ORIGINAL ARTICLE

Rivaroxaban in Rheumatic Heart Disease–Associated Atrial Fibrillation

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ABSTRACT

BACKGROUND

Testing of factor Xa inhibitors for the prevention of cardiovascular events in patients with rheumatic heart disease–associated atrial fibrillation has been limited.

METHODS

We enrolled patients with atrial fibrillation and echocardiographically documented rheumatic heart disease who had any of the following: a CHA_2DS_2VASc score of at least 2 (on a scale from 0 to 9, with higher scores indicating a higher risk of stroke), a mitral-valve area of no more than 2 cm^2, left atrial spontaneous echo contrast, or left atrial thrombus. Patients were randomly assigned to receive standard doses of rivaroxaban or dose-adjusted vitamin K antagonist. The primary efficacy outcome was a composite of stroke, systemic embolism, myocardial infarction, or death from vascular (cardiac or noncardiac) or unknown causes. We hypothesized that rivaroxaban therapy would be noninferior to vitamin K antagonist therapy. The primary safety outcome was major bleeding according to the International Society of Thrombosis and Hemostasis.

RESULTS

Of 4565 enrolled patients, 4531 were included in the final analysis. The mean age of the patients was 50.5 years, and 72.3% were women. Permanent discontinuation of trial medication was more common with rivaroxaban than with vitamin K antagonist therapy at all visits. In the intention-to-treat analysis, 560 patients in the rivaroxaban group and 446 in the vitamin K antagonist group had a primary-outcome event. Survival curves were nonproportional. The restricted mean survival time was 1599 days in the rivaroxaban group and 1675 days in the vitamin K antagonist group (difference, –76 days; 95% confidence interval [CI], –121 to –31; P<0.001). A higher incidence of death occurred in the rivaroxaban group than in the vitamin K antagonist group (restricted mean survival time, 1608 days vs. 1680 days; difference, –72 days; 95% CI, –117 to –28). No significant between-group difference in the rate of major bleeding was noted.

CONCLUSIONS

Among patients with rheumatic heart disease–associated atrial fibrillation, vitamin K antagonist therapy led to a lower rate of a composite of cardiovascular events or death than rivaroxaban therapy, without a higher rate of bleeding. (Funded by Bayer; INVICTUS ClinicalTrials.gov number, NCT02832544.)

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Atrial fibrillation may occur because of different pathophysiological conditions that lead to remodeling of the left atrium. Patients with atrial fibrillation are at increased risk for embolic stroke owing to formation of thrombus in the left atrium, which can embolize and occlude branches of the intracerebral circulation. In high-income countries, the development of atrial disease and atrial fibrillation is most often a consequence of systemic hypertension, ischemic heart disease, or advanced age. However, in low- and middle-income countries, rheumatic heart disease remains an important cause of atrial enlargement and atrial fibrillation.[1,2]

Randomized trials have shown the efficacy of vitamin K antagonists for stroke prevention in patients with atrial fibrillation.[3] Because of many dietary and pharmacologic interactions, vitamin K antagonist therapy is difficult to administer, and regular blood sampling to monitor anticoagulation status with the international normalized ratio of prothrombin time (INR) is required. The need for drugs that do not require any monitoring led to the development of the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban. Randomized clinical trials have shown that these non–vitamin K antagonist oral anticoagulants are as effective as vitamin K antagonist therapy for stroke prevention and have a lower risk of intracranial hemorrhage.[4] However, the randomized trials that have established the efficacy and safety of both vitamin K antagonist and non–vitamin K antagonist oral anticoagulants for stroke prevention in patients with atrial fibrillation excluded patients who had atrial fibrillation due to rheumatic heart disease.

Patients with atrial fibrillation due to rheumatic heart disease differ substantially from other patients with atrial fibrillation; they are usually much younger, are more often female, and often have advanced valvular disease.[1,2] Because of these differences and limited evidence from clinical trials, guidelines do not recommend the use of non–vitamin K antagonist oral anticoagulants for stroke prevention in patients with rheumatic heart disease–associated atrial fibrillation, and rivaroxaban is not approved for this indication in these patients.[5] However, an anticoagulant that does not require monitoring would be very useful in low- and middle-income countries, where most patients with rheumatic heart disease live and where regular INR monitoring and dose adjustment of vitamin K antagonists is often a challenge, owing to difficulties in travel and to limitations in health care resources. On the basis of these considerations, we performed a randomized, noninferiority trial to evaluate the efficacy and safety of the factor Xa inhibitor rivaroxaban, as compared with vitamin K antagonist therapy, in patients with rheumatic heart disease–associated atrial fibrillation in Africa, Asia, and Latin America.

