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ORIGINAL ARTICLE

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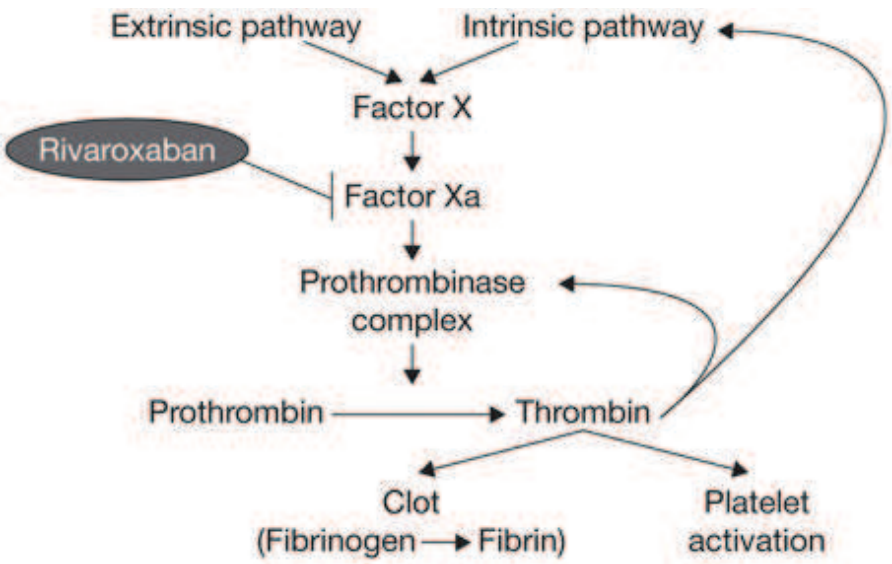

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BACKGROUND

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.

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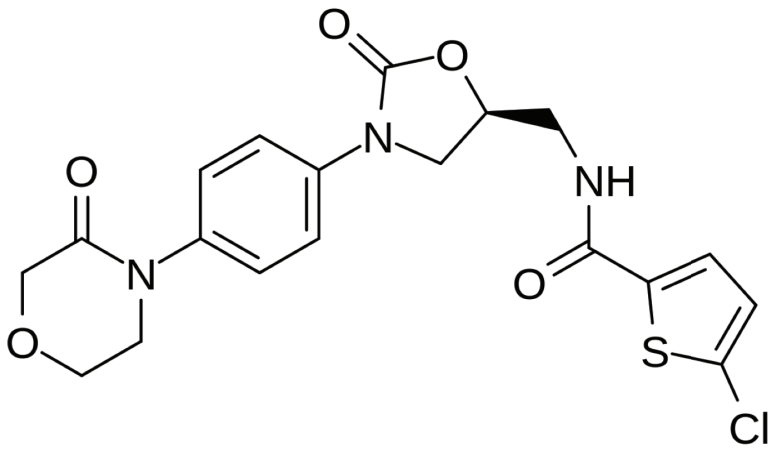

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METHODS

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.

