ΠΑΝΕΠΙΣΤΗΜΙΑΚΗ
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ΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΑΛΕΞΑΝΔΡΟΥΠΟΛΗΣ

ΔΗΜΟΚΡΙΤΕΙΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΡΑΚΗΣ | DEMOCRITUS UNIVERSITY OF THRACE

INVICTUS

Rivaroxaban in Rheumatic Heart Disease- Associated Atrial Fibrillation

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The need for this trial

Special characteristics of patients with rheumatic heart disease associated AF

- Younger age
- Mostly women
- Valvular disease

- Underdeveloped countries (hard INR monitoring)
- Lack of evidence (exclusion of rheumatic patients from other trials)

Study method

International, multi-center, Randomization, Parallel, Open-label

Total number of enrollees: 4,531

(n = 2,275)

Rivaroxaban 20 mg daily (15 mg daily if creatinine clearance <50 ml/min)

(n = 2,256)

Vitamin K antagonist (international normalized ratio [INR] range 2.0-3.0)

Monthly INR

- 1st Follow up in 1 month
- Then every 6 months
- Duration of follow-up: 3.1 years

- Mean patient age: 50 years
- Percentage female: 72%
- Percentage with diabetes: 6.4%

INCLUCION CRITERIA

- At least 18 years of age with rheumatic heart disease
- Atrial fibrillation or atrial flutter
- At least one of the following:
  - CHA_2DS_2-VASc score >1,
  - mitral valve area <2 cm^2,
  - echocardiographic evidence of either left atrial spontaneous echo contrast or left atrial thrombus

EXCLUSION CRITERIA

- Presence of a mechanical heart valve or the likelihood of receiving one within the next 6 months
- Dual antiplatelet therapy
- Treatment with dual strong inhibitors of CYP3A4 and P-glycoprotein
- eGFR <15 ml/min/1.73 m^2
- Pregnancy

Patient characteristics

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.

Results ITT

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.

Results ITT

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Outcome	Rivaroxaban (N=2275)			Vitamin K Antagon (N=2256)				
	No. of Patients	Rate %/yr	RMST days	No. of Patients	Rate %/yr			
Stroke, systemic embolism, myocardial infarction, or death from vascular or unknown causes	560	8.21	1599	446	6.49			
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)

More patients in the rivaroxaban group than in the vitamin K antagonist group had a stroke, a finding that was almost entirely due to a higher rate of ischemic stroke in the rivaroxaban group

* 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.

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Stroke of uncertain cause	12	0.17	1991	10	0.14			
Systemic embolism	6	0.09	1995	10	0.14			
Stroke or systemic embolism	94	1.38	1926	75	1.09			
Myocardial infarction	5	0.07	1996	3	0.04			
Death	552	7.95	1608	442	6.35			
Death due to vascular causes†	439	6.33	1683	337	4.84			
Sudden cardiac death	141	2.03	1894	94	1.35	1929	1.51 (1.16 to 1.96)	−36 (−58 to −13)
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More patients in the rivaroxaban group than in the vitamin K antagonist group had a stroke, a finding that was almost entirely due to a higher rate of ischemic stroke in the rivaroxaban group

