HCor Research Institute

SOCESP Sociedade de Cardiologia do Estado de São Paulo

PROADI-SUS Programa de Apoio ao Desenvolvimento Institucional do Sistema Único de Saúde

River

Rivaroxaban Versus Warfarin In Patients With Atrial Fibrillation and Bioprosthetic Mitral Valves:

The RIVER Randomized Trial

Otavio Berwanger (MD; PhD) on Behalf of the RIVER Trial Steering Committee

Trial Oversight

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SETTING

49 Sites in Brazil

FUNDING

PROADI-SUS

Bayer

River

Background and Rationale

- Patients with atrial fibrillation and a bioprosthetic mitral valve require long-term anticoagulation, but the optimal therapeutic strategy remains uncertain.

- The efficacy and safety of DOACs in patients with atrial fibrillation and a mitral bioprosthetic valve are based on subgroup analyses of pivotal trials.

  - **ARISTOTLE** (apixaban) N = 31 patients
  - **ENGAGE-TIMI 48** (edoxaban) N = 131 patients

- Patients with bioprosthetic valves were excluded from the ROCKET-AF trial.

Study Design

Patients with atrial fibrillation or flutter and a bioprosthethic mitral valve

Randomized
(Concealed)
Open-label

Rivaroxaban

20 mg daily
15 mg for Cr Cl 30-49 ml/min

ITT

Warfarin

INR target
(2.0-3.0 inclusive)

ITT

Follow-up 12 months

Noninferiority RCT

Primary Endpoint*: death, major CV events**, or major bleeding

* adjudicated by a blinded Clinical Events Classification Committee
** stroke, TIA, valve thrombosis, systemic embolism not related to the central nervous system, or hospitalization for heart failure.

River

Secondary Endpoints

- **Efficacy**
  - Composite outcome of CV death or thromboembolic events (stroke, TIA, valve thrombosis, venous thromboembolism, or non-CNS systemic embolism)
  - Individual components of the combined endpoints

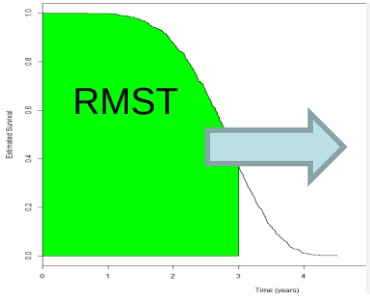
- **Safety**
  - Bleeding events (major, minor, minimal, or fatal)
  - Bleeding events are classified based on the ROCKET-AF definition, but also using the TIMI and BARC criteria

All endpoints were adjudicated by a blinded Clinical Events Classification Committee

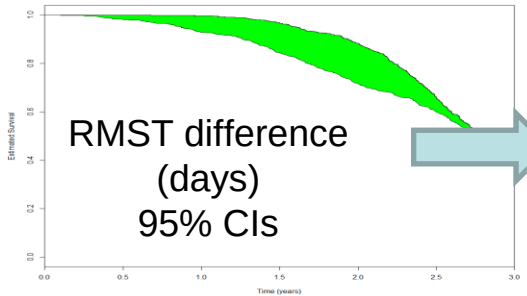
Statistical Analysis

- **Primary Endpoint Analysis**
  - Restricted Mean Survival Time (RMST)*:

