ORIGINAL ARTICLE

Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease

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ABSTRACT

BACKGROUND

Heart failure is associated with activation of thrombin-related pathways, which predicts a poor prognosis. We hypothesized that treatment with rivaroxaban, a factor Xa inhibitor, could reduce thrombin generation and improve outcomes for patients with worsening chronic heart failure and underlying coronary artery disease.

METHODS

In this double-blind, randomized trial, 5022 patients who had chronic heart failure, a left ventricular ejection fraction of 40% or less, coronary artery disease, and elevated plasma concentrations of natriuretic peptides and who did not have atrial fibrillation were randomly assigned to receive rivaroxaban at a dose of 2.5 mg twice daily or placebo in addition to standard care after treatment for an episode of worsening heart failure. The primary efficacy outcome was the composite of death from any cause, myocardial infarction, or stroke. The principal safety outcome was fatal bleeding or bleeding into a critical space with a potential for causing permanent disability.

RESULTS

Over a median follow-up period of 21.1 months, the primary end point occurred in 626 (25.0%) of 2507 patients assigned to rivaroxaban and in 658 (26.2%) of 2515 patients assigned to placebo (hazard ratio, 0.94; 95% confidence interval [CI], 0.84 to 1.05; P=0.27). No significant difference in all-cause mortality was noted between the rivaroxaban group and the placebo group (21.8% and 22.1%, respectively; hazard ratio, 0.98; 95% CI, 0.87 to 1.10). The principal safety outcome occurred in 18 patients who took rivaroxaban and in 23 who took placebo (hazard ratio, 0.80; 95% CI, 0.43 to 1.49; P=0.48).

CONCLUSIONS

Rivaroxaban at a dose of 2.5 mg twice daily was not associated with a significantly lower rate of death, myocardial infarction, or stroke than placebo among patients with worsening chronic heart failure, reduced left ventricular ejection fraction, coronary artery disease, and no atrial fibrillation. (Funded by Janssen Research and Development; COMMANDER HF ClinicalTrials.gov number, NCT01877915.)

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After an episode of worsening chronic heart failure, rates of readmission to the hospital and of death are high, especially in the first few months.[1,2] Activation of thrombin-related pathways may contribute to disease progression by inducing inflammation, endothelial dysfunction, and arterial and venous thrombosis.[3] However, warfarin has not improved outcomes among patients with heart failure and reduced ejection fraction who are in sinus rhythm, and patients receiving warfarin have been found to have higher rates of bleeding complications than patients who receive antiplatelet agents or no antithrombotic therapy.[4-7]

Rivaroxaban is an oral direct factor Xa inhibitor that reduces thrombin generation.[8,9] In doses of 10 to 20 mg daily, this agent is approved for a variety of indications, including the treatment and prevention of venous thromboembolism and the prevention of stroke or systemic embolism in patients with atrial fibrillation.[10-12] Lower doses of rivaroxaban (e.g., 2.5 mg twice daily), in combination with antiplatelet agents, have been found to reduce the risk of death from cardiovascular causes, myocardial infarction, and stroke in patients with acute coronary syndromes or stable coronary artery disease.[13,14] We designed a trial to test the hypothesis that rivaroxaban at a dose of 2.5 mg twice daily, added to background antiplatelet therapy, would be associated with lower rates of death and cardiovascular events than placebo among patients with recent worsening of chronic heart failure, reduced ejection fraction, coronary artery disease, and no atrial fibrillation.

Methods

Trial Design and Oversight

The COMMANDER HF trial (A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction, or Stroke in Participants with Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure) was a multicenter, randomized, double-blind, placebo-controlled, event-driven trial.[15] The sponsor was Janssen Research and Development. The trial was conducted and reported in accordance with the protocol and the statistical analysis plan, both of which are available with the full text of this article at NEJM.org. The pertinent national regulatory authorities and ethics committees at participating centers approved the protocol. An international steering committee, made up of members from academic institutions and one member from Janssen, designed the trial, were responsible for overseeing the conduct of the trial, retained the ability to present the data, and made the decision to submit the manuscript for publication. The steering committee vouches for the accuracy and completeness of the data and all analyses and for the fidelity of the trial to the protocol.

The sponsor contracted with members of the steering committee, selected and contracted with the trial sites, provided the rivaroxaban and placebo, performed site monitoring and oversight, collected and managed the data, and performed the data analysis. The first draft was completed by the first and last authors, reviewed and revised by all authors, and supported by Janssen. An independent data and safety monitoring committee had complete access to unblinded data during the conduct of the trial and were responsible for the safety of the enrolled patients as well as for the performance of a single, prespecified interim analysis for efficacy.