Study Design

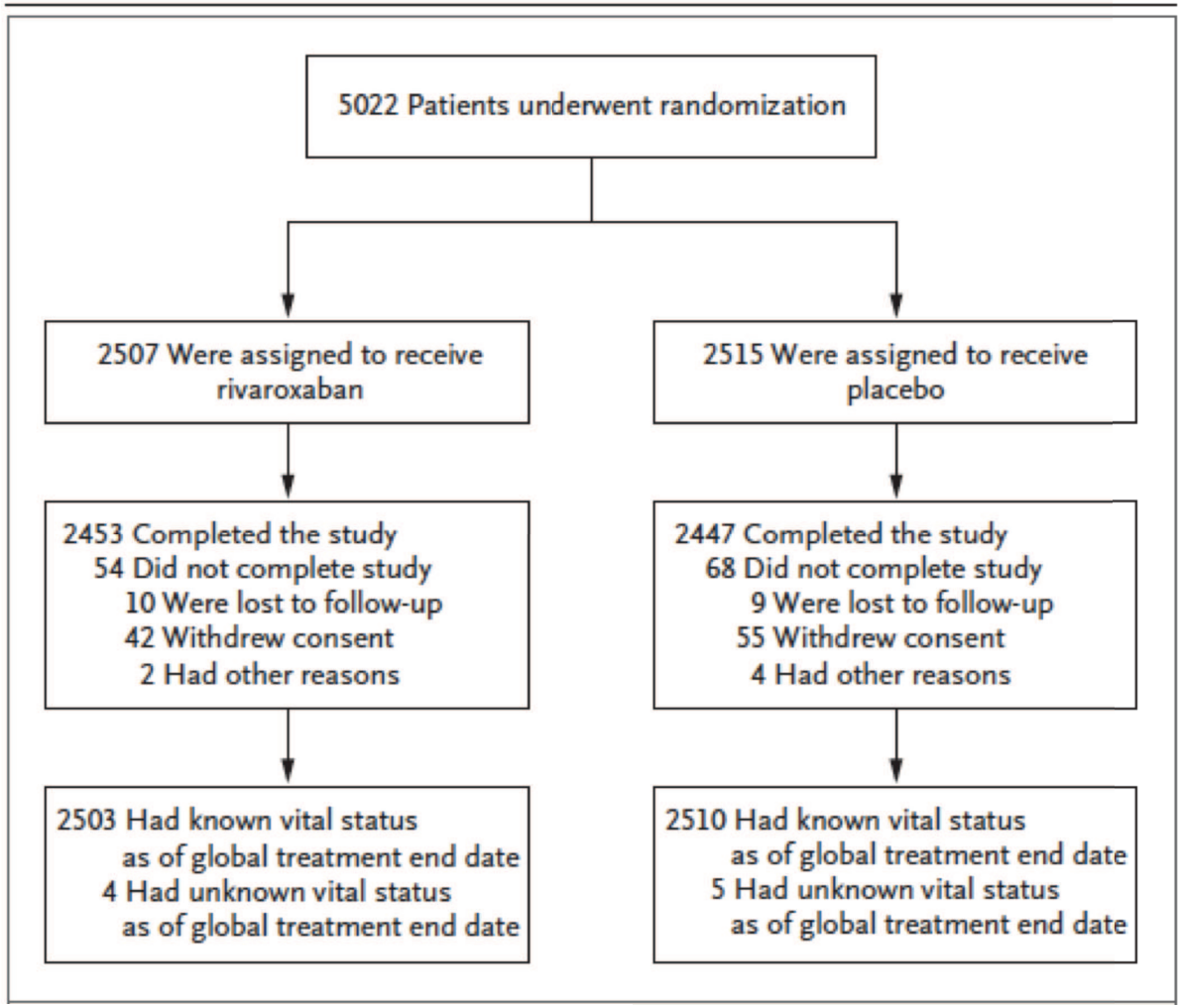

Figure 1. Randomization and Follow-up.

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.

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.

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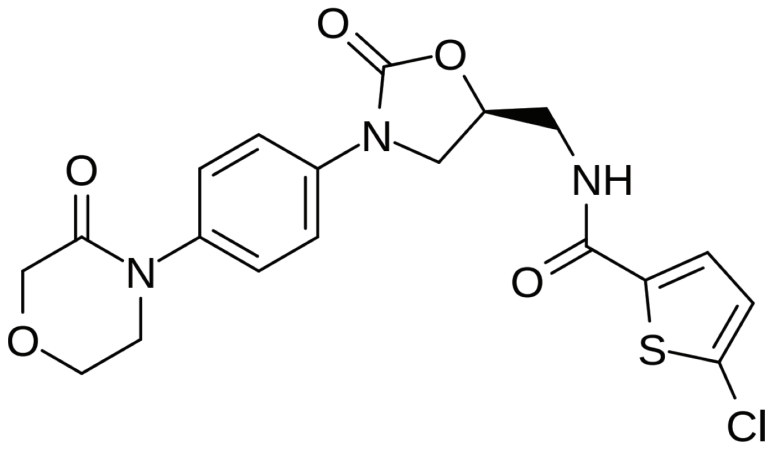

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RESULTS

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).