Methods

Trial Organization

The Investigation of Rheumatic AF Treatment Using Vitamin K Antagonists, Rivaroxaban or Aspirin Studies (INVICTUS) is an international research program in rheumatic heart disease that includes both a registry and a randomized trial in which we compared once-daily rivaroxaban (at a dose of 20 mg or 15 mg, according to renal function) with a dose-adjusted vitamin K antagonist in patients with documented rheumatic heart disease and atrial fibrillation. The trial was open-label, with blinded assessment of outcomes. The trial protocol, which is available with the full text of this article at NEJM.org, was approved by the institutional review boards and ethics committees at all the participating sites and by relevant regulatory authorities. Written informed consent was obtained from all the patients before randomization.

The trial was planned and led by the Population Health Research Institute, which designed, conducted, analyzed, and reported the trial results. The steering committee vouches for the accuracy and completeness of the data and made the decision to submit the manuscript for publication. The first author wrote the first draft of the manuscript. No one who is not an author contributed to writing the manuscript. The Population Health Research Institute received an unrestricted grant from Bayer to cover the costs of the trial, without any agreements regarding confidentiality. The authors vouch for the adherence of the trial to the protocol.

Patient Enrollment and Treatments

The complete details of the patient enrollment criteria have been published previously.[6] Patients

were eligible for inclusion if they were 18 years of age or older and had echocardiographically proven rheumatic heart disease and documented atrial fibrillation or atrial flutter at any time. For patients to be eligible, at least one of the following criteria was additionally required: a CHA_2DS_2VASc score of at least 2 (on a scale from 0 to 9, with higher scores indicating a higher risk of stroke), mitral stenosis with a mitral-valve area of no more than 2 cm^2, or echocardiographic evidence of either left atrial spontaneous echo contrast or left atrial thrombus. Key exclusion criteria were the presence of a mechanical heart valve or the likelihood of receiving one within the next 6 months, the use of dual antiplatelet therapy, treatment with dual strong inhibitors of CYP3A4 and P-glycoprotein, and the presence of severe renal insufficiency (estimated glomerular filtration rate, <15 ml per minute). Women of child-bearing age were excluded if they were pregnant or were not using a form of contraception that the trial had deemed to be effective.

Patients were randomly assigned in a 1:1 ratio, with the use of Web-based randomization system, to receive either rivaroxaban or a locally available vitamin K antagonist. Randomization was stratified according to site. Rivaroxaban was administered at a daily dose of 20 mg daily in patients with an estimated creatinine clearance of at least 50 ml per minute or at a daily dose of 15 mg in patients with an estimated creatinine clearance of less than 50 ml per minute. Patients who were assigned to the vitamin K antagonist group received any locally approved vitamin K antagonist. Dose adjustment was expected to occur with a measurement of the INR obtained no less than monthly in order to maintain the INR in the range of 2.0 to 3.0. Patients were seen in follow-up at 1 month after randomization and every 6 months thereafter.

OUTCOME MEASURES

In the original trial design, the primary efficacy outcome was a composite of total stroke or systemic embolism. Key secondary outcomes were myocardial infarction and death from vascular (cardiac or noncardiac) causes. The primary analysis was planned as a noninferiority analysis, with potential testing for superiority; the noninferiority margin was 1.46 (upper boundary of the one-sided 97.5% confidence interval of the hazard ratio). The trial was expected to continue until the occurrence of 254 primary-outcome events. The primary safety outcome was major bleeding as defined by the International Society of Thrombosis and Hemostasis (Table S5 in the Supplementary Appendix, available at NEJM.org). Primary efficacy and safety outcomes were independently adjudicated.

During the course of the trial, we observed (with blinding to treatment) that the overall rate of stroke was substantially lower than the expected rate and that the overall mortality rate was much higher than expected. Because the trial was event-driven, it became clear that it would not be practical for the required number of strokes to occur in a reasonable time period in order for the trial to have the planned statistical power. On the basis of blinded review of total event rates, the steering committee decided to change the primary outcome and to adopt both the primary outcome and the noninferiority margin of the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) W trial, which was also a noninferiority trial comparing a new treatment (clopidogrel plus aspirin) with vitamin K antagonist therapy in patients with atrial fibrillation.[7,8] The primary outcome in the ACTIVE W trial was a composite of stroke, systemic embolism, myocardial infarction, or death from vascular causes, and the noninferiority margin for that outcome was a hazard ratio of 1.186.[7,8] In our trial, death from unknown causes was added to the composite primary outcome because we reasoned that most of the deaths would have a vascular cause. The trial remained event-driven, with a target of 1079 total primary outcomes necessary for the trial to have 80% power with the revised primary outcome and noninferiority margin. Stroke or systemic embolism remained an important secondary outcome.

Adherence to rivaroxaban therapy was assessed by comparison of the number of pills administered to patients in this group with the pill counts made at subsequent visits. No pill counts were done for patients assigned to the vitamin K antagonist group.

STATISTICAL ANALYSIS

We planned to use proportional-hazards modeling to test the primary and secondary outcomes, unless strong evidence of nonproportionality of the Kaplan–Meier survival curves was seen, in which case we would also use a restricted mean

survival time analysis. Time-dependent analysis showed clear evidence of nonproportionality for the primary outcome. Therefore, we performed restricted mean survival time analyses, truncating follow-up at the time of the last follow-up visit. Because randomization was stratified according to site, both proportional-hazards and restricted mean survival time analyses with adjustment for site are presented.