Participants

We enrolled patients who had at least a 3-month history of chronic heart failure, a left ventricular ejection fraction of 40% or less, and coronary artery disease and who had been treated for an episode of worsening heart failure (i.e., the index event) within the previous 21 days. After the enrollment of 1155 patients (23.0%), a protocol amendment required patients to also have a plasma concentration of brain natriuretic peptide (BNP) that was at least 200 pg per milliliter or N-terminal pro–brain natriuretic peptide (NT-proBNP) that was at least 800 pg per milliliter measured at any time during the screening period before randomization.

Exclusion criteria were a high risk of bleeding, atrial fibrillation or another condition that required long-term anticoagulation, either acute myocardial infarction or surgical or percutaneous coronary artery intervention during the index event, an estimated glomerular filtration rate of less than 20 ml per minute per 1.73 m^2, recent stroke or previous intracranial hemorrhage, or heart failure due to a cause other than coronary artery disease. Definitions of all the inclusion and exclusion criteria are provided in the Supplementary Appendix, available at NEJM.org. Written informed consent was obtained from all the patients.

RANDOMIZATION AND TRIAL REGIMEN

Using an interactive Web response system and permuted blocks of four, we randomly assigned patients in a 1:1 ratio to receive 2.5 mg of rivaroxaban twice daily or matching placebo, within strata defined according to country. After randomization, patients were seen at week 4 and week 12 and then every 12 weeks thereafter for assessment of safety and to ascertain the occurrence of outcome events. Patients who temporarily discontinued the trial regimen could restart it at any time, provided they continued to meet all the inclusion criteria and none of the exclusion criteria. All the patients were to receive standard care for heart failure and coronary artery disease as prescribed by their treating physician. Single or dual antiplatelet therapy was allowed.

OUTCOMES

The primary efficacy outcome was the composite of death from any cause, myocardial infarction, or stroke. Secondary efficacy outcomes included death from cardiovascular causes, rehospitalization for worsening heart failure, rehospitalization for cardiovascular events, and the composite of death from cardiovascular causes or rehospitalization for worsening heart failure. Before unblinding, the statistical analysis plan was amended to include an analysis of the composite of death from any cause or rehospitalization for worsening heart failure. Other efficacy outcomes included symptomatic deep-vein thrombosis or pulmonary embolism. The principal safety outcome was the composite of fatal bleeding or bleeding into a critical space with a potential for causing permanent disability. Secondary safety outcomes included bleeding events requiring hospitalization and clinically overt major bleeding events as defined by the International Society on Thrombosis and Haemostasis (ISTH) (i.e., associated with a decrease in hemoglobin level of ≥2 g per deciliter, transfusion of 2 or more units of packed red cells or whole blood, a critical site [intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal], or a fatal outcome).

An independent clinical-events adjudication committee was not used in this trial because it was anticipated that the most common outcome would be death. In addition, outcomes were ascertained by investigators using an extensive, dedicated case-report form, with source-data verification by the sponsor's clinical operations team. A complete list of outcome-event definitions is provided in the Supplementary Appendix. Data on serious adverse events or any event leading to permanent discontinuation of rivaroxaban or placebo were also collected and classified with the use of the Medical Dictionary for Regulatory Activities (MedDRA), version 20.1.

SAMPLE SIZE AND INTERIM ANALYSIS

The original protocol specified 984 primary efficacy outcomes for this event-driven trial. On the basis of a blinded review of accumulated data indicating a lower event rate and higher rate of discontinuation of the trial regimen than originally estimated, several changes were made to the trial plan by the steering committee in November 2016. Follow-up was extended, and the target number of primary events was increased to 1200. The original goal of 5000 patients was retained. With an expected discontinuation rate of 13 per 100 person-years, a total of 1200 events of the primary efficacy outcome was calculated to provide 80% power to detect a 20% lower hazard of the primary outcome in the rivaroxaban group than in the placebo group, with a two-sided type I error rate of 0.05.

An independent data and safety monitoring committee performed a single, prespecified interim analysis to consider early termination of the trial for efficacy when 632 primary efficacy events had occurred. For this analysis, O'Brien–Fleming boundaries and the Lan–DeMets spending function were used.

STATISTICAL ANALYSIS

The trial groups were analyzed according to the intention-to-treat principle for all the efficacy outcomes. A hierarchical analysis plan stipulated that if the primary efficacy outcome did not differ significantly between the trial groups, secondary efficacy outcomes would be reported without claims of statistical significance. Safety outcome comparisons were restricted to patients who took at least one dose of rivaroxaban or placebo. We used time-to-event methods, including the log-rank test (stratified according to five geographic regions), Cox models, and Kaplan–Meier estimates of the cumulative risk. Data on vital status were censored on March 5, 2018 (the global treatment

end date of the trial), or the date of last known contact. For all efficacy and safety outcomes, estimated hazard ratios and 95% confidence intervals are cited along with event rates per 100 person-years. The proportional-hazards assumption was tested and confirmed for the primary outcome by including an interaction term between the treatment indicator and log-transformed follow-up time.

