ORIGINAL ARTICLE

Rivaroxaban in Patients with Atrial Fibrillation and a Bioprosthetic Mitral Valve

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ABSTRACT

BACKGROUND

The effects of rivaroxaban in patients with atrial fibrillation and a bioprosthetic mitral valve remain uncertain.

METHODS

In this randomized trial, we compared rivaroxaban (20 mg once daily) with dose-adjusted warfarin (target international normalized ratio, 2.0 to 3.0) in patients with atrial fibrillation and a bioprosthetic mitral valve. The primary outcome was a composite of death, major cardiovascular events (stroke, transient ischemic attack, systemic embolism, valve thrombosis, or hospitalization for heart failure), or major bleeding at 12 months.

RESULTS

A total of 1005 patients were enrolled at 49 sites in Brazil. A primary-outcome event occurred at a mean of 347.5 days in the rivaroxaban group and 340.1 days in the warfarin group (difference calculated as restricted mean survival time, 7.4 days; 95% confidence interval [CI], –1.4 to 16.3; P<0.001 for noninferiority). Death from cardiovascular causes or thromboembolic events occurred in 17 patients (3.4%) in the rivaroxaban group and in 26 (5.1%) in the warfarin group (hazard ratio, 0.65; 95% CI, 0.35 to 1.20). The incidence of stroke was 0.6% in the rivaroxaban group and 2.4% in the warfarin group (hazard ratio, 0.25; 95% CI, 0.07 to 0.88). Major bleeding occurred in 7 patients (1.4%) in the rivaroxaban group and in 13 (2.6%) in the warfarin group (hazard ratio, 0.54; 95% CI, 0.21 to 1.35). The frequency of other serious adverse events was similar in the two groups.

CONCLUSIONS

In patients with atrial fibrillation and a bioprosthetic mitral valve, rivaroxaban was noninferior to warfarin with respect to the mean time until the primary outcome of death, major cardiovascular events, or major bleeding at 12 months. (Funded by PROADI-SUS and Bayer; RIVER ClinicalTrials.gov number, NCT02303795.)

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*A list of the RIVER investigators and committee members is provided in the Supplementary Appendix, available at NEJM.org.

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Patients with atrial fibrillation and a bioprosthetic mitral valve require long-term anticoagulation,[1,2] but questions remain about the most effective therapeutic strategy.[3,4] Recommendations for the use of vitamin K antagonists in patients with bioprosthetic valves are guided by limited evidence from randomized trials.[1,5,6] The efficacy and safety of direct oral anticoagulants in patients with atrial fibrillation and a bioprosthetic mitral valve are based on subgroup analyses of pivotal trials of apixaban and edoxaban that included a total of 31 and 131 patients, respectively, and on the findings of a pilot trial of dabigatran that enrolled 27 patients.[7-9]

Rivaroxaban was shown to be noninferior to warfarin for the prevention of stroke or systemic embolism in 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),[10] but patients with bioprosthetic valves were excluded from the trial. Therefore, we conducted the Rivaroxaban for Valvular Heart Disease and Atrial Fibrillation (RIVER) trial to assess the efficacy and safety of rivaroxaban as compared with warfarin in patients with atrial fibrillation and a bioprosthetic mitral valve.

METHODS

TRIAL OVERSIGHT

This multicenter trial had a randomized, noninferiority, open-label design with blinded adjudication of outcomes, as led by an academic steering committee.[11] The trial protocol (available with the full text of this article at NEJM.org) was approved by the institutional ethics board at each participating site. An independent data and safety monitoring board reviewed unblinded patient-level data for safety on an ongoing basis during the trial. Data were gathered by trained research personnel at 49 sites in Brazil. This investigator-initiated trial was supported by the Brazilian Ministry of Health (Programa de Apoio ao Desenvolvimento Institucional do Sistema Único de Saúde [PROADI-SUS]) and Bayer. The funders had no role in the conduct of the trial, in the interpretation of the data, or in the decision to submit the manuscript for publication.