** not dependent on the number of events and on the assumption of proportional hazards*



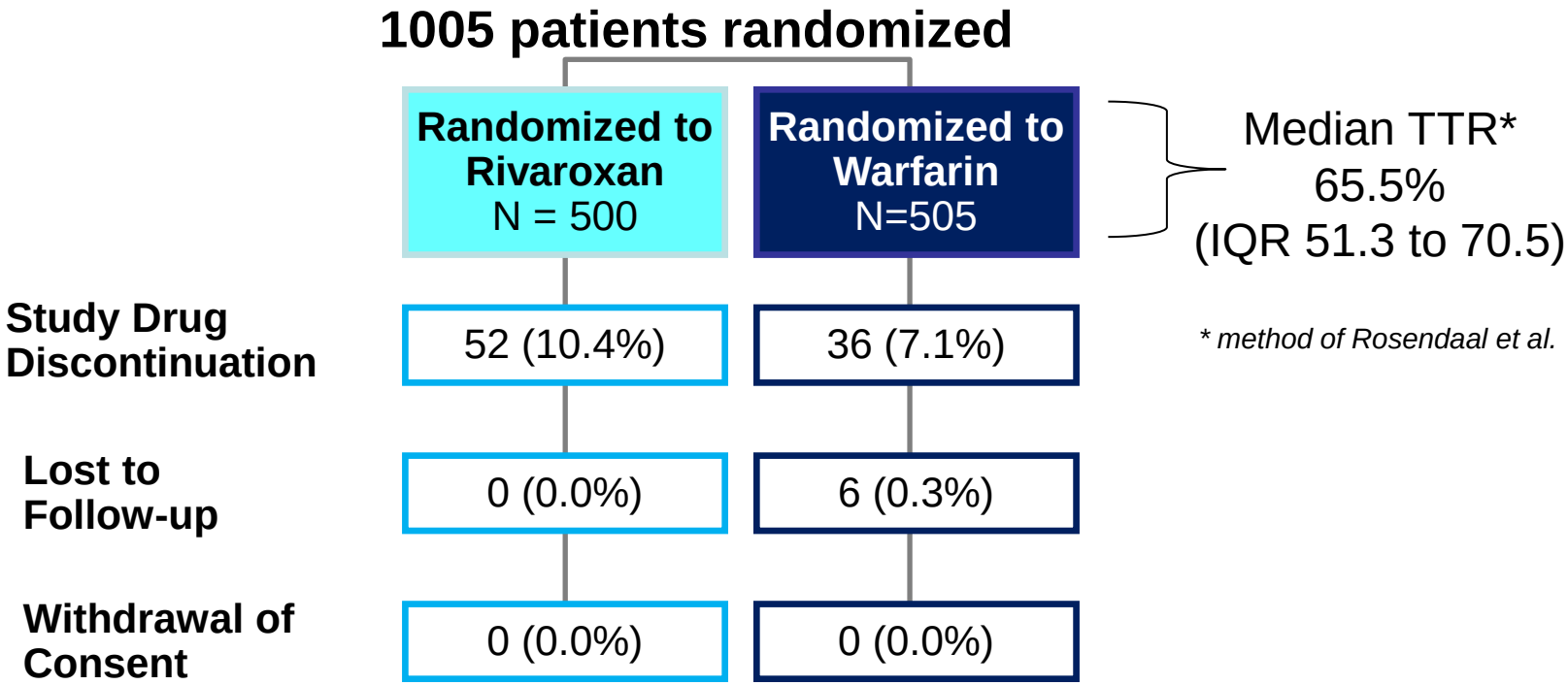
the mean time free from an outcome event up to 365 days, reflecting the area under the survival curve



rivaroxaban minus warfarin, so negative values indicate an increased risk from rivaroxaban treatment

- **Sample Size**
  - Noninferiority margin: between-group difference of - 8 days in the RMST (approximately 2% of 365 days). N =1000 patients
  - 80% power, event rate of 14.5% in the warfarin group, with a hazard ratio of 0.79 and an alpha level of 5%.