The intention-to-treat population included all the patients who underwent randomization. The efficacy analyses were performed on the basis of the intention-to-treat principle. We also analyzed all the outcomes using the on-treatment principle, which specified that only patients who received at least one dose of trial medication would be included and that the analysis would include only events that occurred up to 5 days after permanent discontinuation of trial medication. Two interim analyses of efficacy were planned, with the use of a modified Haybittle–Peto testing approach to evaluate the possibility of greater-than-expected efficacy. A difference in favor of treatment greater than 4 SD at the first analysis or greater than 3 SD at the second analysis could lead to a recommendation to terminate the trial early for greater-than-expected efficacy. The first such formal interim analysis was performed in August 2021, and the committee recommended that the trial continue at that time. The second formal interim analysis was not done.

We did not correct for multiplicity when conducting tests for secondary or other outcomes; results are reported as point estimates with 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used in place of a hypothesis test. Prespecified subgroups were defined according to the presence or absence of moderate-to-severe mitral stenosis (estimated valve area, <2.0 cm^2), sex, age, body weight, the calculated creatinine clearance, and time in the therapeutic range of the INR that was observed at each participating center (according to quartile).

RESULTS

PATIENT ENROLLMENT

From August 2016 through September 2019, a total of 4565 patients were enrolled from 138 trial sites across 24 countries. A total of 2292 patients were assigned to the rivaroxaban group, and 2273 to the vitamin K antagonist group. Data for 28 patients at 1 trial site were not included in any analysis because the site was closed during the trial owing to concern about data validity. The intention-to-treat analysis included 4531 patients: 2275 in the rivaroxaban group and 2256 in the vitamin K antagonist group (Fig. S1). A total of 136 patients were lost to follow-up, and 16 patients withdrew consent. Final vital status was known for 4379 patients (2194 in the rivaroxaban group and 2185 in the vitamin K antagonist group). On February 4, 2022, the data and safety monitoring board recommended that the trial be terminated because the primary question addressed by the trial had been satisfactorily answered.

The mean (±SD) duration of follow-up was 3.1±1.2 years. Patients were enrolled in Africa, Asia, and Latin America. Details of the ethnic groups of the patients are shown in Table S1. The baseline clinical characteristics of the patients were well balanced between the treatment groups (Table 1). The mean age of the patients was 50.5 years, and 72.3% were women. Moderate-to-severe mitral stenosis (valve area, ≤2.0 cm^2) was present in 81.9% of the patients. Nearly half the patients had a CHA_2DS_2VASc score of less than 2. Vitamin K antagonist therapy was being used before enrollment in 52.8% of the patients.

DELIVERY OF TRIAL TREATMENT

In the vitamin K antagonist group, warfarin was used predominantly (in 79 to 85% of the patients, with the percentage varying between visits), and acenocoumarol was used in almost all the other patients. The INR that was recorded immediately before trial enrollment was in the therapeutic range (2.0 to 3.0) in 33.2% of the patients in the vitamin K antagonist group, and the INR that was recorded at trial visits was in the therapeutic range in 56.1% of the patients at 6 months, in 59.0% at 1 year, in 65.3% at 2 years, in 65.1% at 3 years, and in 64.1% at 4 years.