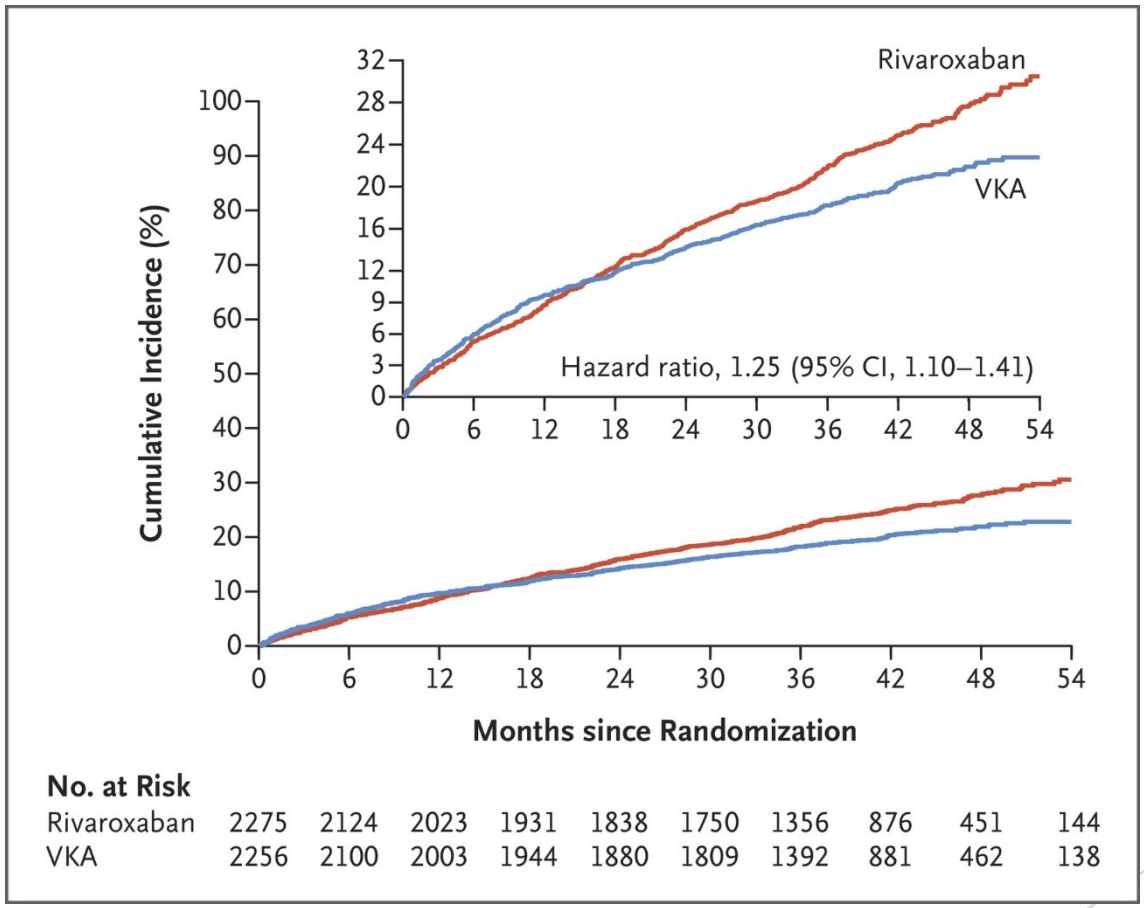
A total of 552 patients in the rivaroxaban group and in 442 in the vitamin K antagonist group died. The difference in mortality was almost entirely due to lower rates of sudden cardiac death and of death due to mechanical or pump failure in the vitamin K antagonist group than in the rivaroxaban group

* 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.

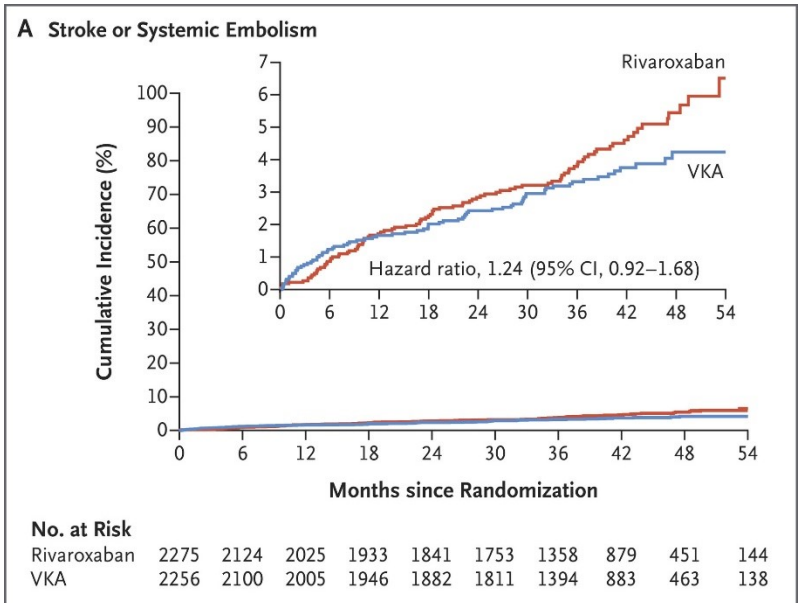
† Vascular causes could be cardiac or noncardiac. Deaths due to vascular causes other than sudden death or death due to mechanical or pump failure occurred in 61 patients in the rivaroxaban group and in 69 in the vitamin K antagonist group.

