

Rivaroxaban for rheumatic heart disease associated atrial fibrillation - INVICTUS

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28th August 2022

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Background and rationale

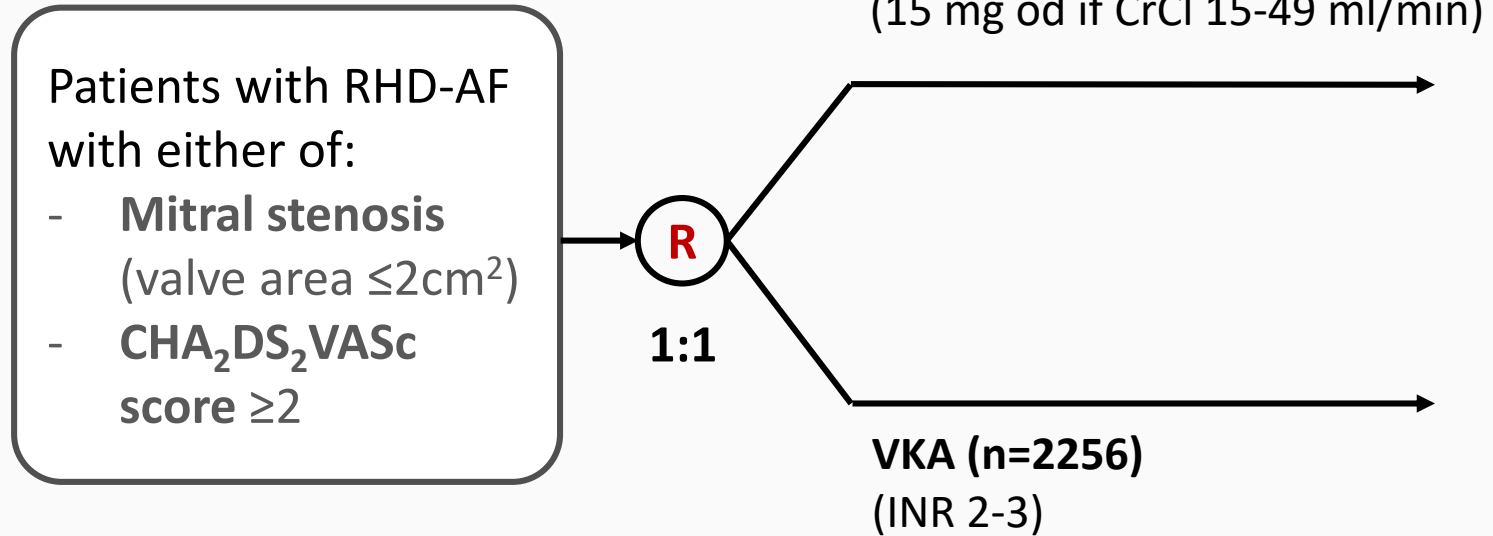
- RHD affects over 40 million people, mainly in LMICs
- About 20% of symptomatic RHD patients have AF
- **No RCTs** of anticoagulation in RHD-AF
- Less than ½ the patients are prescribed VKA, and just 1/3rd achieve therapeutic INRs

An anticoagulant that does not need monitoring would be of great benefit

Design

- **Design** Investigator-initiated, international, open-label, randomized, non-inferiority trial, with blinded outcome assessment
- Designed and coordinated by **Population Health Research Institute, Canada**
- **Funding:** Unrestricted grant from Bayer AG

Patients and interventions



Outcomes and analysis

- **Primary outcome:** Composite of **stroke/systemic embolism***, MI, death due to vascular or unknown cause
 - *Original primary outcome
- **Primary safety** outcome: ISTH major bleeding
- 4500 patients, 80% power for non-inferiority, with margin at HR of 1.186 (upper bound of the 97.5% CI)

Centres and countries



- 138 centres in 24 countries
- Africa, Asia, and Latin America
- **PHRI, Hamilton Coordinating Centre**

Baseline characteristics

	Rivaroxaban (n=2275)	VKA (n=2256)
Age, years, mean	50.7	50.3
Female sex, n (%)	1648 (72.4)	1626 (72.1)
Mitral valve stenosis, n (%)	1927 (85.5)	1903 (85.2)
Congestive HF, n (%)	879 (38.6)	866 (38.4)
Hypertension, n (%)	522 (22.9)	535 (23.7)
Diabetes, n (%)	158 (6.9)	132 (5.9)
Stroke, n (%)	248 (10.9)	257 (11.4)
Coronary artery disease, n (%)	32 (1.4)	20 (0.9)
CHA₂DS₂-VASc score 0-1, n (%)	978 (43)	993 (44)