CONSORT Diagram



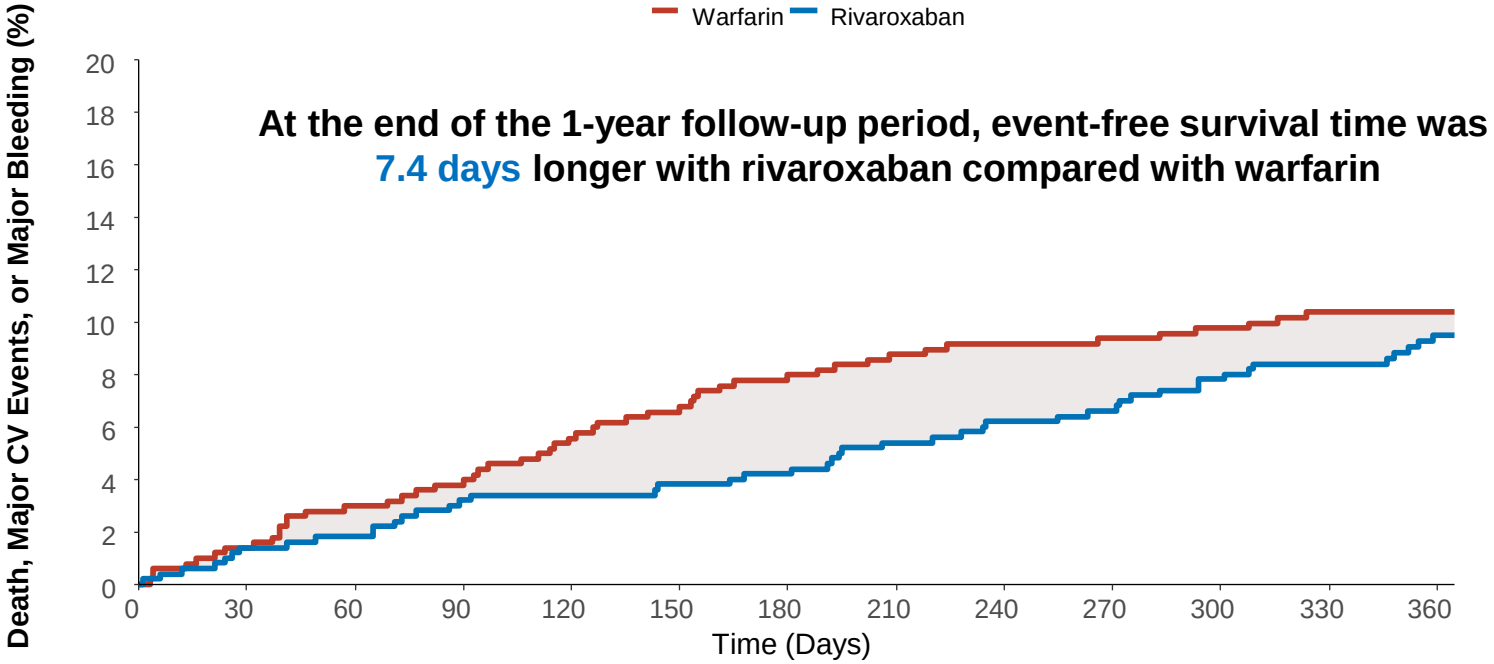
Baseline Characteristics

	Rivaroxaban (N=500)	Warfarin (N=505)
Age (y), mean ± SD	59.4 ±12.4	59.3 ± 11.8
Female sex (%)	62.2	58.6
Congestive Heart Failure (%)	40.4	37.2
Hypertension (%)	61.6	59.8
Diabetes Mellitus (%)	14.8	12.7
Prior Stroke/TIA (%)	15.0	15.3
Prior CAD (%)	21.2	19.1
CHA_2DS_2-VASc Score, mean ± SD	2.7 ± 1.5	2.5 ± 1.3
Atrial fibrillation (%)	96.0	95.3
Flutter (%)	4.0	4.7

Time from Mitral Valve Surgery to Randomization

	Rivaroxaban (N=500)	Warfarin (N=505)
Time from Mitral Valve Implantation		
Up to 3 months (%)	18.8	18.8
≥ 3 months and < 1 year (%)	18.2	15.4
≥ 1 years and < 5 years (%)	32.0	32.4
≥ 5 years and < 10 years (%)	29.6	31.6
Unknown (%)	1.4	1.5