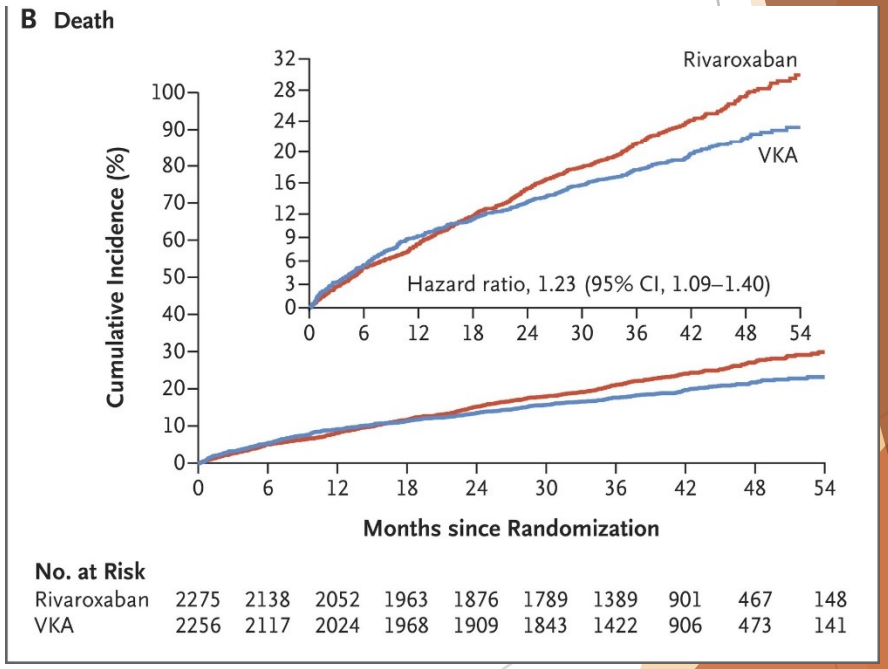
Primary Endpoint

Composite of Stroke, Systemic Embolism, Myocardial Infarction, or Death from Vascular or Unknown Causes



Secondary Endpoint





Safety and OTA

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. 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.

Safety and OTA

The between-group differences in the rates of stroke and death were similar in the on-treatment analyses and the intention-to-treat analyses

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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)	
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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)	
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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.

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

Limitations

- Overall rates of stroke were lower than expected; therefore, the trial had reduced power for the outcome of stroke.
- Although outcome assessments were blinded, patients were aware of the treatment assignments.
- Patients in the vitamin K antagonist group had more physician interactions owing to the need for anticoagulation monitoring, and their time in the anticoagulation range improved during the trial.

CONCLUSIONS

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Rivaroxaban in Rheumatic Heart Disease–Associated Atrial Fibrillation

Connolly SJ et al. DOI: 10.1056/NEJMoa2209051

CLINICAL PROBLEM

Trials showing that factor Xa inhibitors such as rivaroxaban reduce stroke risk among patients with atrial fibrillation have not included patients with rheumatic heart disease. Such patients are treated with vitamin K antagonists, which require frequent blood sampling to measure anticoagulation status.

CLINICAL TRIAL

Design: A randomized trial in Africa, Asia, and Latin America compared cardiovascular outcomes among patients with atrial fibrillation associated with rheumatic disease treated with rivaroxaban or vitamin K antagonist (VKA) therapy.

Intervention: 4565 adults with rheumatic heart disease and atrial fibrillation or flutter were assigned to receive a vitamin K antagonist or rivaroxaban. The primary outcome was a composite of stroke, systemic embolism, myocardial infarction, or death from vascular or unknown causes.

RESULTS

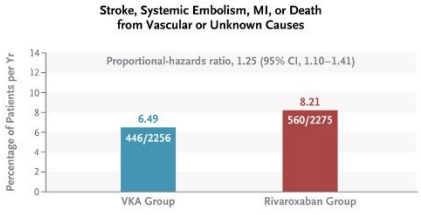
Efficacy: Primary-outcome events occurred in more patients in the rivaroxaban group than in the vitamin K antagonist group.

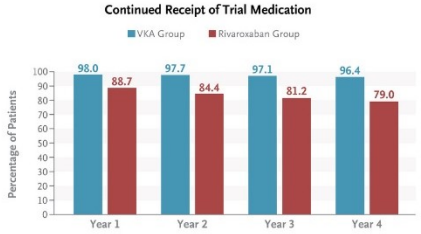
Safety: Rates of major bleeding did not differ significantly between the treatment groups. More patients in the rivaroxaban group discontinued trial treatment.

LIMITATIONS AND REMAINING QUESTIONS

- Overall rates of stroke were lower than expected; therefore, the trial had reduced power for the outcome of stroke.
- Although outcome assessments were blinded, patients were aware of the treatment assignments.
- Patients in the vitamin K antagonist group had more physician interactions owing to the need for anticoagulation monitoring, and their time in the anticoagulation range improved during the trial.

Links: Full Article | NEJM Quick Take | Editorial





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.

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Thank you