The percentage of patients with permanent discontinuation of trial medication was higher in the rivaroxaban group than in the vitamin K antagonist group. Detailed reasons for permanent discontinuation are shown in Table S2. The most common reasons for permanent discontinuation in the two trial groups were hospitalization for valve surgery and decision by the patient. Of the 513 patients who discontinued rivaroxaban per-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Overall (N=4531)	Rivaroxaban (N=2275)	Vitamin K Antagonist (N=2256)
Age — yr	50.5±14.6	50.7±14.8	50.3±14.4
Female sex — no. (%)	3274 (72.3)	1648 (72.4)	1626 (72.1)
Systolic blood pressure — mm Hg	115.7±17.5	116.0±17.7	115.5±17.4
Body-mass index†	24.5±5.9	24.4±5.7	24.6±6.1
Creatinine clearance — ml/min	80.6±30.4	80.0±30.2	81.1±30.7
Congestive heart failure — no. (%)	1745 (38.5)	879 (38.6)	866 (38.4)
Hypertension — no. (%)	1057 (23.3)	522 (22.9)	535 (23.7)
Diabetes mellitus — no. (%)	290 (6.4)	158 (6.9)	132 (5.9)
Stroke — no. (%)	505 (11.1)	248 (10.9)	257 (11.4)
Transient ischemic attack — no. (%)	147 (3.2)	75 (3.3)	72 (3.2)
Coronary artery disease — no. (%)	52 (1.1)	32 (1.4)	20 (0.9)
Percutaneous valvuloplasty — no. (%)	506 (11.2)	265 (11.6)	241 (10.7)
Mitral-valve repair — no. (%)	155 (3.4)	75 (3.3)	80 (3.5)
CHA_2DS_2-VASc score‡	1.9±1.4	2.0±1.4	1.9±1.4
Inclusion criteria met — no. (%)			
CHA_2DS_2-VASc score ≥2	2557 (56.4)	1295 (56.9)	1262 (55.9)
Moderate-to-severe mitral stenosis§	3711 (81.9)	1871 (82.2)	1840 (81.6)
Left atrial spontaneous echo contrast	527 (11.6)	278 (12.2)	249 (11.0)
Left atrial thrombus on echocardiography	304 (6.7)	151 (6.6)	153 (6.8)
CHA_2DS_2-VASc score ≥2 as only criterion	697 (15.4)	342 (15.0)	355 (15.7)
Moderate-to-severe mitral stenosis as only criterion	1657 (36.6)	827 (36.4)	830 (36.8)
CHA_2DS_2-VASc score ≥2 and moderate-to-severe mitral stenosis	1788 (39.5)	916 (40.3)	872 (38.7)
Echocardiographic findings — no./total no. (%)¶			
Mitral-valve stenosis			
Absent	647/4489 (14.4)	324/2255 (14.4)	323/2234 (14.5)
Present	3830/4489 (85.3)	1927/2255 (85.5)	1903/2234 (85.2)
Valve area <1.0 cm^2	1042/3830 (27.2)	506/1927 (26.3)	536/1903 (28.2)
Mitral-valve regurgitation			
Absent	766/4489 (17.1)	390/2255 (17.3)	376/2234 (16.8)
Present	3709/4489 (82.6)	1860/2255 (82.5)	1849/2234 (82.8)
Moderate	1317/3709 (35.5)	667/1860 (35.9)	650/1849 (35.2)
Severe	831/3709 (22.4)	421/1860 (22.6)	410/1849 (22.2)
Medications received — no. (%)			
Any vitamin K antagonist	2394 (52.8)	1218 (53.5)	1176 (52.1)
Prophylaxis for rheumatic fever	1445 (31.9)	715 (31.4)	730 (32.4)
Beta-blocker	3276 (72.3)	1612 (70.9)	1664 (73.8)
ACE inhibitor or ARB	1283 (28.3)	651 (28.6)	632 (28.0)
Digoxin	1925 (42.5)	991 (43.6)	934 (41.4)
Calcium-channel blocker	267 (5.9)	136 (6.0)	131 (5.8)
Diuretic	3825 (84.4)	1931 (84.9)	1894 (84.0)
Treatment for HIV infection or AIDS	58 (1.3)	25 (1.1)	33 (1.5)

* Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme, AIDS acquired immunodeficiency syndrome, ARB angiotensin-receptor blocker, and HIV human immunodeficiency virus.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ CHA_2DS_2-VASc scores (an assessment of the risk of stroke among patients with atrial fibrillation) range from 0 to 9, with higher scores indicating a higher risk of stroke.
§ Moderate-to-severe mitral stenosis was defined as a valve area of less than 2.0 cm^2.
¶ With regard to echocardiographic findings, results on mitral-valve stenosis were unknown for four patients in the rivaroxaban group and for eight in the vitamin K antagonist group; results on mitral-valve regurgitation were unknown for five and nine, respectively.

Table 2. Intention-to-Treat Analysis of Efficacy Outcomes.*

Outcome	Rivaroxaban (N = 2275)			Vitamin K Antagonist (N = 2256)			Proportional-Hazards Ratio (95% CI)	Difference in RMST (95% CI)	P Value
	No. of Patients	Rate	RMST	No. of Patients	Rate	RMST			
		%/yr	*days*		%/yr	*days*		*days*	
Stroke, systemic embolism, myocardial infarction, or death from vascular or unknown causes	560	8.21	1599	446	6.49	1675	1.25 (1.10 to 1.41)	−76 (−121 to −31)	<0.001
Stroke	90	1.32	1929	65	0.94	1950	1.37 (1.00 to 1.89)	−21 (−40 to −2)	
Ischemic stroke	74	1.08	1941	48	0.70	1963	1.53 (1.06 to 2.20)	−23 (−40 to −6)	
Hemorrhagic stroke	7	0.10	1995	7	0.10	1994	1.00 (0.35 to 2.86)	0.3 (−6 to 6)	
Stroke of uncertain cause	12	0.17	1991	10	0.14	1993	1.21 (0.52 to 2.79)	−1 (−8 to 5)	
Systemic embolism	6	0.09	1995	10	0.14	1992	0.59 (0.22 to 1.63)	4 (−3 to 10)	
Stroke or systemic embolism	94	1.38	1926	75	1.09	1942	1.24 (0.92 to 1.68)	−16 (−36 to 4)	
Myocardial infarction	5	0.07	1996	3	0.04	1998	1.67 (0.40 to 6.97)	−1 (−5 to 3)	
Death	552	7.95	1608	442	6.35	1680	1.23 (1.09 to 1.40)	−72 (−117 to −28)	
Death due to vascular causes†	439	6.33	1683	337	4.84	1751	1.29 (1.12 to 1.49)	−68 (−110 to −26)	
Sudden cardiac death	141	2.03	1894	94	1.35	1929	1.51 (1.16 to 1.96)	−36 (−58 to −13)	
Death due to mechanical or pump failure	237	3.42	1817	174	2.50	1862	1.35 (1.11 to 1.64)	−45 (−83 to −8)	
Death due to nonvascular causes	46	0.66	1962	36	0.52	1971	1.26 (0.81 to 1.94)	−9 (−25 to 7)	
Death due to unknown cause	67	0.97	1941	69	0.99	1946	0.96 (0.69 to 1.35)	−4 (−26 to 17)	
Any hospitalization	687	11.71	1432	622	10.44	1467	1.08 (0.97 to 1.21)	−36 (−80 to 9)	
Hospitalization for heart failure	240	3.61	1779	219	3.28	1794	1.08 (0.89 to 1.29)	−16 (−47 to 16)	
Valve surgery	187	2.85	1852	157	2.36	1873	1.19 (0.97 to 1.48)	−21 (−50 to 9)	
Valve surgery or valvuloplasty	205	3.14	1838	175	2.65	1859	1.17 (0.95 to 1.43)	−21 (−52 to 10)	