The initial draft of the manuscript was written by the first, second, and last authors, who had full access to all the data and revised the manuscript on the basis of comments from the coauthors. All the analyses were conducted by the academic coordinating center for the trial. All the authors made the decision to submit the manuscript for publication and vouch for the integrity, accuracy, and completeness of the data and for the fidelity of the trial to the protocol. No one who is not an author contributed to the writing of the manuscript.

PATIENTS

We included in the trial adults (≥18 years of age) who had permanent, paroxysmal, or persistent atrial fibrillation or flutter and a bioprosthetic mitral valve and who were receiving (or planning to receive) oral anticoagulation for thromboembolism prophylaxis. Patients were eligible for inclusion in the trial at any time at least 48 hours after undergoing mitral-valve surgery. The main exclusion criteria were a contraindication to either rivaroxaban or warfarin, an extremely high risk of bleeding, transient atrial fibrillation caused by surgery, and the placement of mechanical valves. Details regarding the eligibility criteria are provided in Table S1 in the Supplementary Appendix, available at NEJM.org. All the patients provided written informed consent.

TRIAL PROCEDURES

Eligible patients were randomly assigned to receive rivaroxaban or warfarin in a 1:1 ratio in permuted blocks of variable size that were stratified according to site with the use of a central concealed, Web-based, automated randomization system. Patients were assigned to receive oral rivaroxaban at a dose of 20 mg once daily; those with a calculated creatinine clearance of 30 to 49 ml per minute per 1.73 m^2 of body-surface area received a reduced dose of 15 mg once daily. In patients assigned to receive warfarin, the dose was adjusted to maintain a target international normalized ratio (INR) of 2.0 to 3.0. The INR was measured at least every 4 weeks. In the warfarin group, the method of Rosendaal et al.[12] was used to calculate the overall time that INR values fell within the therapeutic range.

Baseline assessments included demographic characteristics, risk factors, medical history, and laboratory data. Follow-up was scheduled at 30 days and then at 3, 6, 9, and 12 months to identify any outcome events or procedures that had occurred and to assess vital status.

Stroke and bleeding risks were assessed with the use of two scores. The first was the score on the CHA_2DS_2-VASc scale, which provides weighted scores on the basis of the presence of congestive heart failure, hypertension, diabetes mellitus, or vascular disease; a history of stroke or TIA; an age of 65 to 74 years or 75 years or older; and sex. This scale, which is used to evaluate patients with atrial fibrillation who are not receiving anticoagulant therapy, ranges from 0 to 9, with scores above 1 considered to indicate high risk. The second was the score on the HAS-BLED scale, which reflects the risk of bleeding among patients with atrial fibrillation who are receiving anticoagulant therapy; scores range from 0 to 9, with higher scores indicating greater risk.

PRIMARY AND SECONDARY OUTCOMES

All suspected trial outcomes were adjudicated by an independent clinical-events committee, whose members were unaware of the trial group assignments. Details regarding the outcome definitions are provided in the Supplementary Appendix.

The primary outcome was a composite of death, major cardiovascular events, or major bleeding at 12 months. Major cardiovascular events were stroke, transient ischemic attack (TIA), valve thrombosis, systemic embolism not related to the central nervous system (CNS), or hospitalization for heart failure. The key secondary efficacy outcome was a composite of death from cardiovascular causes or thromboembolic events (stroke, TIA, deep venous thrombosis, pulmonary embolism, valve thrombosis, or systemic embolism not related to the CNS). We also report results for the individual components of the composite primary and secondary efficacy outcomes. Safety outcomes were bleeding events (major, clinically relevant nonmajor, minor, and total). Bleeding events were classified according to the ROCKET AF trial criteria[10] (main analysis for safety) and the criteria of the Thrombolysis in Myocardial Infarction (TIMI) and Bleeding Academic Research Consortium (BARC).[13]