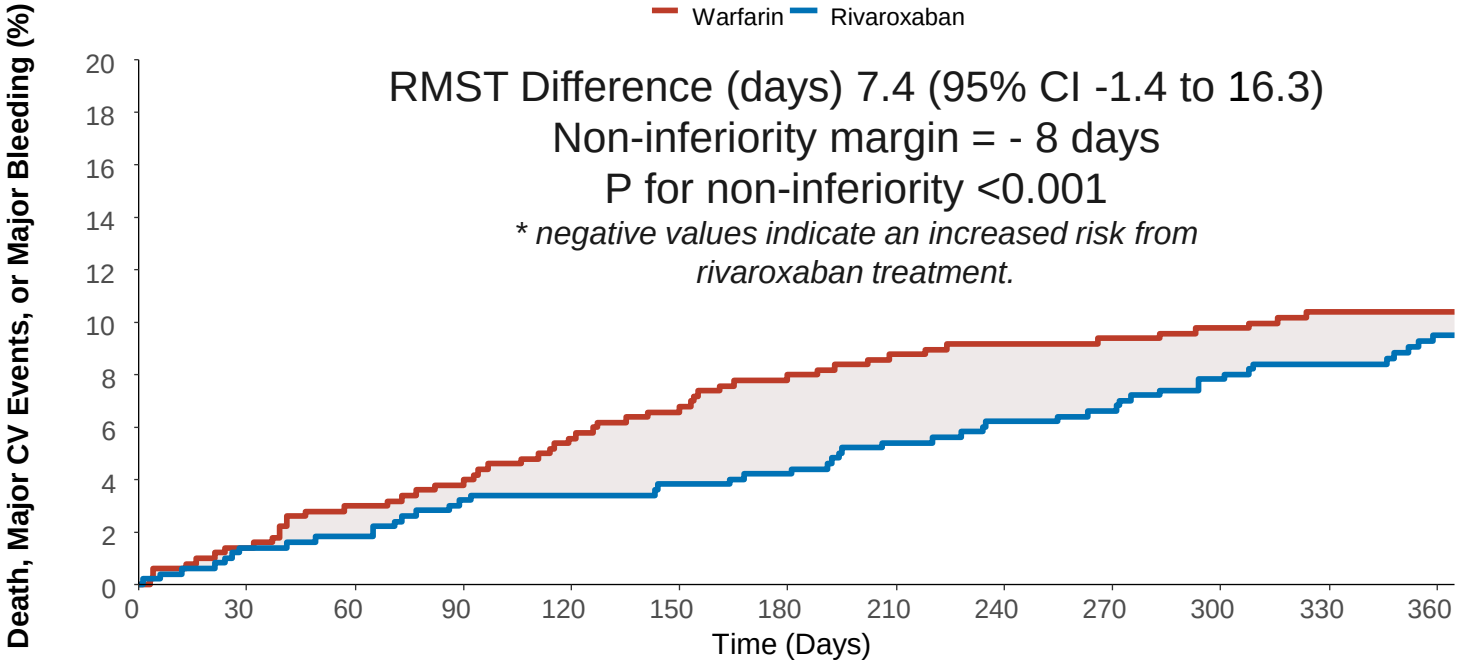
Primary Endpoint



Patients at risk

Rivaroxaban	500	493	491	484	483	481	479	473	469	466	459	453	340
Warfarin	505	496	487	483	474	469	463	458	456	455	450	445	346

Primary Endpoint



Patients at risk

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Primary Endpoint

Analysis	RMST Difference, days (95% CI)	P value	
	Rivaroxaban - Warfarin	Noninferiority	Superiority
ITT	7.4 (-1.4 to 6.3)	<0.001	0.10
Per-protocol	9.6 (2.2 to 16.9)	<0.001	0.01
As-treated	10.5 (1.9 to 19.1)	<0.001	0.01

Primary Endpoint: death, major CV events, or major bleeding
RMST: restricted mean survival time

Secondary Efficacy Endpoints

Endpoint	Rivaroxaban (N=500)	Warfarin (N=505)	HR (95% CI)	P value
CV mortality or thromboembolic events (%)	3.4	5.1	0.65 (0.35 to 1.20)	0.17
Total Stroke (%)	0.6	2.4	0.25 (0.07 to 0.88)	0.03
CV Death (%)	2.2	2.6	0.85 (0.38 to1.90)	0.69
All-cause Death (%)	4.0	4.0	1.01 (0.54 to 1.87)	0.98
Valve thrombosis (%)	1.0	0.6	1.68 (0.40 to 7.01)	0.48
Non-CNS embolism (%)	0.0	0.2	-	-