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

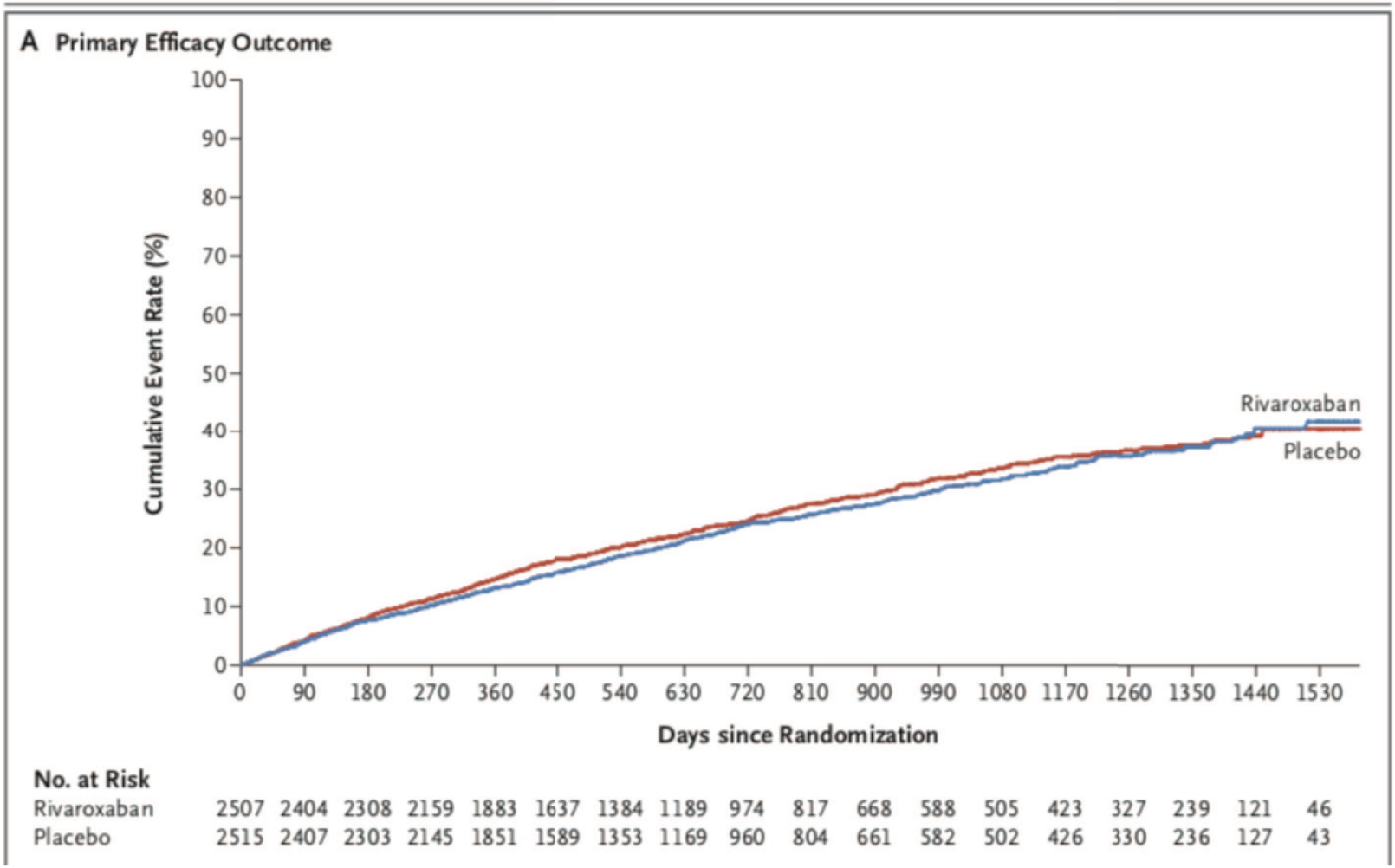
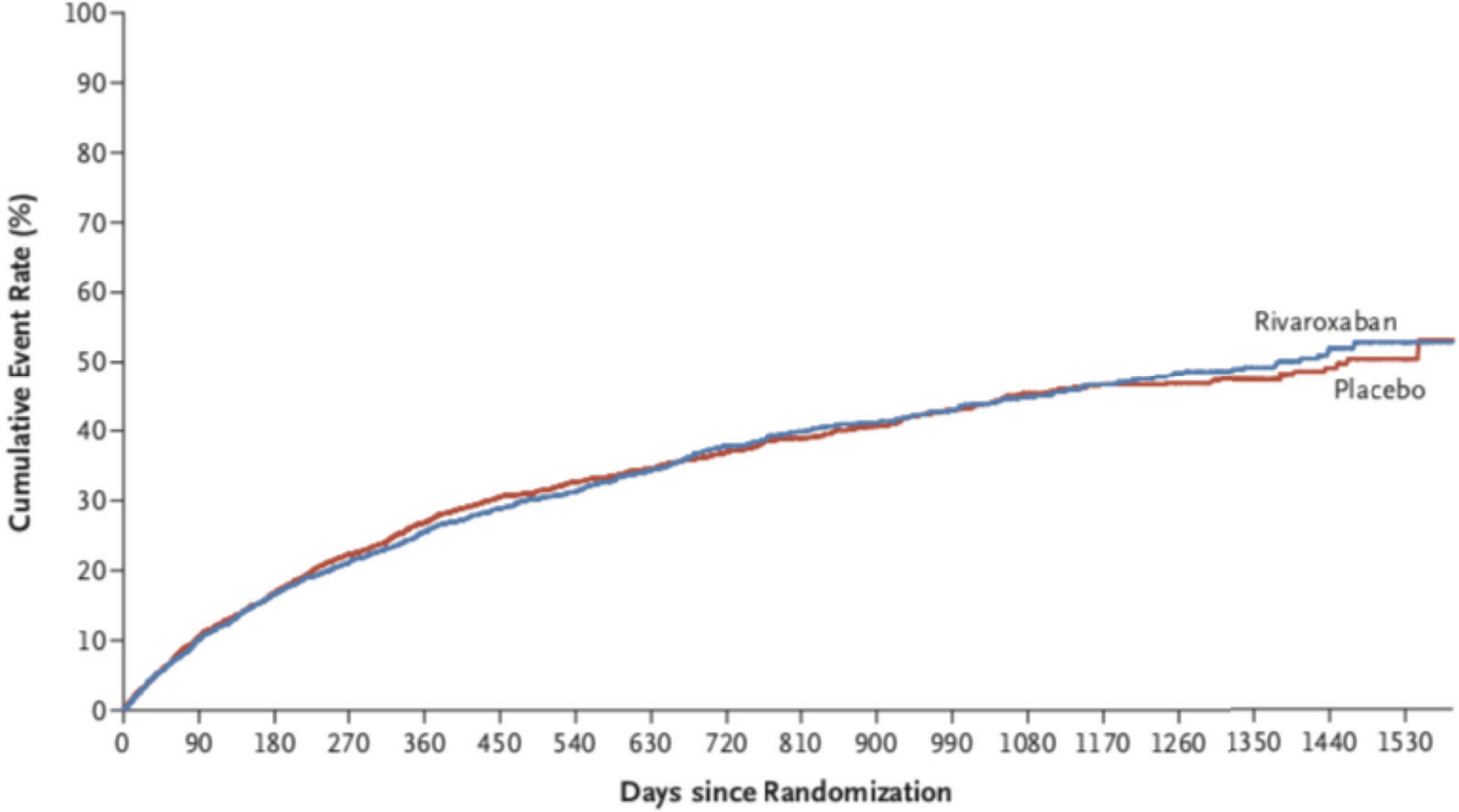


