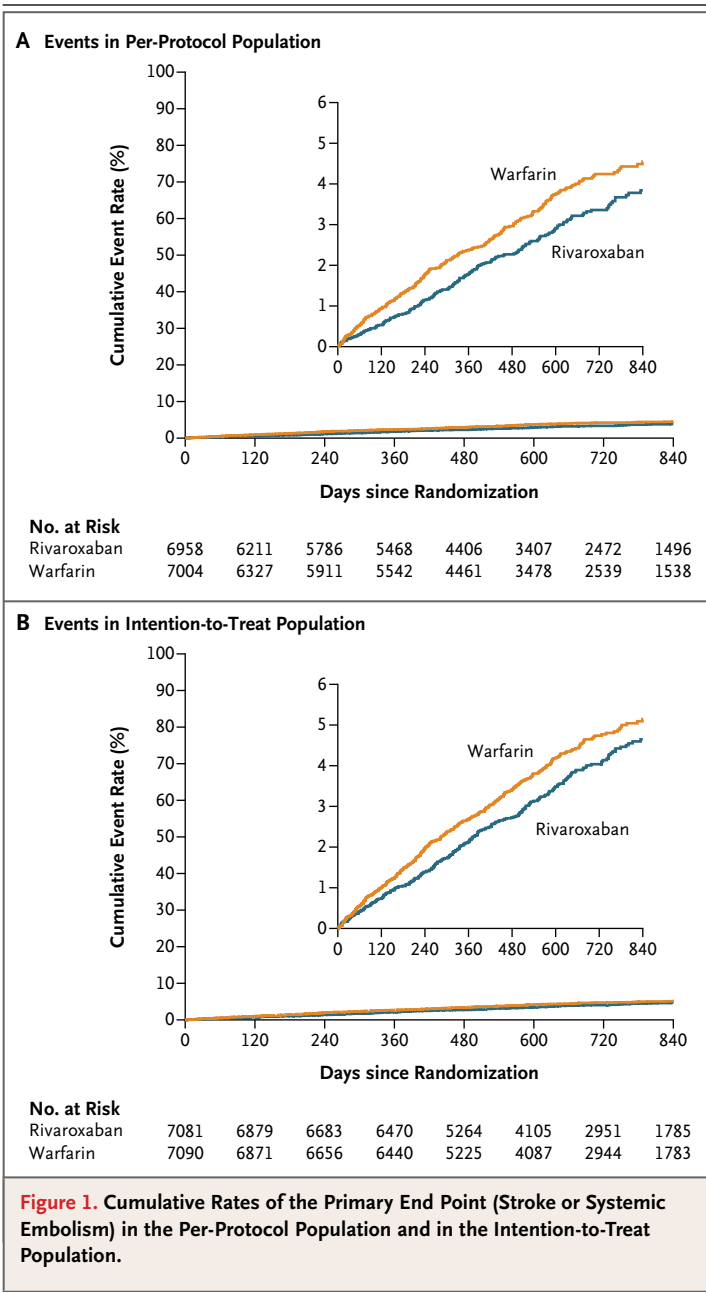
A Events in Per-Protocol Population

No. at Risk

Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538

B Events in Intention-to-Treat Population

No. at Risk

Rivaroxaban	7081	6879	6683	6470	5264	4105	2951	1785
Warfarin	7090	6871	6656	6440	5225	4087	2944	1783

Figure 1. Cumulative Rates of the Primary End Point (Stroke or Systemic Embolism) in the Per-Protocol Population and in the Intention-to-Treat Population.

thermore, the effect of rivaroxaban did not differ across quartiles of the duration of time that INR values were within the therapeutic range according to study center (P=0.74 for interaction) (Table 5 in the Supplementary Appendix). Within the highest quartile according to center, the hazard ratio with rivaroxaban versus warfarin was 0.74 (95% CI, 0.49 to 1.12).

DISCUSSION

In this randomized trial, we compared rivaroxaban with warfarin for the prevention of stroke or systemic embolism among patients with nonvalvular atrial fibrillation who were at moderate-to-high risk for stroke. In both the primary analysis, which included patients in the per-protocol population, and in the intention-to-treat analysis, we found that rivaroxaban was noninferior to warfarin. In the primary safety analysis, there was no significant difference between rivaroxaban and warfarin with respect to rates of major or nonmajor clinically relevant bleeding.