Drug compliance and INR control

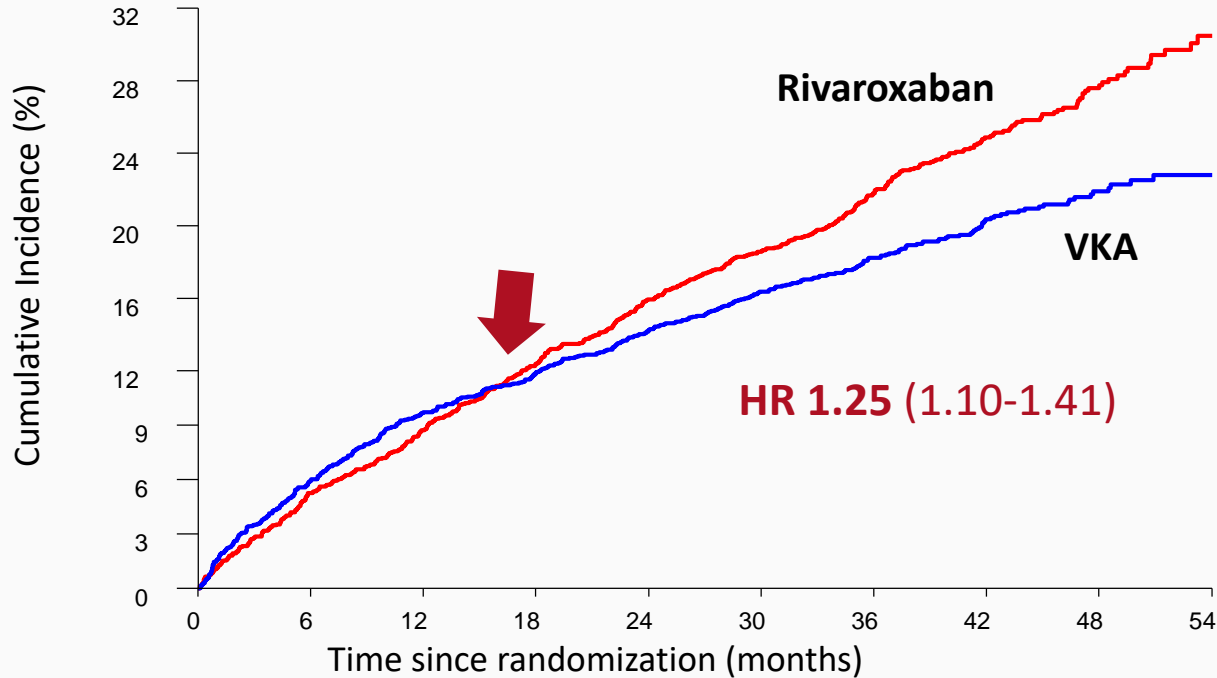
Drug compliance by visit (%)		
Visit	Riva	VKA
I year	88.7	98
II year	84.4	97.7
III year	81.2	97.1
IV year	79	96.4

INR control by visit	
Visit	INRs between 2-3, (%)
Baseline	33.2
I year	59.0
II year	65.3
III year	65.1
IV year	64.1

Permanent discontinuation: Riva 23%, VKA 6%

Results: Stroke, SE, MI or death (vascular or unknown)

4531 patients, 97% follow-up, average of 3.1 years



Proportional hazards assumption NOT met

Results: Efficacy - Intention-to-treat

Outcomes % per year (n)	Rivaroxaban (n=2275)	VKA (n=2256)	HR (95% CI)	RMST difference, days (95% CI)	p value (RMST)
Primary composite	8.2 (560)	6.5 (446)	1.25 (1.10-1.41)	-76 (-121, -31)	0.001
Death	8.0 (552)	6.4 (442)	1.23 (1.09-1.40)	-72 (-117, -28)	0.001
Ischemic stroke	1.1 (74)	0.7 (48)	1.53 (1.06-2.20)	-23 (-40, -6)	0.01

Few systemic embolism (16), and MI (8) events

On-treatment analysis showed similar results

Results: Safety - On treatment

Outcome % per year (n)	Rivaroxaban (n=2265)	VKA (n=2251)	HR (95% CI)	p value (RMST)
Major bleeding	0.7 (40)	0.8 (56)	0.76 (0.51-1.15)	0.18
- <i>Life-threatening</i>	0.4 (22)	0.5 (31)	0.77 (0.44-1.32)	0.31
- <i>Intracranial</i>	0.1 (8)	0.2 (14)	0.63 (0.26-1.50)	0.27
- <i>Fatal</i>	0.1 (4)	0.2 (15)	0.29 (0.10-0.88)	0.02

Difference in death unanticipated

- Not explained by difference in stroke
 - VKA prevented **26 ischemic strokes** vs. **110 deaths**
- Difference in mortality driven entirely by **HF and sudden deaths**
- No difference in bleeding
- More frequent healthcare contact in the VKA arm for INR
- Delayed effect - apparent only after 3 years

Conclusions

- In RHD-AF, compared to rivaroxaban, VKAs reduced ischemic stroke and mortality, without increasing the risk of major bleeding
- VKAs should remain the standard of care for RHD-AF
- Mortality benefit of VKA in RHD requires further study

INVICTUS study team

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ORIGINAL ARTICLE

Rivaroxaban in Rheumatic Heart Disease– Associated Atrial Fibrillation

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