* The intention-to-treat population included all the patients who underwent randomization, except for 34 patients, whose data were excluded owing to duplicate randomization, potentially fraudulent data, or inability to obtain required re-consent. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used in place of a hypothesis test. RMST denotes restricted mean survival time.

† Vascular causes could be cardiac or noncardiac. Deaths due to vascular causes other than sudden death or death due to mechanical or pump failure occurred in 61 patients in the rivaroxaban group and in 69 in the vitamin K antagonist group.

manently, 161 (31.4%) stopped rivaroxaban owing to an indication for valve-replacement surgery that required the use of a vitamin K antagonist. Many patients who discontinued rivaroxaban subsequently received a vitamin K antagonist, whereas those who discontinued vitamin K antagonist therapy did not usually receive an oral anticoagulant thereafter. At the trial visits, the percentages of patients in the vitamin K antagonist group receiving trial medication (not permanently or temporarily discontinued) were 98.0% at 1 year, 97.7% at 2 years, 97.1% at 3 years, and 96.4% at 4 years; in the rivaroxaban group, the corresponding percentages were 88.7%, 84.4%, 81.2%, and 79.0%. At the trial visits, the percentages of patients in the rivaroxaban group who either were receiving rivaroxaban or had switched to a vitamin K antagonist were 94.9% at 1 year, 92.4% at 2 years, 91.5% at 3 years, and 87.5% at 4 years. Reasons for permanent discontinuation of rivaroxaban, in a comparison of patients who subsequently started a vitamin K antagonist with those who did not, are shown in Table S3. On the basis of the expected number of pills administered and the pills returned, the mean adherence to rivaroxaban therapy was 83.7±16.5%.

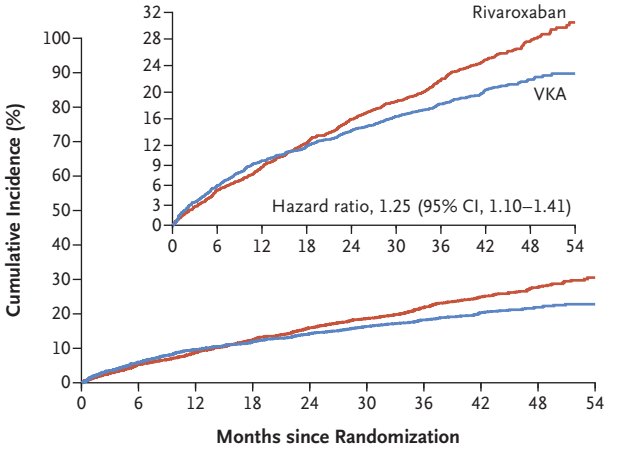

Figure 1. Cumulative Incidence of the Composite of Stroke, Systemic Embolism, Myocardial Infarction, or Death from Vascular or Unknown Causes (Primary Outcome).

Vascular causes could be cardiac or noncardiac. The inset shows the same data on an expanded y axis. VKA denotes vitamin K antagonist.