Heterogeneity of the treatment effect for the primary efficacy outcome was evaluated by assessing treatment interactions across subgroups in expanded Cox models. Results for these analyses should be interpreted with caution because there was no adjustment for type I error, and statistical power was limited.

RESULTS

PARTICIPANTS AND FOLLOW-UP

From September 2013 through October 2017, a total of 5022 patients were randomly assigned to receive rivaroxaban (2.5 mg twice daily) or matching placebo at 628 sites in 32 countries (Fig. 1). The characteristics of the patients and therapies for heart failure and coronary artery disease were well balanced between the trial groups at baseline (Table 1, and Table S1 in the Supplementary Appendix).

Coronary artery disease was identified by the presence of at least one of the following characteristics: previous myocardial infarction (75.7% of patients), angiographic evidence of at least 50% stenosis in one or more coronary arteries (59.4%), history of percutaneous coronary intervention (51.4%), history of coronary-artery bypass grafting (19.8%), or pathologic Q waves on electrocardiography with corresponding wall-motion abnormalities (34.7%). The median ejection fraction was 34% (interquartile range, 28 to 38), 53% of patients were in New York Heart Association functional class III or IV heart failure at baseline, and more than 50% of patients underwent randomization within 5 days after discharge.

At baseline, almost all the patients (99.5%) were taking diuretics, 92.8% were taking angiotensin-converting–enzyme inhibitors or angiotensin-receptor blockers, 76.5% were taking mineralocorticoid-receptor antagonists, and 92.4% were taking beta-blockers. This pattern of guideline-based therapy was maintained throughout the trial (Table S2 in the Supplementary Appendix). Aspirin, alone or in combination with a thienopyridine, was taken by 93.1% of the patients, with 34.8% taking dual antiplatelet therapy at baseline.

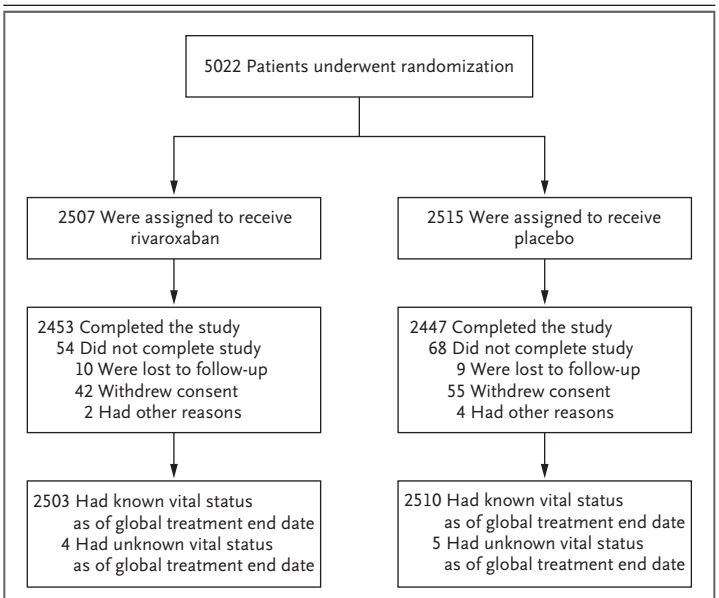

Figure 1. Randomization and Follow-up.

Three patients (one in the rivaroxaban group and two in the placebo group) underwent randomization twice; only the first randomization was counted. Patients were considered to have completed the trial if they died or were followed according to the visit schedule until the end-of-trial visit. "Had other reasons" primarily includes patients at sites in Ukraine and Turkey that were affected by local military action. Data on vital status were collected as of the global treatment end date (March 5, 2018) and included all sources allowed by local regulations.

On the global treatment end date, data on vital status were available for 5013 patients (99.8%), and the median follow-up duration was 21.1 months (interquartile range, 12.9 to 32.8). The rates of permanent discontinuation of the trial regimen before a primary efficacy event were 16.3 and 13.6 per 100 person-years in the rivaroxaban and placebo groups, respectively. The reasons for discontinuation are provided in Table S3 in the Supplementary Appendix.

