RIVAROXABAN NEI PAZIENTI CON FIBRILLAZIONE ATRIALE E VALVULOPATIA REUMATICA

RISULTATI DEL TRIAL INVICTUS

BACKGROUND

- In low- and middle-income countries, rheumatic heart disease remains an important cause of atrial enlargement and atrial fibrillation (AF).
- Patients with AF due to rheumatic heart disease differ substantially from other patients with AF; they are usually much younger, are more often female, and often have advanced valvular disease.
- RCTs have shown that non–vitamin K antagonist oral anticoagulants (NOAC) are as effective as vitamin K antagonist (VKA) therapy for stroke prevention and have a lower risk of intracranial hemorrhage. However, they excluded patients who had AF due to rheumatic heart disease.
- Guidelines do not recommend the use of NOAC for stroke prevention in patients with rheumatic heart disease–associated AF.
- 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 VKA is often a challenge, owing to difficulties in travel and to limitations in health care resources.

Rivaroxaban in Rheumatic Heart Disease–Associated Atrial Fibrillation

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AIM

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.

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METHODS

- Patients with AF and echocardiographically documented rheumatic heart disease who had any of the following:
  - a CHA2DS2VASc score ≥ 2
  - a mitral-valve area ≤2 cm2,
  - left atrial spontaneous echo contrast or left atrial thrombus.
- Patients were randomly assigned to receive standard doses of rivaroxaban or dose-adjusted VKA.
- Primary efficacy outcome was a composite of stroke, systemic embolism, myocardial infarction, or death from vascular (cardiac or noncardiac) or unknown causes.
- Primary safety outcome was major bleeding according to the International Society of Thrombosis and Hemostasis.

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BASELINE CHARACTERISTICS

- Mean age: 50.5 years, 72.3% women.
- Mean follow-up 3.1±1.2 yrs.
- Moderate-to-severe mitral stenosis in 81.9%
- ~50% CHA_2DS_2VASc <2.
- VKA before enrollment in 52.8%.
- INR in range: baseline in 33.2% 6mo in 56.1%, 1yr in 59.0%, 2 yrs in 65.3%, 3 yrs in 65.1%, 4 yrs in 64.1%

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)

STUDY DRUG DISCONTINUATION

- The % of pts with permanent discontinuation was higher in the rivaroxaban group.
- Most common reasons were hospitalization for valve surgery and decision by the patient.
- Many pts who discontinued rivaroxaban subsequently received a VKA, whereas those who discontinued VKA did not usually receive an oral anticoagulant thereafter.

	Overall		Rivaroxaban		VKA	
	N	%	N	%	N	%
Patients randomized	4531		2275		2256	
ON study drug at the time of final visit	3867	85.35	1749	76.88	2118	93.88
Never interrupted	3104	68.51	1343	59.03	1761	78.06
Restarted after interruption	763	16.84	406	17.85	357	15.82
OFF study drug at the time of final visit	664	14.65	526	23.12	138	6.12
Never started	12	0.26	9	0.40	3	0.13
Permanently discontinued	652	14.39	517	22.73	135	5.98
Reasons for permanent discontinuation*						
Outcome event	62	9.51	46	8.90	16	11.85
Serious adverse event	13	1.99	8	1.55	5	3.70
Non-serious adverse event	28	4.29	19	3.68	9	6.67
Hospitalization	166	25.46	135	26.11	31	22.96
Participant decision	159	24.39	128	24.76	31	22.96
Pregnancy	8	1.23	5	0.97	3	2.22
Poor/Non-compliance	55	8.44	42	8.12	13	9.63
COVID	6	0.92	5	0.97	1	0.74
Valve surgery- crossover	64	9.82	62	11.99	2	1.48
Cross-over (other)	6	0.92	6	1.16	0	0.00
Physician decision	14	2.15	10	1.93	4	2.96
Travel difficulty/regional insecurity	9	1.38	8	1.55	1	0.74
Other	59	9.05	41	7.93	18	13.33