As prespecified in the statistical-analysis plan, we analyzed the trial data in a variety of ways because we anticipated that some patients would discontinue the study treatment and we wished to evaluate both noninferiority and superiority. Although an intention-to-treat analysis is the standard method for assessing superiority in a randomized trial, noninferiority is best established when patients are actually taking the randomized treatment.[16-19] Thus, the primary analysis was performed in the per-protocol population during receipt of the randomly assigned therapy. In the intention-to-treat population, we found no significant between-group difference in a conventional superiority analysis. In contrast, in the analyses of patients receiving at least one dose of a study drug who were followed for events during treatment, we found that rivaroxaban was superior to warfarin. The difference between these results reflects the fact that among patients who discontinued therapy before the conclusion of the trial, no significant difference in outcomes would have been anticipated, and none was seen.

The most worrisome complication of anticoagulation is bleeding. Rates of major and nonmajor clinically relevant bleeding, the main measure of treatment safety, were similar in the rivaroxaban and warfarin groups. Bleeding that proved fatal or involved a critical anatomical site occurred less frequently in the rivaroxaban group, mainly

P=0.07). In addition, in the intention-to-treat analysis throughout the trial, there were 582 deaths in the rivaroxaban group and 632 deaths in the warfarin group (4.5% and 4.9% per year, respectively; hazard ratio, 0.92; 95% CI, 0.82 to 1.03; P=0.15).

SELECTED SUBGROUP ANALYSES

The effect of rivaroxaban, as compared with warfarin, in both efficacy and safety analyses was consistent across all prespecified subgroups (Fig. 3, 4, and 5 in the Supplementary Appendix). Fur-

because of lower rates of hemorrhagic stroke and other intracranial bleeding. In contrast, bleeding from gastrointestinal sites, including upper, lower, and rectal sites, occurred more frequently in the rivaroxaban group, as did bleeding that led to a drop in the hemoglobin level or bleeding that required transfusion. Even though patients in our trial were at increased risk for bleeding events, rates of major bleeding were similar to those in other recent studies involving patients with atrial fibrillation.[4,15,22,23]

Among patients in our study who survived and did not reach the primary end point, the rate of premature, permanent cessation of randomized treatment (14.3% in year 1) was slightly higher than in other studies (average, 11%).[15,23] This may have been a consequence of the trial's double-blind design or the inclusion of patients with more co-existing illnesses. Among patients who permanently discontinued their assigned treatment before the end of the study, only about half were treated thereafter with a vitamin K antagonist. This observation suggests that for at least some of the patients who participated in the trial, the risks of open-label therapy with currently available anticoagulants were ultimately judged to outweigh the risk of stroke or systemic embolism. Event rates were similar at 30 days and 1 year after withdrawal, suggesting that the mechanism of events did not involve hypercoagulability early after withdrawal of rivaroxaban. Events occurring at the end of the study were probably related to increased difficulty in achieving the transition from blinded trial therapy to the open-label use of a vitamin K antagonist when the patient had previously been assigned to the rivaroxaban group, since presumably many patients who had previously been assigned to the warfarin group would have already had a therapeutic INR.

Among patients in the warfarin group, the proportion of time in which the intensity of anticoagulation was in the therapeutic range (mean, 55%), which was calculated from all INR values during the study and for 7 days after warfarin interruptions, was lower than in previous studies of other new anticoagulants in patients with atrial fibrillation (range, 64 to 68%). Among these trials, the only study of blinded treatment was limited to North American sites, which may have facilitated trial compliance.[15] Most earlier trials of warfarin included fewer high-risk patients,[3] and no previous studies addressed patient populations with overall levels of coexisting illnesses and geographic diver-