STATISTICAL ANALYSIS

We included all the patients who had undergone randomization in the primary analysis, according to the intention-to-treat principle. We calculated the baseline categorical variables as relative and absolute frequencies and continuous variables as mean (±SD) values or median values and interquartile ranges. Results for the primary outcome are reported according to restricted mean survival time (RMST).[14] We used the Kaplan–Meier method to calculate the RMST, which represents the mean time free from an outcome event up to a prespecified time point and thus reflects the area under the survival curve.[15-17] Details regarding the statistical methods are provided in the Supplementary Appendix.[18] In this case, the treatment effect is presented as a between-group difference in the RMST (rivaroxaban minus warfarin), so negative values indicate an increased risk from rivaroxaban treatment. The RMST method was selected because it is not dependent on the number of events and on the assumption of proportional hazards, as is the case in time-to-event analyses. In addition, we performed two other analyses of the primary outcome. In the as-treated analysis, data for patients were analyzed according to the treatment received (i.e., patients in the rivaroxaban group who received warfarin in error or were intentionally switched were evaluated in the warfarin group and vice versa). The per-protocol analysis included all the patients who had undergone randomization with the exception of those with major protocol deviations that occurred before enrollment or while they were receiving either treatment.

We calculated that the enrollment of 1000 patients would provide a power of approximately 80% to detect a noninferiority margin of 8 days in the primary analysis, assuming an event rate of 14.5% in the warfarin group, with a hazard ratio of 0.79 and an alpha level of 5%. At the time the trial was designed, no reliable data were available to assess the effects of direct oral anticoagulants in patients with atrial fibrillation and a bioprosthetic valve. Therefore, we estimated the effect size on the basis of the findings from ROCKET AF of rivaroxaban,[10] which was the best available evidence. We estimated event rates using ROCKET AF data and unpublished data from institutional databases in Brazil. On the basis of these data, the executive committee determined that a between-group difference of 8 days in the RMST (approximately 2% of 365 days) was an appropriate noninferiority margin. A similar threshold has been used previously in cardiovascular trials.[15]

We created Kaplan–Meier survival curves to express the time until the occurrence of secondary outcomes and calculated hazard ratios derived

from Cox regression models to express treatment effects. We used the RMST method to perform analyses of the secondary efficacy and safety outcomes. The widths of the 95% confidence intervals that were estimated for all effect measures of secondary outcomes have not been adjusted for multiple comparisons, so inferences drawn from these analyses may not be reproducible. Subgroup analyses were performed with respect to age, sex, concomitant antiplatelet use, time from mitral-valve implantation, and renal function. All analyses were performed with the use of R software (R Foundation for Statistical Computing).

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Rivaroxaban (N=500)	Warfarin (N=505)	All Patients (N=1005)
Age			
Mean — yr	59.4±2.4	59.2±11.8	59.3±12.1
≥65 yr — no. (%)	179 (35.8)	176 (34.9)	355 (35.3)
Female sex — no. (%)	311 (62.2)	296 (58.6)	607 (60.4)
Medical history — no. (%)			
Diabetes mellitus	74 (14.8)	64 (12.7)	138 (13.7)
Hypertension	308 (61.6)	302 (59.8)	610 (60.7)
Dyslipidemia	176 (35.2)	162 (32.1)	338 (33.6)
Percutaneous valve intervention	39 (7.8)	37 (7.3)	76 (7.5)
Myocardial infarction	24 (4.8)	24 (4.8)	48 (4.7)
Percutaneous coronary intervention	16 (3.2)	16 (3.2)	32 (3.1)
Myocardial revascularization	27 (5.4)	19 (3.8)	46 (4.5)
Stroke	63 (12.6)	66 (13.1)	129 (12.8)
Transient ischemic attack	12 (2.4)	14 (2.8)	26 (2.5)
Peripheral vascular disease	10 (2.0)	6 (1.2)	16 (1.5)
Carotid artery disease	8 (1.6)	7 (1.4)	15 (1.4)
Congestive heart failure	202 (40.4)	188 (37.2)	390 (38.8)
Chronic kidney disease†	7 (1.4)	11 (2.2)	18 (1.7)
Current smoker — no. (%)	16 (3.2)	23 (4.6)	39 (3.8)
Median body-mass index (IQR)‡	26.6 (23.4–29.9)	25.5 (22.8–29.3)	26.0 (23.2–29.7)
Race or ethnic group — no. (%)§			
White	294 (58.8)	270 (53.5)	564 (56.1)
Black	63 (12.6)	69 (13.7)	132 (13.1)
Multiracial	138 (27.6)	159 (31.5)	297 (29.5)
Asian	5 (1.0)	7 (1.4)	12 (1.1)
Type of atrial rhythm — no. (%)			
Paroxysmal fibrillation	114 (22.8)	109 (21.6)	223 (22.2)
Permanent fibrillation	311 (62.2)	310 (61.4)	621 (61.7)
Persistent fibrillation	55 (10.9)	62 (12.3)	117 (11.6)
Flutter	20 (4.0)	24 (4.8)	44 (4.3)
Median serum creatinine (IQR) — mg/dl	0.9 (0.7–1.1)	0.9 (0.7–1.1)	0.9 (0.7–1.1)
Median creatinine clearance (IQR) — ml/min	77.4 (58.8–95.7)	77.7 (59.1–96.8)	77.5 (58.9–96.0)
Mean CHA_2DS_2-VASc score¶	2.7±1.5	2.5±1.3	2.6±1.4
Mean HAS-BLED score‖	1.6±0.6	1.6±0.9	1.6±0.9