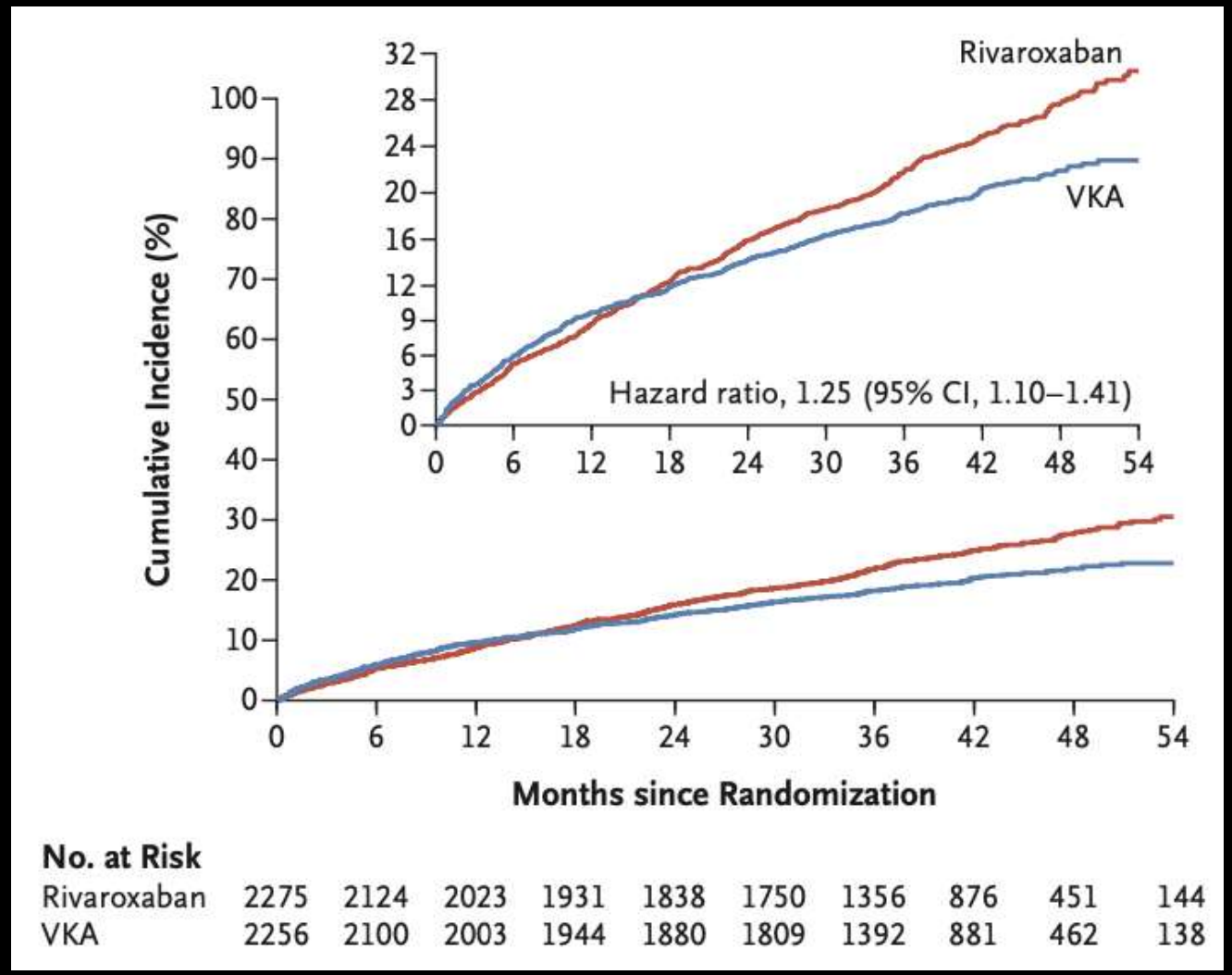
*- % are based on permanent discontinuation

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 %/yr	RMST days	No. of Patients	Rate %/yr	RMST 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)	