PRIMARY EFFICACY OUTCOME

The primary efficacy outcome occurred in 626 patients (25.0%) assigned to rivaroxaban and 658 patients (26.2%) assigned to placebo (hazard ratio, 0.94; 95% confidence interval [CI], 0.84 to 1.05; P=0.27) (Table 2). The Kaplan–Meier estimates of the cumulative percentage of patients

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Rivaroxaban (N=2507)	Placebo (N=2515)
Age — yr	66.5±10.1	66.3±10.3
Female sex — no. (%)	551 (22.0)	599 (23.8)
Race — no. (%)†		
White	2063 (82.3)	2065 (82.1)
Black	29 (1.2)	36 (1.4)
Asian	362 (14.4)	365 (14.5)
Other	53 (2.1)	49 (1.9)
Region — no. (%)		
Eastern Europe	1610 (64.2)	1614 (64.2)
North America	74 (3.0)	75 (3.0)
Asia-Pacific	367 (14.6)	366 (14.6)
Latin America	229 (9.1)	229 (9.1)
Western Europe or South Africa	227 (9.1)	231 (9.2)
Body-mass index‡	27.6±5.1	27.8±5.3
eGFR — no. (%)		
<30 ml/min/1.73 m^2	81 (3.2)	82 (3.3)
30 to <60 ml/min/1.73 m^2	884 (35.3)	898 (35.7)
60 to <90 ml/min/1.73 m^2	1101 (43.9)	1137 (45.2)
≥90 ml/min/1.73 m^2	441 (17.6)	398 (15.8)
Clinical features of heart failure		
Median BNP level (IQR) — pg/ml§	702.0 (403.4–1237.0)	695.5 (380.0–1266.3)
Median NT-proBNP level (IQR) — pg/ml§	2840.0 (1537.0–6394.0)	2900.0 (1520.0–6270.5)
Median D-dimer level (IQR) — μg/liter	360 (215–680)	360 (215–650)
Median ejection fraction (IQR) — %	35 (28–38)	34 (27–38)
New York Heart Association classification — no. (%)		
I	80 (3.2)	69 (2.7)
II	1122 (44.8)	1096 (43.6)
III	1208 (48.2)	1254 (49.9)
IV	96 (3.8)	96 (3.8)
Medical history — no. (%)		
Myocardial infarction	1911 (76.2)	1892 (75.2)
Stroke	208 (8.3)	245 (9.7)
Diabetes	1024 (40.8)	1028 (40.9)
Hypertension	1897 (75.7)	1886 (75.0)

* Plus–minus values are means ±SD. There were no significant differences between the groups with regard to any characteristic. More details about the baseline characteristics are provided in Table S1 in the Supplementary Appendix. Percentages may not total 100 because of rounding. BNP denotes brain natriuretic peptide, eGFR estimated glomerular filtration rate, IQR interquartile range, and NT-proBNP N-terminal pro–brain natriuretic peptide.
† Race was reported by the patient.
‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Data on natriuretic peptides were obtained after protocol amendment. Data on BNP were obtained for 965 patients, and data on NT-proBNP were obtained for 2862 patients.

Table 2. Efficacy and Safety Outcomes.*

Outcome	Rivaroxaban (N=2507)		Placebo (N=2515)		Rivaroxaban vs. Placebo†	
	No. (%)	Events/ 100 Patient-Yr	No. (%)	Events/ 100 Patient-Yr	Hazard Ratio (95% CI)	P Value
Efficacy outcomes‡						
Composite primary efficacy outcome	626 (25.0)	13.44	658 (26.2)	14.27	0.94 (0.84–1.05)	0.27
Death from any cause	546 (21.8)	11.41	556 (22.1)	11.63	0.98 (0.87–1.10)	—
Myocardial infarction	98 (3.9)	2.08	118 (4.7)	2.52	0.83 (0.63–1.08)	—
Stroke	51 (2.0)	1.08	76 (3.0)	1.62	0.66 (0.47–0.95)	—
Secondary and exploratory efficacy outcomes						
Death from a cardiovascular cause or rehospitalization for worsening of heart failure	932 (37.2)	23.32	929 (36.9)	23.46	0.99 (0.91–1.09)	—
Death from a cardiovascular cause	453 (18.1)	9.46	476 (18.9)	9.96	0.95 (0.84–1.08)	—
Rehospitalization for worsening of heart failure	689 (27.5)	17.24	691 (27.5)	17.45	0.98 (0.89–1.09)	—
Rehospitalization for cardiovascular event other than worsening of heart failure	543 (21.7)	13.30	572 (22.7)	14.04	0.95 (0.84–1.07)	—
Death from any cause or rehospitalization for worsening of heart failure	993 (39.6)	24.84	973 (38.7)	24.57	1.01 (0.92–1.10)	—
Symptomatic deep-vein thrombosis	5 (0.2)	0.10	7 (0.3)	0.15	0.71 (0.23–2.24)	—
Symptomatic pulmonary embolism	11 (0.4)	0.23	9 (0.4)	0.19	1.23 (0.51–2.96)	—
	Rivaroxaban (N=2499)		**Placebo (N=2509)**		**Rivaroxaban vs. Placebo†**	
	No. (%)	Events/ 100 Patient-Yr	No. (%)	Events/ 100 Patient-Yr	Hazard Ratio (95% CI)	P Value
Safety outcomes§						
Composite principal safety outcome	18 (0.7)	0.44	23 (0.9)	0.55	0.80 (0.43–1.49)	0.48
Fatal bleeding	9 (0.4)	0.22	9 (0.4)	0.22	1.03 (0.41–2.59)	0.95
Bleeding into a critical space with potential for causing permanent disability	13 (0.5)	0.32	20 (0.8)	0.48	0.67 (0.33–1.34)	0.25
ISTH-defined major bleeding¶	82 (3.3)	2.04	50 (2.0)	1.21	1.68 (1.18–2.39)	0.003
Hemoglobin decrease of ≥2 g/dl	55 (2.2)	1.37	30 (1.2)	0.73	1.87 (1.20–2.91)	0.005
Transfusion of ≥2 units of packed red cells or whole blood	31 (1.2)	0.77	18 (0.7)	0.43	1.74 (0.98–3.12)	0.06
Bleeding at a critical site	25 (1.0)	0.62	23 (0.9)	0.56	1.12 (0.63–1.97)	0.70
Fatal bleeding	3 (0.1)	0.07	7 (0.3)	0.17	0.45 (0.12–1.72)	0.23
Bleeding requiring hospitalization	61 (2.4)	1.52	48 (1.9)	1.16	1.30 (0.89–1.90)	0.17