Table 1. (Continued)

Characteristic	Rivaroxaban (N=500)	Warfarin (N=505)	All Patients (N=1005)
Interval between mitral-valve implantation and randomization — no. (%)			
<3 mo	94 (18.8)	95 (18.8)	189 (18.8)
3 mo to <1 yr	91 (18.2)	78 (15.4)	169 (16.8)
1 yr to <5 yr	160 (32.0)	164 (32.5)	324 (32.2)
5 yr to <10 yr	148 (29.6)	160 (31.7)	308 (30.6)
Missing data	7 (1.4)	8 (1.6)	15 (1.4)

* Plus–minus values are means ±SD. To convert the values for creatinine to micromoles per liter, multiply by 88.4. IQR denotes interquartile range.
† Chronic kidney disease was defined as a creatinine level of more than 1.5 mg per deciliter.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Race or ethnic group was determined by the investigator and recorded on the case-report form.
¶ Scores on the CHA_2DS_2-VASc scale reflect the risk of stroke, with values ranging from 0 to 9 and with higher scores indicating greater risk.
‖ HAS-BLED scores reflect the risk of major bleeding among patients with atrial fibrillation who are receiving anticoagulant therapy, with values ranging from 0 to 9 and with higher scores indicating greater risk.

RESULTS

PATIENTS AND FOLLOW-UP

From April 14, 2016, through July 22, 2019, a total of 1005 patients were enrolled and randomly assigned to receive either rivaroxaban (500 patients) or warfarin (505 patients) (Fig. S1). Twelve-month data were missing owing to a loss of follow-up for 6 patients (0.6%). No patients withdrew consent.

The two groups were well balanced with respect to baseline characteristics (Table 1). The median age was 59.3 years; 60.4% of the patients were women. Of the trial patients, 60.7% had hypertension, 38.8% had heart failure, and 15.4% had a history of stroke or TIA. A total of 95.6% of the patients had atrial fibrillation, and 4.3% had atrial flutter. The mean (±SD) risk score for stroke from atrial fibrillation was 2.6±1.4 on the CHA_2DS_2-VASc scale. Data regarding the patients' medication use at baseline are provided in Table S2. The interval between mitral-valve surgery and randomization was less than 3 months for 18.8% of the patients, between 3 months and less than 1 year for 16.8%, between 1 year and less than 5 years for 32.2%, and 5 years or more for 30.6%; data were missing for 1.6% of the patients.