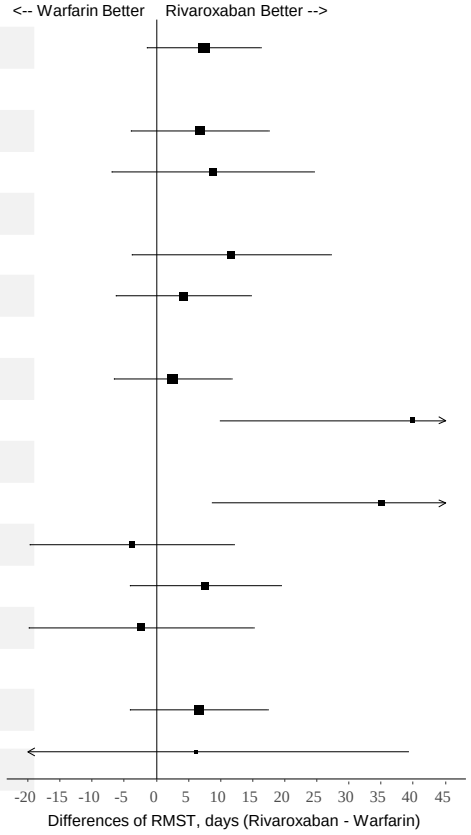
Bleeding Events

Endpoint	Rivaroxaban (N=500)	Warfarin (N=505)	HR (95% CI)	P value
Major (%)	1.4	2.6	0.54 (0.21 to1.35)	0.18
Intracranial bleeding (%)	0.0	1.0	-	-
Fatal bleeding (%)	0.0	0.4	-	-
Clinically Relevant non major (%)	4.8	4.6	1.05 (0.60 to1.87)	0.85
Minor (%)	7.4	9.7	0.75 (0.49 to1.15)	0.18
Total (%)	13.0	15.4	0.83 (0.59 to1.15)	0.25