EFFICACY AND SAFETY OUTCOMES

A primary-outcome event (stroke, systemic embolism, myocardial infarction, or death from vascular or unknown causes) occurred in 560 of 2275 patients in the rivaroxaban group and in 446 of 2256 patients in the vitamin K antagonist group (proportional-hazards ratio, 1.25; 95% confidence interval [CI], 1.10 to 1.41) (Table 2 and Fig. 1). The restricted mean survival time was 1599 days in the rivaroxaban group and 1675 days in the vitamin K antagonist group (difference, –76 days; 95% CI, –121 to –31 days; P<0.001 for superiority). More patients in the rivaroxaban group than in the vitamin K antagonist group had a stroke (90 vs. 65 patients), a finding that was almost entirely due to a higher rate of ischemic stroke in the rivaroxaban group. A total of 552 patients in the rivaroxaban group and in 442 in the vitamin K antagonist group died (difference in restricted mean survival time, –72 days; 95% CI, –117 to –28). The difference in mortality was almost entirely due to lower rates of sudden cardiac death and of death due to mechanical or pump failure in the vitamin K antagonist group than in the rivaroxaban group (Fig. 2). No between-group differences in the rate of hospitalization for heart failure were observed. The rates of valve-replacement surgery or mitral valvuloplasty did not differ significantly between the two groups. The between-group differences in the rates of stroke and death were similar in the on-treatment analyses and the intention-to-treat analyses (Table 3). A competing-risk analysis of the primary outcome showed a result that was similar to that of the primary analysis (Table S4). Rates of major bleeding did not differ significantly between the treatment groups (Table 3). However, the rate of fatal bleeding was lower with rivaroxaban than with vitamin K antagonists. No significant interactions were found for effect of the intervention on the primary outcome according to the prespecified subgroups.

DISCUSSION

In patients with atrial fibrillation not related to rheumatic heart disease, treatment with rivaroxaban or other factor Xa inhibitors has been shown to be noninferior to warfarin therapy for stroke prevention, with large reduction in the risk of hemorrhagic stroke.[4] The patients in the present

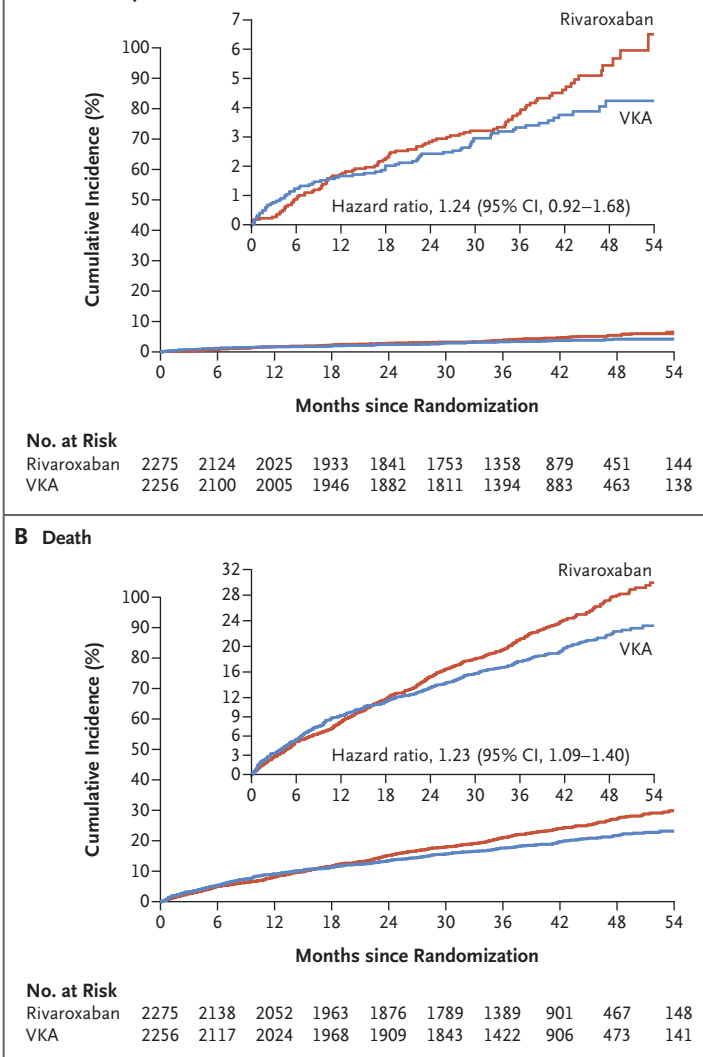

Figure 2. Cumulative Incidences of Stroke or Systemic Embolism and of Death.

The insets show the same data on expanded y axes.

trial were much younger (mean age, 50.5 years) and more likely to be women (72% of the patients) than in recent trials including only patients without rheumatic heart disease.[4] A lower percentage of patients in this trial had hypertension (23%) than in previous trials. However, on the basis of previous trials, we expected to find a similar or higher risk of stroke because mitral stenosis has been associated with a high risk of stroke. We expected generally similar results in the present trial on the basis of the expectation that, despite a different underlying cardiac condition, the underlying stroke mechanism of embolism of left atrial thrombus would be similar in rheumatic heart disease as in other types of atrial fibrillation. We did not expect to observe a difference in mortality. The phase 3 trials confirming the safety and efficacy of the new oral anticoagulants, which included patients with atrial fibrillation not due to rheumatic heart disease and which compared non–vitamin K antagonist oral anticoagulants with vitamin K antagonists, showed consistent effects between patients with (nonrheumatic) valvular heart disease and those without such disease.[9] A randomized trial comparing rivaroxaban with vitamin K antagonist therapy in patients with atrial fibrillation and bioprosthetic mitral valves showed a lower risk with rivaroxaban of stroke at 1 year of follow-up and no significant difference in mortality.[10] Thus, the results of the present trial were unexpected.