Figure 2. Cumulative Rates of the Primary End Point during Treatment and after Discontinuation in the Intention-to-Treat Population.
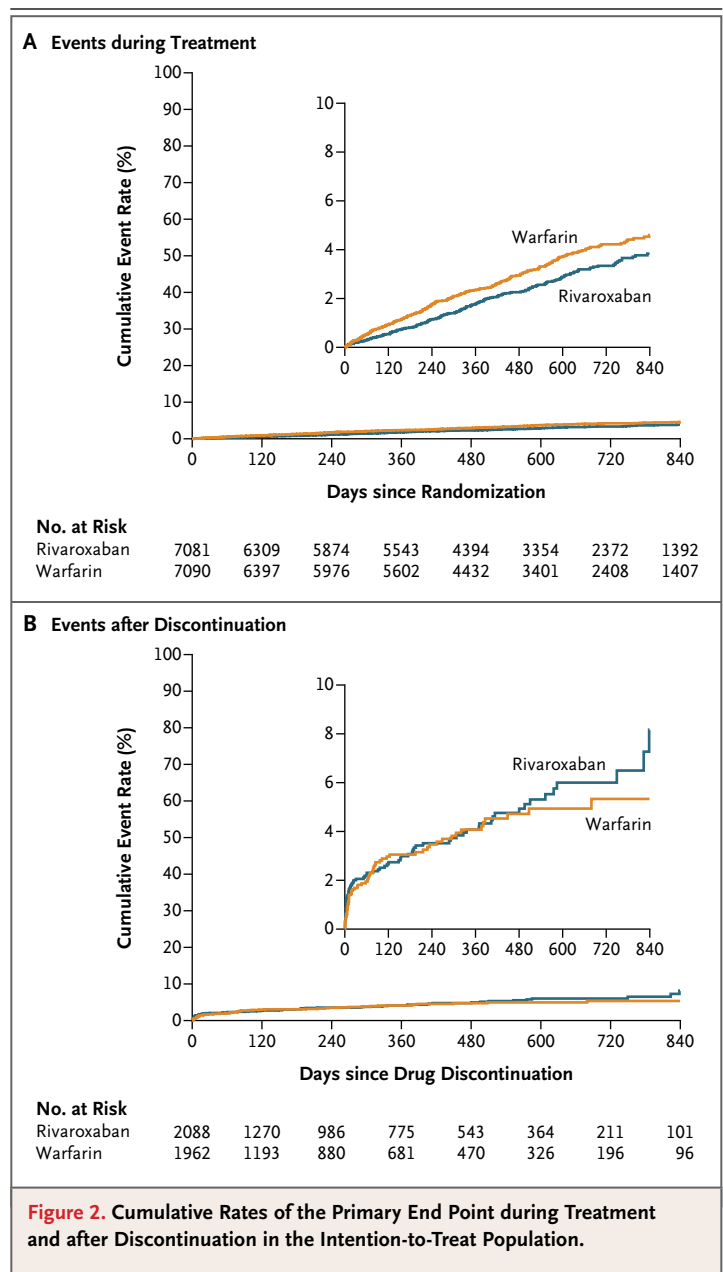
sity that were similar to those of the patients in our study.[24] Significant variations in the duration of time in the therapeutic range may reflect regional differences and differential skill in managing warfarin.[25] In a recent analysis of anticoagulation management involving more than 120,000 patients in the Veterans Affairs health care system, the mean proportion of time in the therapeutic range was 58%, with significant variation across sites.[24] The efficacy of rivaroxaban, as compared with warfarin, was as favorable in centers with the best INR control as in those with poorer control.

Table 3. Rates of Bleeding Events.*

Variable	Rivaroxaban (N=7111)		Warfarin (N=7125)		Hazard Ratio (95% CI)†	P Value‡
	Events	Event Rate	Events	Event Rate		
	no. (%)	no./100 patient-yr	no. (%)	no./100 patient-yr		
Principal safety end point: major and nonmajor clinically relevant bleeding§	1475 (20.7)	14.9	1449 (20.3)	14.5	1.03 (0.96–1.11)	0.44
Major bleeding						
Any	395 (5.6)	3.6	386 (5.4)	3.4	1.04 (0.90–1.20)	0.58
Decrease in hemoglobin ≥2 g/dl	305 (4.3)	2.8	254 (3.6)	2.3	1.22 (1.03–1.44)	0.02
Transfusion	183 (2.6)	1.6	149 (2.1)	1.3	1.25 (1.01–1.55)	0.04
Critical bleeding¶	91 (1.3)	0.8	133 (1.9)	1.2	0.69 (0.53–0.91)	0.007
Fatal bleeding	27 (0.4)	0.2	55 (0.8)	0.5	0.50 (0.31–0.79)	0.003
Intracranial hemorrhage	55 (0.8)	0.5	84 (1.2)	0.7	0.67 (0.47–0.93)	0.02
Nonmajor clinically relevant bleeding	1185 (16.7)	11.8	1151 (16.2)	11.4	1.04 (0.96–1.13)	0.35