* For each composite outcome, only the first event in a given patient was included; for the individual components of that outcome, all first events of that component outcome were included.

† Hazard ratios and 95% confidence intervals are from a Cox proportional-hazards model stratified according to region, with trial-group assignment as the only effect. P values (two-sided) are from the log-rank test stratified according to region. The 95% confidence intervals have not been adjusted for multiplicity, and inferences drawn from these intervals may not be reproducible.

‡ The primary efficacy outcome was a composite of death from any cause, myocardial infarction, or stroke. Data are from the intention-to-treat population during the observation period from randomization through the global treatment end date (March 5, 2018).

§ The principal safety outcome was a composite of fatal bleeding or bleeding into a critical space with a potential for causing permanent disability. Safety outcome comparisons included only the patients who took at least one dose of rivaroxaban or placebo. Events are those that occurred during the observation period from the first dose of rivaroxaban or placebo through 2 days after the last dose.

¶ Major bleeding is defined by the International Society on Thrombosis and Haemostasis (ISTH) as overt bleeding associated with a decrease in hemoglobin level of at least 2 g per deciliter, transfusion of two or more units of packed red cells or whole blood, a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or a fatal outcome.

with this primary outcome were 13.2%, 24.1%, and 31.8% after 12, 24, and 36 months, respectively, among those assigned to rivaroxaban and 14.7%, 24.7%, and 33.7% among those assigned to placebo (Fig. 2).

With regard to the three components of the composite primary outcome, the rates of death from any cause were 21.8% in the rivaroxaban group and 22.1% in the placebo group (hazard ratio, 0.98; 95% CI, 0.87 to 1.10), the rates of myo-