Possible explanations for these findings include the reduced power of this trial for the outcome of stroke, because the rates of stroke in the two groups were lower than expected; in addition, the difference in the rate of stroke was modest, which suggests that the difference could be due to chance. The rate of the composite outcome of stroke or systemic embolism, which is widely accepted in trials of stroke prevention in patients with atrial fibrillation, did not differ between the two treatment groups. However, the difference in mortality was large and is therefore unlikely to be due to chance. Patients in the vitamin K antagonist group had more physician interactions than those in the rivaroxaban group because of the need for monthly monitoring of INR control. This situation could have resulted in better overall care and fewer strokes and deaths. It is possible that adherence to rivaroxaban therapy was worse than to vitamin K antagonist therapy because patients in the rivaroxaban group knew that they were not having the INR monitored. The difference in stroke rates between the two groups could also be, in part, related to the higher incidence of discontinuation of rivaroxaban, even though many of the patients who discontinued rivaroxaban then received a vitamin K antagonist. The most common reasons given for the discontinuation of rivaroxaban were hospitalization for valve surgery and patient decision. Some patients in the rivaroxaban group received mechanical valves, which necessitated a switch to vitamin K antagonist therapy to prevent valve

Table 3. On-Treatment Analysis of Safety Outcomes and Selected Efficacy Outcomes.*

Outcome	Rivaroxaban (N=2265)			Vitamin K Antagonist (N=2251)			Proportional-Hazards Ratio (95% CI)	Difference in RMST (95% CI)	P Value
	No. of Patients	Rate	RMST	No. of Patients	Rate	RMST			
		%/yr	*days*		%/yr	*days*		*days*	
Safety outcomes									
Major bleeding	40	0.67	1965	56	0.83	1954	0.76 (0.51 to 1.15)	11 (–5 to 28)	0.18
Fatal bleeding	4	0.07	1996	15	0.22	1988	0.29 (0.10 to 0.88)	8 (1 to 16)	
Bleeding in a critical area or organ	2	0.03	1998	4	0.06	1997	0.52 (0.09 to 2.81)	2 (–3 to 6)	
Intracranial hemorrhage	8	0.13	1993	14	0.21	1989	0.63 (0.26 to 1.50)	4 (–3 to 12)	
Life-threatening bleeding	22	0.36	1981	31	0.46	1975	0.77 (0.44 to 1.32)	6 (–6 to 18)	
Clinically relevant nonmajor bleeding	65	1.09	1943	71	1.06	1942	0.96 (0.68 to 1.34)	1 (–18 to 20)	
Major or clinically relevant nonmajor bleeding	102	1.72	1912	120	1.81	1901	0.89 (0.68 to 1.16)	10 (–14 to 35)	
Selected efficacy outcomes									
Stroke, systemic embolism, myocardial infarction, or death from vascular or unknown causes	481	8.06	1619	426	6.33	1686	1.26 (1.10 to 1.43)	–67 (–110 to –24)	0.002
Stroke	83	1.39	1926	59	0.87	1955	1.54 (1.10 to 2.16)	–29 (–49 to –9)	
Systemic embolism	6	0.10	1995	9	0.13	1993	0.71 (0.25 to 2.01)	2 (–4 to 9)	
Myocardial infarction	5	0.08	1996	3	0.04	1998	1.85 (0.44 to 7.77)	–2 (–6 to 3)	
Death from vascular causes	362	5.98	1712	319	4.68	1761	1.26 (1.08 to 1.47)	–49 (–87 to –10)	
Death from unknown cause	58	0.96	1941	65	0.95	1948	1.00 (0.70 to 1.42)	–7 (–30 to 16)	
Death	459	7.58	1638	416	6.10	1694	1.23 (1.08 to 1.40)	–57 (–98 to –15)	
Any hospitalization	627	11.49	1447	606	10.35	1473	1.06 (0.95 to 1.19)	–26 (–71 to 19)	
Hospitalization for heart failure	222	3.80	1775	214	3.27	1795	1.09 (0.90 to 1.32)	–20 (–52 to 13)	
Valve surgery or valvuloplasty	172	2.87	1853	173	2.67	1858	1.06 (0.86 to 1.31)	–5 (–36 to 26)	

* The on-treatment population included all the patients who received at least one dose of trial medication, and the on-treatment analysis included only events that occurred up to 5 days after permanent discontinuation of trial medication. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used in place of a hypothesis test.

thrombosis. However, the discontinuation of rivaroxaban does not explain the observed benefit of vitamin K antagonist therapy because the on-treatment analysis, which excluded any events that occurred more than 5 days after the discontinuation of trial treatment, showed results that were almost identical to those of the intention-to-treat analysis.