TRIAL DRUGS

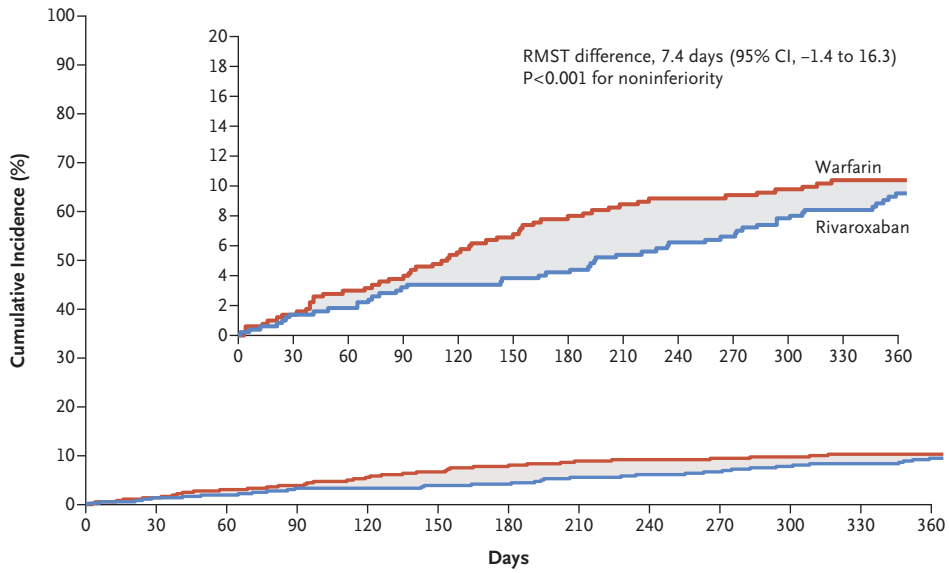
Permanent discontinuation of either rivaroxaban or warfarin was reported in 52 patients (10.4%) in the rivaroxaban group and in 36 (7.1%) in the warfarin group (Table S3). Patients in the warfarin group had an INR in the therapeutic range (2.0 to 3.0) for a median of 65.5% (interquartile range, 51.3 to 70.5) of the time.

PRIMARY OUTCOME

The mean time until a primary-outcome event was 347.5 days in the rivaroxaban group and 340.1 days in the warfarin group (RMST difference, 7.4 days; 95% confidence interval [CI], –1.4 to 16.3; P<0.001 for noninferiority and P=0.10 for superiority) (Fig. 1, Fig. S2, and Table S4). In the as-treated analysis, the mean time until a primary-outcome event was 350.1 days in the rivaroxaban group and 339.6 days in the warfarin group (RMST difference, 10.5 days; 95% CI, 1.9 to 19.1); in the per-protocol analysis, the time until the event was 356.7 days and 347.1 days, respectively (RMST difference, 9.6 days; 95% CI, 2.2 to 16.9).

SECONDARY OUTCOMES

At 12 months, the composite secondary outcome of death from cardiovascular causes or thromboembolic events occurred in 17 patients (3.4%) in the rivaroxaban group and in 26 (5.1%) in the warfarin group (hazard ratio, 0.65; 95% CI, 0.35 to 1.20) (Table 2). The incidence of total stroke was 0.6% in the rivaroxaban group and 2.4% in the warfarin group (hazard ratio, 0.25; 95% CI,



No. at Risk													
Warfarin	505	496	487	483	474	469	463	458	456	455	450	445	346
Rivaroxaban	500	493	491	484	483	481	479	473	469	466	459	453	340

Figure 1. Kaplan–Meier Analysis of the Primary Outcome.

Shown is the primary outcome (death, major cardiovascular events, or major bleeding) in the rivaroxaban group and the warfarin group, as calculated according to the restricted mean survival time (RMST) method. The inset shows the same data on an expanded y axis.

0.07 to 0.88). Valve thrombosis occurred in 5 patients in the rivaroxaban group and in 3 in the warfarin group (1.0% vs. 0.6%). Other secondary efficacy outcomes were not significantly different in the two groups. Results of analyses by means of RMST calculations for secondary efficacy outcomes were consistent with the results of the time-to-event analyses (Table S5).