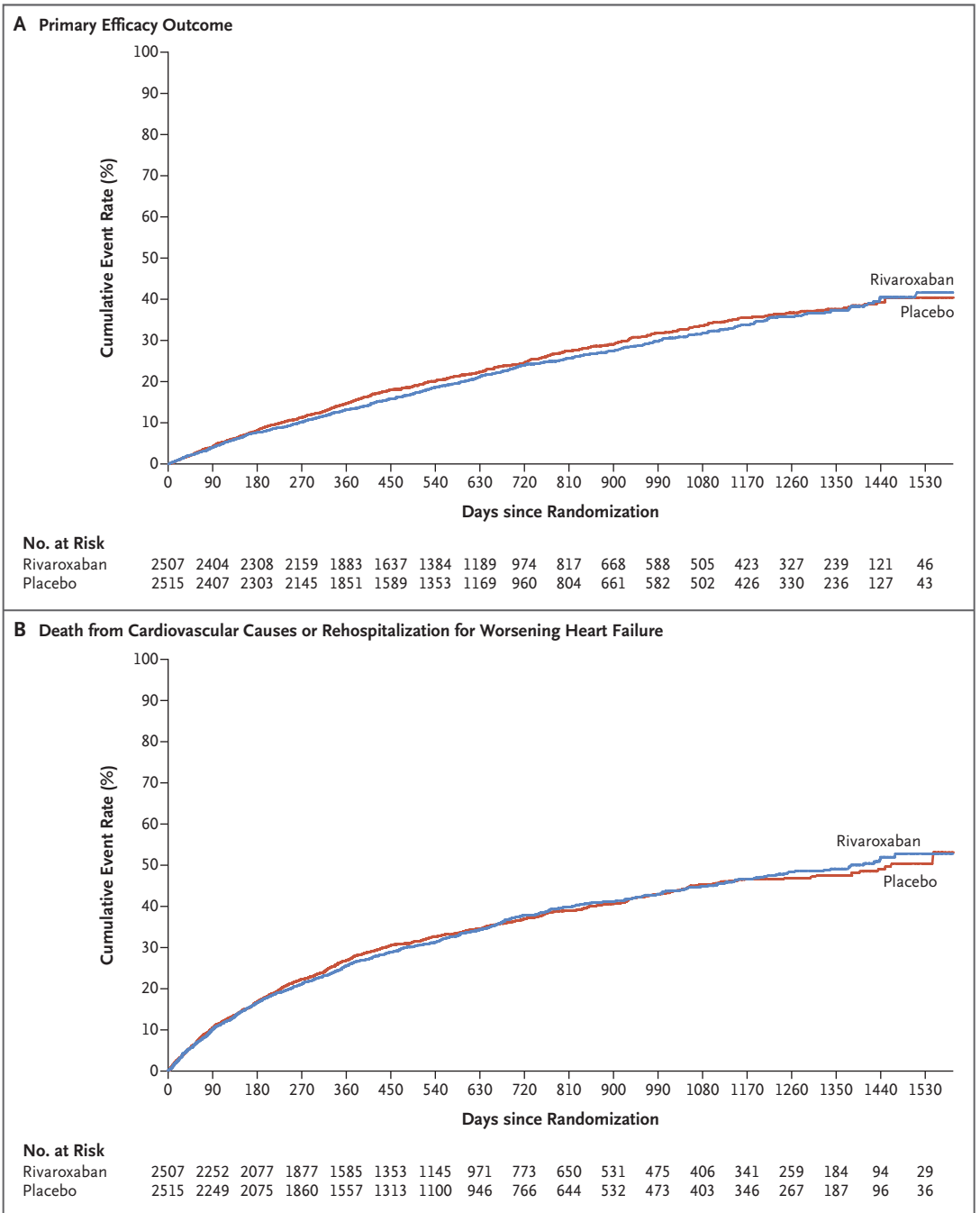

Figure 2. Kaplan–Meier Analysis of the Primary Efficacy Outcome and of Death from Cardiovascular Causes or Rehospitalization for Worsening Heart Failure.

The primary efficacy outcome was the composite of death from any cause, myocardial infarction, or stroke.

cardial infarction were 3.9% and 4.7%, respectively (hazard ratio, 0.83; 95% CI, 0.63 to 1.08), and the rates of stroke were 2.0% and 3.0%, respectively (hazard ratio, 0.66; 95% CI, 0.47 to 0.95). Across all subgroups, the findings were generally consistent with the overall efficacy result (Fig. 3, and Fig. S1 in the Supplementary Appendix).