A mortality difference in favor of either treatment was not expected. In a meta-analysis of trials of non–vitamin K antagonist anticoagulants as compared with warfarin, mortality was 10% lower with non–vitamin K antagonist anticoagulants.[4] This difference appears to be driven mostly by the large reductions in the risk of hemorrhagic stroke with the newer agents. The effect of vitamin K antagonist therapy on mortality in the present trial appears to be mostly unrelated to stroke prevention. The absolute number of strokes prevented was small (25 strokes), as compared with the absolute number of deaths prevented (110 deaths). The lower mortality that was observed with vitamin K antagonist therapy than with rivaroxaban therapy in this trial is also clearly not related to any effect on bleeding, given that bleeding was not less common with vitamin K antagonist therapy than with rivaroxaban therapy. Treatment with a vitamin K antagonist does not appear to have slowed the progression of heart-valve deterioration, because rates of valve replacement surgery or valvuloplasty were similar in the two groups. The use of a vitamin K antagonist led to a lower rate of death from vascular causes than rivaroxaban therapy, with lower rates of both sudden cardiac death and death from mechanical or pump failure. Thus, the lower rates of sudden cardiac death and of death from mechanical or pump failure with vitamin K antagonist therapy than with rivaroxaban therapy are not readily explained by effects on stroke, bleeding, or valve deterioration.

During the first 12 to 18 months of follow-up, little difference was seen between the vitamin K antagonist group and the rivaroxaban group (Figs. 1 and 2). After that, a lower rate of the primary composite outcome in the vitamin K antagonist group than in the rivaroxaban group became evident and was substantial beyond 3 years. We speculate that a delayed effect could be occurring, in part owing to improvement in the management of vitamin K antagonist therapy during the initial phase of the trial. It is also possible that there was a delay in the onset of the benefit from a vitamin K antagonist over rivaroxaban that is independent of INR control.

A delay in the onset of a benefit of vitamin K antagonist therapy was also seen in the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial.[11] The WARCEF trial tested whether warfarin therapy would lead to a lower rate of death or stroke than aspirin among patients with heart failure due to a reduced ejection fraction without atrial fibrillation. The trial showed no benefit overall, but a time-varying Cox analysis showed a benefit of warfarin therapy that emerged only later in follow-up, as in the INVICTUS trial. The hazard ratio in favor of vitamin K antagonist therapy decreased by a factor of 0.89 per year (95% CI, 0.80 to 0.998; P=0.046) and became significant by year 4 (hazard ratio, 0.76; P=0.04).

No evidence suggests that rivaroxaban therapy increases mortality among patients with other heart conditions. Treatment with rivaroxaban reduces mortality substantially among patients with atherosclerotic vascular disease.[12] Thus, our data support the hypothesis that vitamin K antagonist therapy reduces the risk of death from vascular causes among patients with rheumatic heart disease; this effect appears to be independent of the prevention of atrial fibrillation–related stroke and suggests a direct effect on the disease process of rheumatic heart disease. Our trial showed that as compared with rivaroxaban, vitamin K antagonist therapy led to a lower rate of ischemic stroke among patients with rheumatic heart disease–associated atrial fibrillation and lower mortality due to vascular causes, without significantly increasing the rate of major bleeding. The results of this trial support current guidelines, which recommend vitamin K antagonist therapy for the prevention of stroke in patients with rheumatic heart disease in whom atrial fibrillation develops.

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APPENDIX

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REFERENCES

1. Iung B, Leenhardt A, Extramiana F. Management of atrial fibrillation in patients with rheumatic mitral stenosis. Heart 2018;104:1062-8.
2. Stambler BS, Ngunga LM. Atrial fibrillation in Sub-Saharan Africa: epidemiology, unmet needs, and treatment options. Int J Gen Med 2015;8:231-42.
3. 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.
4. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955-62.
5. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2019;74:104-32.
6. Karthikeyan G, Connolly SJ, Ntsekhe M, et al. The INVICTUS rheumatic heart disease research program: rationale, design and baseline characteristics of a randomized trial of rivaroxaban compared to vitamin K antagonists in rheumatic valvular disease and atrial fibrillation. Am Heart J 2020;225:69-77.
7. The Active Steering Committee. Rationale and design of ACTIVE: the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events. Am Heart J 2006;151:1187-93.
8. The ACTIVE Writing Group on behalf of the ACTIVE Investigators. 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.
9. Pan K-L, Singer DE, Ovbiagele B, Wu Y-L, Ahmed MA, Lee M. Effects of non-vitamin K antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and valvular heart disease: a systematic review and meta-analysis. J Am Heart Assoc 2017;6(7):e005835.
10. Guimarães HP, de Barros E Silva PGM, Liporace IL, et al. A randomized clinical trial to evaluate the efficacy and safety of rivaroxaban in patients with bioprosthetic mitral valve and atrial fibrillation or flutter: rationale and design of the RIVER trial. Am Heart J 2021;231:128-36.
11. Homma S, Thompson JLP, Pullicino PM, et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. N Engl J Med 2012;366:1859-69.
12. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med 2017;377:1319-30.