Figure 2. Kaplan–Meier Analysis of the Primary Efficacy Outcome and of Death from Cardiovascular Causes or Rehospitalization for Worsening Heart Failure.

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

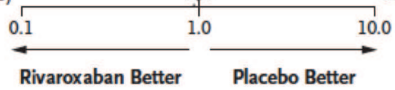
B Death from Cardiovascular Causes or Rehospitalization for Worsening Heart Failure



No. at Risk

Rivaroxaban	2507	2252	2077	1877	1585	1353	1145	971	773	650	531	475	406	341	259	184	94	29
Placebo	2515	2249	2075	1860	1557	1313	1100	946	766	644	532	473	403	346	267	187	96	36

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)	



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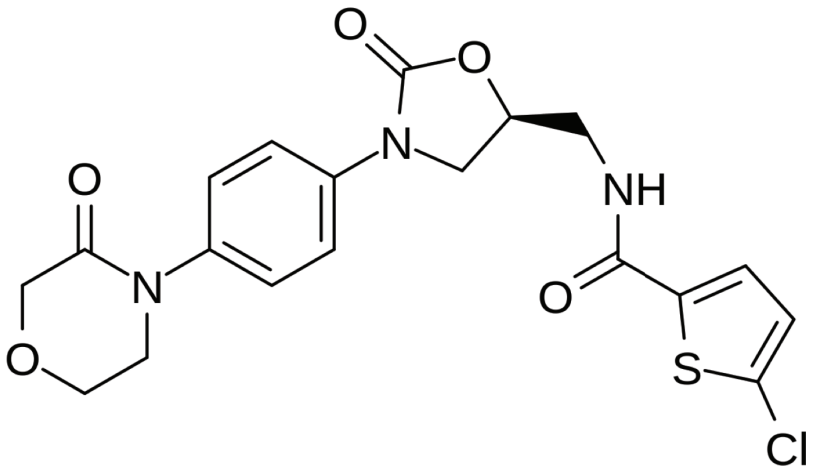

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CONCLUSIONS

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.)