SAFETY EVENTS

With respect to bleeding events at 12 months, major bleeding occurred in 7 patients (1.4%) in the rivaroxaban group and in 13 (2.6%) in the warfarin group (hazard ratio, 0.54; 95% CI, 0.21 to 1.35) (Table 3). The incidence of clinically relevant nonmajor bleeding was similar in the rivaroxaban group and the warfarin group (4.8% and 4.6%, respectively). There were no reported intracranial bleeding events in the rivaroxaban group and 5 (1.0%) in the warfarin group. Similarly, the incidence of fatal bleeding was 0% in the rivaroxaban group and 0.4% in the warfarin group. The incidence of total bleeding events was not significantly different in the two groups. The results were similar for bleeding events according to TIMI and BARC criteria (Table S6). The results of analyses that used the RMST method to evaluate bleeding outcomes were consistent with those in the time-to-event analyses (Table S7). Other serious adverse events occurred in similar percentages of patients in the rivaroxaban and warfarin groups (5.8% vs. 6.9%) (Table S8).

SUBGROUP ANALYSES

Results for the primary outcome were generally consistent across most subgroups (Fig. 2 and Tables S9 and S10). Among the patients who underwent randomization up to 3 months after mitral-valve surgery, the mean time until a primary-outcome event was 348.6 days in the rivaroxaban group and 313.5 days in the warfarin group (RMST difference, 35.1 days; 95% CI, 8.6 to 61.7). Similarly, in this subgroup, the incidence of a primary-outcome event was 6.4% in the rivaroxaban group and 18.9% in the warfarin group (hazard ratio, 0.31; 95% CI, 0.12 to 0.79).

Table 2. Secondary Efficacy Outcomes.*

Secondary Outcome	Rivaroxaban (N=500)		Warfarin (N=505)		Hazard Ratio (95% CI)†
	no. (%)	*rate per 100 patient-yr*	*no. (%)*	*rate per 100 patient-yr*	
Death from cardiovascular causes or thromboembolic events — no. (%)‡	17 (3.4)	3.53	26 (5.1)	5.44	0.65 (0.35–1.20)
Stroke					
Any	3 (0.6)	0.62	12 (2.4)	2.50	0.25 (0.07–0.88)
Nonfatal	2 (0.4)	0.41	10 (2.0)	2.09	0.20 (0.04–0.91)
Fatal	1 (0.2)	0.20	2 (0.4)	0.39	0.50 (0.05–5.50)
Hemorrhagic	0	0	5 (1.0)	1.03	NA
Ischemic	3 (0.6)	0.62	7 (1.4)	1.45	0.43 (0.11–1.66)
Transient ischemic attack	0	0	1 (0.2)	0.21	NA
Death					
Any	20 (4.0)	4.12	20 (4.0)	4.11	1.01 (0.54–1.87)
From cardiovascular causes	11 (2.2)	2.27	13 (2.6)	2.67	0.85 (0.38–1.90)
Valve thrombosis	5 (1.0)	1.04	3 (0.6)	0.62	1.68 (0.40–7.01)
Non-CNS systemic embolism	0	0	1 (0.2)	0.21	NA
Hospitalization for heart failure	22 (4.4)	4.43	19 (3.8)	3.78	1.15 (0.62–2.13)

* CI denotes confidence interval, CNS central nervous system, and NA not applicable.
† The hazard ratios were calculated by a Cox proportional-hazards model.
‡ This outcome was a composite of death from cardiovascular causes, stroke, transient ischemic attack, valve thrombosis, venous thromboembolism, or non-CNS systemic embolism.

Table 3. Bleeding End Points.*

Bleeding Event	Rivaroxaban (N=500)		Warfarin (N=505)		Hazard Ratio (95% CI)†
	no. (%)	*rate per 100 patient-yr*	*no. (%)*	*rate per 100 patient-yr*	
Any bleeding	65 (13.0)	14.71	78 (15.4)	17.99	0.83 (0.59–1.15)
Major bleeding	7 (1.4)	1.46	13 (2.6)	2.72	0.54 (0.21–1.35)
Intracranial bleeding	0	0	5 (1.0)	1.03	NA
Fatal bleeding	0	0	2 (0.4)	0.41	NA
Clinically relevant nonmajor bleeding	24 (4.8)	5.12	23 (4.6)	4.87	1.05 (0.60–1.87)
Minor bleeding	37 (7.4)	8.03	49 (9.7)	10.84	0.75 (0.49–1.15)

* The incidence of all bleeding events was estimated according to the criteria of 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). The listed events were analyzed on the basis of the randomized group assignment.
† Hazard ratios were calculated by means of a Cox proportional-hazards model.