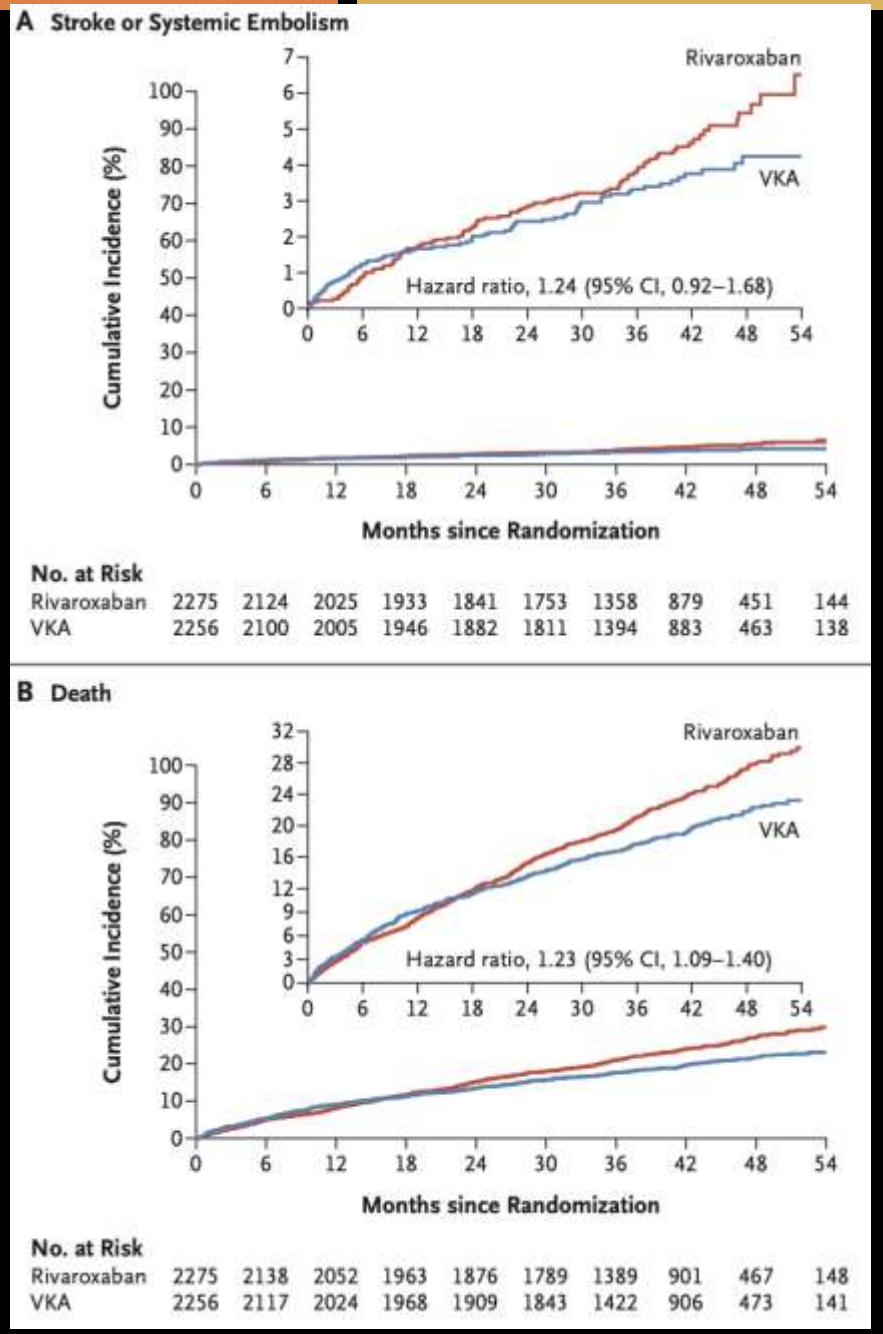
CUMULATIVE INCIDENCE OF THE PRIMARY OUTCOME.

- The restricted mean survival time was 1599 days in the rivaroxaban group and 1675 days in the VKA group (difference, −76 days; 95% CI, −121 to −31 days; P<0.001 for superiority).



CUMULATIVE INCIDENCES OF STROKE OR SYSTEMIC EMBOLISM AND OF DEATH

- More patients in the rivaroxaban group had a stroke (90 vs. 65 pts), almost entirely due to a higher rate of ischemic stroke.
- A total of 552 pts in the rivaroxaban group and in 442 in the VKA 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 VKA group



ON-TREATMENT ANALYSIS OF SAFETY OUTCOMES AND SELECTED EFFICACY OUTCOMES

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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 %/yr	RMST days	No. of Patients	Rate %/yr	RMST 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)	

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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