É seguro utilizar novos anticoagulantes em pacientes reumáticos?

O recém publicado trial *INVICTUS* avaliou a utilização de rivaroxabana em pacientes com fibrilação causada por doença cardíaca reumática. Este estudo foi apresentado no último congresso da Sociedade Europeia de Cardiologia – ESC 2022 em Barcelona e publicado simultaneamente no *New England Journal of Medicine*.

De acordo com este estudo a utilização de rivaroxabana (inibidor do fator Xa) associou-se a um risco 25% maior de AVC, embolismo sistêmico, infarto do miocárdio ou morte por causas vascular ou causas desconhecidas – o desfecho primário de eficácia – quando comparado com antagonistas da vitamina K (VKA), uma diferença dirigida principalmente por aumento de morte e AVC isquêmico no grupo rivaroxabana.

Base teórica:

Em ensaios clínicos randomizados de fibrilação atrial não valvar, DOACs provaram ser tão efetivos quando comparado com varfarin, com menor risco de hemorragia intracraniana. No estudo *Rocket AF*, rivaroxabana mostrou-se não inferior a varfarin para prevenção de AVC ou embolismo sistêmico, sem diferença no risco de sangramento maior entre os dois grupos, mas com menor taxa de sangramento intracraniano e fatal.

Paciente com AF reumática diferem dos pacientes com FA não valvar por serem mais jovens e mais frequentemente mulheres e frequentemente apresentarem-se com doença valvar avançada, particularmente estenose mitral.

Doença cardíaca reumática afeta 40 milhões de pessoas no mundo, com cerca de 20% dos pacientes que são sintomáticos apresentando AF e elevado risco de AVC. Apenas metade dos pacientes com AF associada à doença cardíaca reumática são tratados com VKA. Entre os pacientes tratados, apenas 1/3 estão com INR dentro do alvo terapêutico.

Desenho do estudo:

4.565 pacientes com AF/flutter e doença cardíaca reumática documentada provenientes de 24 países foram arrolados (média de idade 50,5 anos; 72,3% mulheres) (2292 no grupo rivaroxabana e 2273 no grupo VKA). A análise *intention-to-treat* incluiu 4531 pacientes (2275 no grupo rivaroxabana e 2256 no grupo VKA).

Para serem incluídos, os pacientes deveriam apresentar 1 dos seguintes critérios: CHA_2DS_2-VASc score de pelo menos 2; estenose mitral com área < 2.0 cm^2; ou ecocardiograma com evidência de contraste espontâneo no átrio esquerdo ou trombo no átrio esquerdo.

No total, 85% dos pacientes tinham estenose valvar mitral, a maioria classificada como moderada ou grave.

Dose: rivaroxabana 1x ao dia (20 mg ou 15 mg, de acordo com a função renal); VKA dose ajustada pelo IN (alvo 2.0-3.0)

Follow-up médio: 3,1±1,2 anos.

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.

Desfechos:

Desfecho primário de eficácia: desfecho composto de AVC, embolismo sistêmico, infarto do miocárdio, morte por causa vascular (cardíaca ou não cardíaca) ou de causa desconhecida.
Desfecho primário de segurança: sangramento maior

Resultados:

Desfecho primário de eficácia: 560 eventos no grupo rivaroxabana vs. 446 eventos no grupo VKA (HR 1,25; IC 95% 1,10-1,41) (intention-to-treat analysis)

Morte: rivaroxabana aumentou risco em 23% (tempo médio de sobrevida: 1608 dias vs. 1680 dias; diferença −72 dias; IC 95% −117 a −28 dias; mortes: 552 no grupo rivaroxabana vs. 422 no grupo VKA)

AVC: rivaroxabana aumentou risco em 37% (90 pacientes vs. 65 pacientes) (diferença −21; IC 95% −40 a −2)

Sangramento maior, ameaçador à vida ou clinicamente relevante e sangramento intracraniano: sem diferença

Sangramento fatal: menos comum com rivaroxabana (4 vs. 15 eventos)

Descontinuação do tratamento: mais comum em pacientes tratados com rivaroxabana (23% vs. 6%).

Nível de INR: varfarin era utilizada por 52,8% dos pacientes anteriormente ao início do estudo com apenas 33,2% dentro do alvo. Após início do estudo, INR estava no alvo em 56,1% dos pacientes aos 6 meses, 59% com 1 ano, 65,3% com 2 anos, 65,1% com 3 anos, 64,1% com 4 anos.