DISCUSSION

In the RIVER trial involving patients with atrial fibrillation who had undergone bioprosthetic mitral-valve surgery, those who received rivaroxaban for 1 year were free of a composite primary outcome of death, major cardiovascular events, or major bleeding for a mean of 7.4 days longer than their counterparts who received warfarin. In addition, the confidence interval for the pri-

Subgroup	Rivaroxaban	Warfarin	Rivaroxaban	Warfarin
	no. of events/total no. (%)		*no. of days until outcome (95% CI)*	
All patients	47/500 (9.4)	52/505 (10.3)	347.5 (341.8–353.1)	340.1 (333.2–346.9)
Age				
<65 yr	28/321 (8.7)	30/329 (9.1)	349.0 (342.1–355.8)	342.2 (334.0–350.5)
≥65 yr	19/179 (10.6)	22/176 (12.5)	344.8 (335.0–354.7)	336.0 (323.8–348.3)
Sex				
Male	20/189 (10.6)	25/209 (12.0)	345.2 (335.4–355.0)	333.6 (321.6–345.6)
Female	27/311 (8.7)	27/296 (9.1)	348.9 (342.0–355.7)	344.6 (336.6–352.6)
Antiplatelet therapy at baseline				
No	41/425 (9.6)	39/441 (8.8)	346.7 (340.4–353.0)	344.1 (337.4–350.8)
Yes	6/75 (8.0)	13/64 (20.3)	352.2 (340.3–364.0)	312.3 (284.6–339.9)
Time since mitral-valve implantation				
<3 mo	6/94 (6.4)	18/95 (18.9)	348.6 (335.1–362.1)	313.5 (290.6–336.3)
3 mo to <1 yr	6/91 (6.6)	4/78 (5.1)	351.3 (339.3–363.3)	355.1 (344.6–365.6)
1 yr to <5 yr	7/160 (4.4)	14/164 (8.5)	356.2 (348.8–363.6)	348.6 (339.4–357.7)
≥5 yr	27/148 (18.2)	16/160 (10.0)	336.3 (324.1–348.5)	338.6 (326.2–351.1)
Creatinine clearance (ml/min)				
≥50	33/361 (9.1)	36/358 (10.1)	346.8 (339.9–353.7)	340.2 (332.0–348.5)
<50	6/47 (12.8)	10/60 (16.7)	334.8 (310.6–359.0)	328.6 (306.0–351.2)

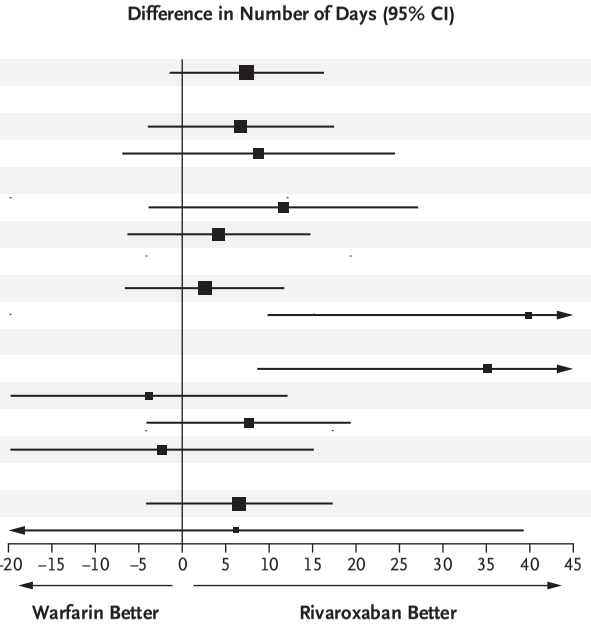


Figure 2. Subgroup Analysis of the Primary Outcome.