Subgroup	No. of Patients	Rivaroxaban	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
		no. of events/total no. (%)			
Overall	5022	626/2507 (25.0)	658/2515 (26.2)	0.94 (0.84–1.05)	
Sex					0.36
Male	3872	487/1956 (24.9)	517/1916 (27.0)	0.92 (0.81–1.04)	
Female	1150	139/551 (25.2)	141/599 (23.5)	1.05 (0.83–1.33)	
Region					0.14
Eastern Europe	3224	389/1610 (24.2)	388/1614 (24.0)	1.00 (0.87–1.15)	
Western Europe and South Africa	458	61/227 (26.9)	78/231 (33.8)	0.76 (0.54–1.06)	
North America	149	17/74 (23.0)	25/75 (33.3)	0.64 (0.35–1.19)	
Asia-Pacific	733	104/367 (28.3)	94/366 (25.7)	1.11 (0.84–1.46)	
Latin America	458	55/229 (24.0)	73/229 (31.9)	0.73 (0.51–1.04)	
Age					0.43
<75 yr	3831	451/1912 (23.6)	470/1919 (24.5)	0.96 (0.85–1.09)	
≥75 yr	1191	175/595 (29.4)	188/596 (31.5)	0.87 (0.70–1.07)	
BMI					0.03
<25	1602	206/809 (25.5)	253/793 (31.9)	0.76 (0.63–0.92)	
25 to <30	1974	265/1016 (26.1)	236/958 (24.6)	1.05 (0.88–1.25)	
≥30	1442	155/680 (22.8)	167/762 (21.9)	1.03 (0.83–1.28)	
Estimated GFR (ml/min/1.73 m^2)					0.18
<30	163	24/81 (29.6)	36/82 (43.9)	0.59 (0.35–1.01)	
30 to <60	1782	274/884 (31.0)	272/898 (30.3)	1.03 (0.87–1.22)	
60 to <90	2238	231/1101 (21.0)	267/1137 (23.5)	0.86 (0.72–1.03)	
≥90	839	97/441 (22.0)	83/398 (20.9)	1.05 (0.78–1.40)	
BNP, NT-proBNP					0.09
≤Median	1950	192/974 (19.7)	185/976 (19.0)	1.03 (0.84–1.26)	
>Median	1949	240/969 (24.8)	289/980 (29.5)	0.82 (0.69–0.97)	
Baseline D-dimer					0.42
≤First quartile	1039	90/516 (17.4)	77/523 (14.7)	1.13 (0.83–1.54)	
>First quartile to ≤median	1027	131/505 (25.9)	125/522 (23.9)	1.03 (0.81–1.32)	
>Median to ≤third quartile	1020	137/491 (27.9)	160/529 (30.2)	0.90 (0.72–1.13)	
>Third quartile	1021	163/525 (31.0)	174/496 (35.1)	0.88 (0.71–1.09)	
Baseline NYHA classification					0.22
I	149	19/80 (23.8)	11/69 (15.9)	1.61 (0.76–3.42)	
II	2218	247/1122 (22.0)	241/1096 (22.0)	1.00 (0.84–1.20)	
III	2462	324/1208 (26.8)	369/1254 (29.4)	0.87 (0.75–1.01)	
IV	192	35/96 (36.5)	37/96 (38.5)	0.98 (0.60–1.59)	
Baseline ejection fraction (%)					0.27
<30	1502	220/717 (30.7)	264/785 (33.6)	0.87 (0.73–1.04)	
≥30	3520	406/1790 (22.7)	394/1730 (22.8)	0.99 (0.86–1.14)	

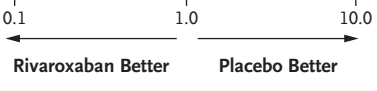

Figure 3. Subgroup Analyses of the Primary Efficacy Outcome.

All the subgroups were prespecified. Additional subgroup analyses are provided in Figure S1 in the Supplementary Appendix. The hazard ratios and 95% confidence intervals are from a Cox proportional-hazards model stratified according to region, with trial-group assignment as the only effect. The dashed vertical line indicates the hazard ratio in the overall trial population. For the region subgroup, the Cox model is unstratified. The P value (two-sided) for the interaction of trial group and each baseline subgroup is based on the Cox proportional-hazards model stratified according to region. The terms in the Cox model are trial group, baseline subgroup, and their interaction. Body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. BNP denotes brain natriuretic peptide, GFR glomerular filtration rate, NT-proBNP N-terminal pro-brain natriuretic peptide, and NYHA New York Heart Association.

SECONDARY EFFICACY OUTCOMES

The composite outcome of death from cardiovascular causes or rehospitalization for heart failure occurred in 932 patients (37.2%) in the rivaroxaban group and 929 patients (36.9%) in the placebo group (hazard ratio, 0.99; 95% CI, 0.91 to 1.09) (Table 2 and Fig. 2). A total of 84.3% of the deaths were attributed to cardiovascular disease; death from cardiovascular causes occurred in 18.1% and 18.9% of patients in the rivaroxaban and placebo groups, respectively (hazard ratio, 0.95; 95% CI, 0.84 to 1.08). The rates of the composite outcome of death from any cause or hospitalization for heart failure were 39.6% and 38.7%, respectively (hazard ratio, 1.01; 95% CI, 0.92 to 1.10). Details of the other outcomes and their components are provided in Table 2.

SAFETY OUTCOMES

The principal safety outcome of fatal bleeding or bleeding into a critical space with a potential for causing permanent disability occurred in 18 patients (0.7%) assigned to rivaroxaban and 23 (0.9%) assigned to placebo (hazard ratio, 0.80; 95% CI, 0.43 to 1.49; P=0.48). Fatal bleeding events occurred in 9 patients in each group, but fewer critical-space bleeding events occurred in the rivaroxaban group than in the placebo group (13 [0.5%] vs. 20 [0.8%]; hazard ratio, 0.67; 95% CI, 0.33 to 1.34; P=0.25) (Table 2).

While taking the trial regimen, patients assigned to rivaroxaban had a higher risk of ISTH-defined major bleeding than those assigned to placebo (3.3% vs. 2.0%; hazard ratio, 1.68; 95% CI, 1.18 to 2.39). This result was mainly driven by the criterion of a decrease in hemoglobin level of at least 2 g per deciliter. Patients assigned to rivaroxaban had more bleeding events requiring hospitalization than those assigned to placebo (Table 2).