* All analyses of rates of bleeding are based on the first event in the safety population during treatment.
† Hazard ratios are for the rivaroxaban group as compared with the warfarin group and were calculated with the use of Cox proportional-hazards models with the study group as a covariate.
‡ Two-sided P values are for superiority in the rivaroxaban group as compared with the warfarin group.
§ Minimal bleeding events were not included in the principal safety end point.
¶ Bleeding events were considered to be critical if they occurred in intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular (with compartment syndrome), or retroperitoneal sites.

In conclusion, in this trial comparing a once-daily, fixed dose of rivaroxaban with adjusted-dose warfarin in patients with nonvalvular atrial fibrillation who were at moderate-to-high risk for stroke, rivaroxaban was noninferior to warfarin in the prevention of subsequent stroke or systemic embolism. There were no significant differences in rates of major and clinically relevant nonmajor bleeding between the two study groups, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.

REFERENCES

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983-8.

2. Idem. Atrial fibrillation: a major contributor to stroke in the elderly: the Framingham Study. Arch Intern Med 1987;147:1561-4.

3. 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.

4. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857-67.

5. Singer DE, Albers GW, Dalen JE, Go AS, Halperin JL, Manning WJ. Antithrombotic therapy in atrial fibrillation: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:Suppl:429S-456S.

6. Albers GW, Yim JM, Belew KM, et al. Status of antithrombotic therapy for patients with atrial fibrillation in university hospitals. Arch Intern Med 1996;156:2311-6.

7. Go AS, Hylek EM, Borowsky LH, Phillips KA, Selby JV, Singer DE. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. Ann Intern Med 1999;131:927-34.

8. Piccini JP, Hernandez AF, Zhao X, et al. Quality of care for atrial fibrillation among patients hospitalized for heart failure. J Am Coll Cardiol 2009;54:1280-9.

9. Kubitza D, Becka M, Wensing G, Voith B, Zuehlsdorf M. Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939 — an oral, direct Factor Xa inhibitor — after multiple dosing in healthy male subjects. Eur J Clin Pharmacol 2005;61:873-80.

10. Kubitza D, Becka M, Roth A, Mueck W. Dose-escalation study of the pharmacokinetics and pharmacodynamics of rivaroxaban in healthy elderly subjects. Curr Med Res Opin 2008;24:2757-65.

11. Eriksson BI, Borris LC, Friedman RJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med 2008;358:2765-75.

12. Lassen MR, Ageno W, Borris LC, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med 2008;358:2776-86.

13. The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363:2499-510.

14. ROCKET AF Study Investigators. 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(3):340.e1-347.e1.

15. Albers GW, Diener HC, Frison L, et al. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. JAMA 2005;293:690-8.

16. Matilde Sanchez M, Chen X. Choosing the analysis population in non-inferiority studies: per protocol or intent-to-treat. Stat Med 2006;25:1169-81.

17. Brittain E, Lin D. A comparison of intent-to-treat and per-protocol results in antibiotic non-inferiority trials. Stat Med 2005;24:1-10.

18. Draft: Guidance for Industry: non-inferiority clinical trials. Silver Spring, MD: Food and Drug Administration, 2010. (http://www.fda.gov/Drugs/Guidance ComplianceRegulatoryInformation/Guidances/default.htm.)

19. Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. JAMA 2006;295:1152-60. [Erratum, JAMA 2006;296:1842.]

20. Soulakova JN. Comparison of several testing strategies for combination drug efficacy trials based on the closure principle. Stat Med 2009;28:260-73.

21. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993;69:236-9.

22. Connolly S, Pogue J, Hart R, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet 2006;367:1903-12.

23. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51. [Erratum, N Engl J Med 2010;363:1877.]

24. Rose AJ, Hylek EM, Ozonoff A, Ash AS, Reisman JI, Berlowitz DR. Risk-adjusted percent time in therapeutic range as a quality indicator for outpatient oral anticoagulation: results of the Veterans Affairs Study to Improve Anticoagulation (VARIA). Circ Cardiovasc Qual Outcomes 2011;4:22-9.

25. Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet 2010;376:975-83.

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