Bleeding events defined by the ROCKET-AF trial criteria

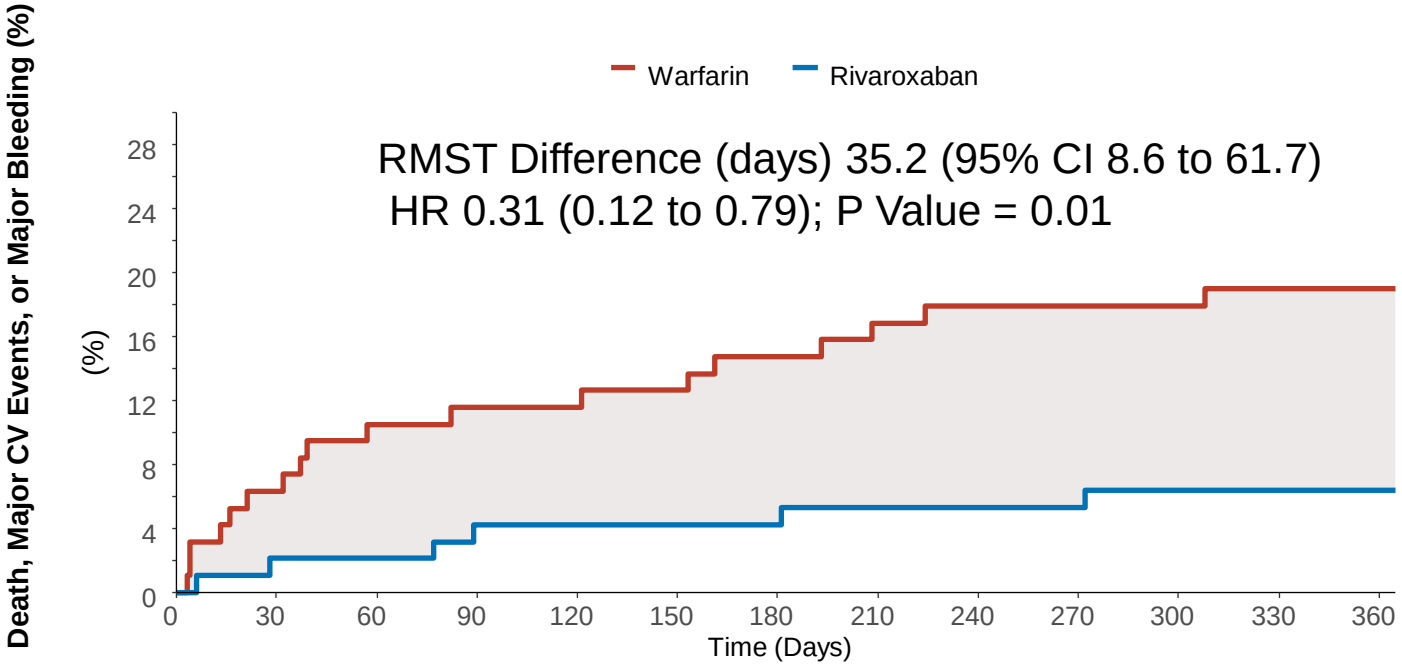
Subgroup Analysis

	Rivaroxaban		Warfarin	
	No./Total No.(%)	RMST [95% CI]	No./Total No.(%)	RMST [95% CI]
All	47/500 (9.4%)	347.5 [341.8 to 353.1]	52/505 (10.3%)	340.1 [333.2 to 346.9]
Age				
< 65	28/321 (8.7%)	349.0 [342.1 to 355.8]	30/329 (9.1%)	342.2 [334.0 to 350.5]
≥ 65	19/179 (10.6%)	344.8 [335.0 to 354.7]	22/176 (12.5%)	336.0 [323.8 to 348.3]
Gender				
Male	20/189 (10.6%)	345.2 [335.4 to 355.0]	25/209 (12.0%)	333.6 [321.6 to 345.6]
Female	27/311 (8.7%)	348.9 [342.0 to 355.7]	27/296 (9.1%)	344.6 [336.6 to 352.6]
Antiplatelet at baseline				
No	41/425 (9.6%)	346.7 [340.4 to 353.0]	39/441 (8.8%)	344.1 [337.4 to 350.8]
Yes	6/75 (8.0%)	352.2 [340.3 to 364.0]	13/64 (20.3%)	312.3 [284.6 to 339.9]
Time from mitral valve implantation				
< 3 months	6/94 (6.4%)	348.6 [335.1 to 362.1]	18/95 (18.9%)	313.5 [290.6 to 336.3]
≥ 3 months and < 1 year	6/91 (6.6%)	351.3 [339.3 to 363.3]	4/78 (5.1%)	355.1 [344.6 to 365.6]
≥ 1 year < 5 years	7/160 (4.4%)	356.2 [348.8 to 363.6]	14/164 (8.5%)	348.6 [339.4 to 357.7]
≥ 5 years	27/148 (18.2%)	336.3 [324.1 to 348.5]	16/160 (10.0%)	338.6 [326.2 to 351.1]
CrCl (mL/mim)				
≥ 50	33/361 (9.1%)	346.8 [339.9 to 353.7]	36/358 (10.1%)	340.2 [332.0 to 348.5]
< 50	6/47 (12.8%)	334.8 [310.6 to 359.0]	10/60 (16.7%)	328.6 [306.0 to 351.2]



Primary Endpoint

Time from mitral valve implantation < 3 months



Patients at risk

Rivaroxaban	94	92	92	90	90	90	90	89	89	88	87	87	69
Warfarin	95	89	85	84	84	83	81	79	78	78	76	74	64

Conclusion

- In conclusion, in patients with atrial fibrillation and a bioprosthetic mitral valve, rivaroxaban is noninferior to warfarin with respect to mean time free from death, major cardiovascular events, or major bleeding.

- Since rivaroxaban does not require monitoring and has a more consistent anticoagulant effect, which is less influenced by food or concomitant medications, it represents an attractive alternative to warfarin for this patient population.

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ORIGINAL ARTICLE

Rivaroxaban in Patients with Atrial Fibrillation and a Bioprosthetic Mitral Valve

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