Serious adverse events were reported in 381 patients (15.2%) assigned to rivaroxaban and 358 patients (14.3%) assigned to placebo (Table S4 in the Supplementary Appendix). The percentage of patients who permanently discontinued the trial regimen because of an adverse event was 7.1% in the rivaroxaban group and 5.8% in the placebo group.

DISCUSSION

In this trial, we tested the hypothesis that rivaroxaban at a dose of 2.5 mg twice daily in addition to standard care, in patients with recent worsening of chronic heart failure, reduced ejection fraction, and coronary artery disease who did not have atrial fibrillation, would be associated with a lower risk of the composite outcome of death from any cause, myocardial infarction, or stroke than placebo. In this population, rivaroxaban was not found to have a benefit with regard to the primary outcome. There was no significant between-group difference in the rate of the principal safety outcome of fatal bleeding or bleeding into a critical space with a potential for causing permanent disability.

In patients with chronic heart failure and reduced ejection fraction, medical therapy directed at activation of neurohormonal systems and devices such as cardiac resynchronization therapy and implantable cardioverter–defibrillators have had a substantial effect on the natural history.[16,17] Yet these patients remain at high long-term risk for death and cardiovascular events despite the existence of treatments that are targeted at a variety of mechanistic pathways.[18-22]

Early evidence suggesting a benefit of anticoagulation in patients with heart failure was observed in a previous study.[23] This study was followed by prospective clinical trials in which warfarin was compared with various antiplatelet agents,[6,7] which did not show clear evidence of efficacy. The development of agents that modify the production or activity of thrombin has led to a growing appreciation that the hemostatic system may trigger inflammation, endothelial dysfunction, and thrombosis, all of which may play a role in the progression of heart failure and in the pathogenesis of clinical events.[24]

Previous studies have suggested that inhibition of thrombin generation with rivaroxaban could be beneficial in patients with heart failure. In the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51 trial (ATLAS ACS 2–TIMI 51), involving patients with a recent acute coronary syndrome, rivaroxaban (2.5 mg twice daily) added to a background of dual antiplatelet therapy was associated with a lower likelihood of the primary end point of death from cardiovascular causes, myocardial infarction, or stroke than placebo.[13] A subgroup analysis from that trial suggested that patients with a history of heart failure were at a higher risk for cardiovascular events and derived

greater benefit from rivaroxaban treatment.[25] In the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, in patients with stable atherosclerotic disease, the combination of rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg daily) but not rivaroxaban (5 mg twice daily) alone was associated with a significantly lower rate of the composite outcome of cardiovascular mortality, stroke, or myocardial infarction than aspirin (100 mg) alone.[14] Analysis of the subgroup of patients with a history of heart failure who were enrolled in the COMPASS trial suggested that they may benefit from treatment with rivaroxaban in combination with aspirin.[26]

The most likely reason for the failure of rivaroxaban at a dose of 2.5 mg twice daily to improve cardiovascular outcomes in the current trial is that thrombin-mediated events are not the major driver of heart failure–related events in patients with recent hospitalization for heart failure. Indeed, readmission to the hospital for heart failure was the single most frequent event in the trial, and it is likely that heart failure, rather than deaths mediated by atherothrombotic events, contributed to a substantial proportion of all deaths. Whether a higher dose of rivaroxaban could have led to a more favorable outcome remains unknown.

This trial has some limitations. Events were not centrally adjudicated, and therefore we cannot comment on possible misclassifications of causes of hospitalization and death. Nonetheless, the systematic collection of prespecified comprehensive details on events with verification of source data reduces the possibility of misclassification. Second, the rate of discontinuation of the trial regimen was higher than estimated. However, increasing the number of events by extending follow-up time allowed us to maintain the initially intended power of 80% to detect a significant effect of rivaroxaban on the primary efficacy end point. Third, in the absence of electrocardiographic monitoring, we cannot exclude the possibility that subclinical atrial fibrillation may have contributed to stroke events and been favorably influenced by rivaroxaban. Finally, the rate of use of cardiac resynchronization therapy and implantable cardioverter–defibrillators was low; however, the rate of use of guideline-based pharmacologic therapy was high and was maintained throughout the trial.

In conclusion, in patients with recent worsening of chronic heart failure and reduced ejection fraction who also had underlying coronary artery disease and were not in atrial fibrillation, low-dose rivaroxaban added to guideline-based therapy was not associated with a lower rate of the composite outcome of death from any cause, myocardial infarction, or stroke than placebo, nor did it favorably influence the rate of rehospitalization for heart failure.

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APPENDIX

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