Shown is the primary outcome (death, major cardiovascular events, or major bleeding) in the rivaroxaban group and the warfarin group, according to the percentage of patients who had an outcome event at 12 months and the number of days until the outcome event, as calculated by the RMST method. The size of the squares showing the between-group difference in the number of days until a primary-outcome event is proportional to the number of patients who were included in the analysis of each subgroup.

mary analysis may have excluded an effect size of more than 1.4 days free from events favoring warfarin, which showed the noninferiority effect of rivaroxaban in this clinical setting.

Secondary efficacy outcomes were generally similar in the two groups; the incidence of total stroke was 0.6% with rivaroxaban and 2.4% with warfarin. The incidence of valve thrombosis was very low and similar in the two groups, as were incidences of bleeding (including major, nonmajor clinically relevant, and total events). Because of the low number of such events, these findings should be interpreted with caution. Nevertheless, the direction of effects was generally consistent with those observed in landmark randomized trials and meta-analyses that tested rivaroxaban and other direct oral anticoagulants involving patients with atrial fibrillation.[10,19-22] Moreover, the analyses of secondary outcomes with the use of RMST methods, which are not dependent on the number of events, yielded results that were consistent with the findings in the time-to-event analyses.

In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial,[7,23] only 31 of the 18,201 patients had a bioprosthetic mitral valve. Overall, there were no significant differences between apixaban and warfarin for any efficacy or safety outcomes in this population. In the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF–TIMI 48) trial,[8] of the 21,105 patients who were enrolled, 131 had undergone placement of a bioprosthetic mitral valve. Patients with bioprosthetic valves who received edoxaban had a significantly lower incidence of the primary clinical outcome than those who received warfarin. The incidence of major bleeding was similar among patients who received the 60-mg dose of edoxaban and those who received warfarin but was lower among those who received the 30-mg dose of edoxaban. Results from observational studies have been consistent with the findings from these trials.[24] It should be acknowledged that patients who had undergone recent (<3 months) bioprosthetic-valve implantation were excluded from both the ARISTOTLE and ENGAGE AF–TIMI 48 trials.

In a recent trial,[25] 218 patients who had undergone bioprosthetic-valve implantation or repair were randomly assigned receive either edoxaban or warfarin for 3 months, regardless of status regarding atrial fibrillation. The incidence of death, thromboembolic events, or intracardiac thrombosis was 0% in the edoxaban group and 3.7% in the warfarin group (P<0.001 for noninferiority of edoxaban). The incidence of major bleeding was similar in the two groups.

In the RIVER trial, which was specifically designed to assess the effects of a direct oral anticoagulant in patients with atrial fibrillation and a bioprosthetic mitral valve in a large population, we confirmed and extended the findings from previous evidence. Our findings provide new information with respect to the use of rivaroxaban within 3 months after mitral-valve surgery. However, findings in this subgroup should be interpreted with caution, and additional studies are needed. Until then, our trial provides important insights about the management of oral anticoagulation after mitral-valve surgery in patients with atrial fibrillation that may inform decisions in clinical practice. Since rivaroxaban does not require monitoring of the INR and has an anticoagulant effect that is more consistent and less influenced by food or concomitant medications than warfarin, it represents an attractive alternative for this patient population.

Our trial has some limitations. The open-label design could have introduced bias in the ascertainment or reporting of events. However, we have attempted to reduce this risk by the implementation of a blinded end-point adjudication process and regular training and monitoring of personnel at the trial sites. In addition, our findings cannot be extrapolated to patients with a bioprosthetic aortic valve or to those with mitral stenosis or with mechanical valves. Trials that have enrolled these populations are ongoing.[26,27] Finally, the as-treated and per-protocol analyses used restricted populations based on post-randomization variables such as adherence to the trial drugs, which could have influenced these results.

In conclusion, in patients with atrial fibrillation and a bioprosthetic mitral valve, rivaroxaban was noninferior to warfarin with respect to the mean time until the occurrence of major clinical events.

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APPENDIX

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