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)	

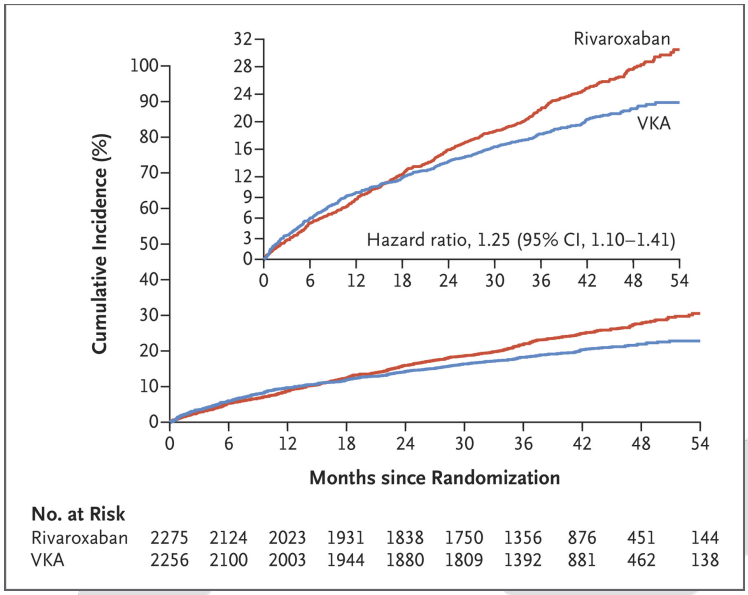
* The intention-to-treat population included all the patients who underwent randomization, except for 34 patients, whose data were excluded owing to duplicate randomization, potentially fraudulent data, or inability to obtain required re-consent. The widths of the confidence intervals have not been adjusted 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.

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

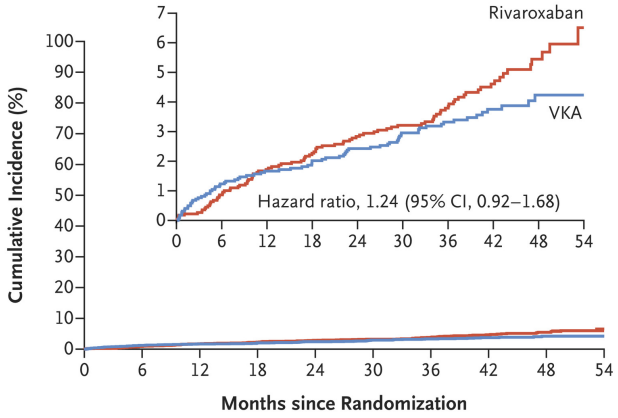
Outcome	Rivaroxaban (N=2265)			Vitamin K Antagonist (N=2251)			Proportional-Hazards Ratio (95% CI)	Difference in RMST (95% CI)	P Value
	No. of Patients	Rate	RMST	No. of Patients	Rate	RMST			
		%/yr	*days*		%/yr	*days*		*days*	
Safety outcomes									
Major bleeding	40	0.67	1965	56	0.83	1954	0.76 (0.51 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.



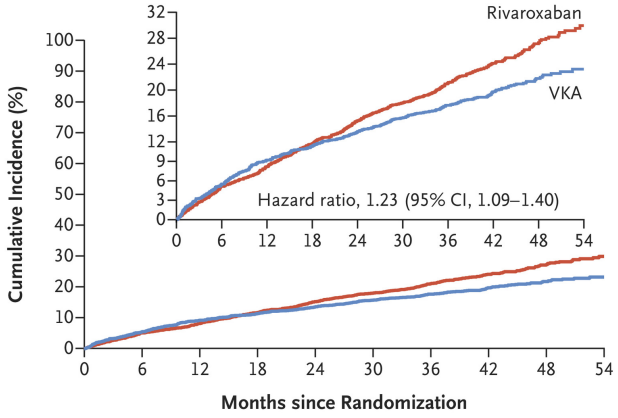
No. at Risk										
Rivaroxaban	2275	2124	2023	1931	1838	1750	1356	876	451	144
VKA	2256	2100	2003	1944	1880	1809	1392	881	462	138

A Stroke or Systemic Embolism



No. at Risk										
Rivaroxaban	2275	2124	2025	1933	1841	1753	1358	879	451	144
VKA	2256	2100	2005	1946	1882	1811	1394	883	463	138

B Death



No. at Risk										
Rivaroxaban	2275	2138	2052	1963	1876	1789	1389	901	467	148
VKA	2256	2117	2024	1968	1909	1843	1422	906	473	141

Conclusão:

Diante destes achados, VKA deve permanecer o tratamento de escolha em pacientes com fibrilação atrial reumática.

Referência:

Connolly SJ, Karthikeyan G, Ntsekhe M, et al. Rivaroxaban in Rheumatic Heart Disease-Associated Atrial Fibrillation [published online ahead of print, 2022 Aug 28]. *N Engl J Med*. 2022;10.1056/NEJMoa2209051. doi:10.1056/NEJMoa2209051