2020 AHA RIVER Study

上海交通大学医学院附属第九人民医院心内科

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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

研究背景及目的

- 植入人工生物二尖瓣的房颤患者需要接受长期的抗凝治疗，但是最佳的抗凝治疗策略却并不明确。
- ROCKET-AF中排除了植入人工生物瓣膜的患者。
- 仅有一些关键研究的亚组分析提供了一些关于植入人工生物二尖瓣的房颤患者中新型口服抗凝药应用情况的相关数据（ARISTOTLE研究31例，ENGAGE-TIMI研究131例）。
- RIVER研究评估了在植入生物二尖瓣的房颤或房扑患者中应用直接口服抗凝剂的安全性和有效性。

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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.

研究方法

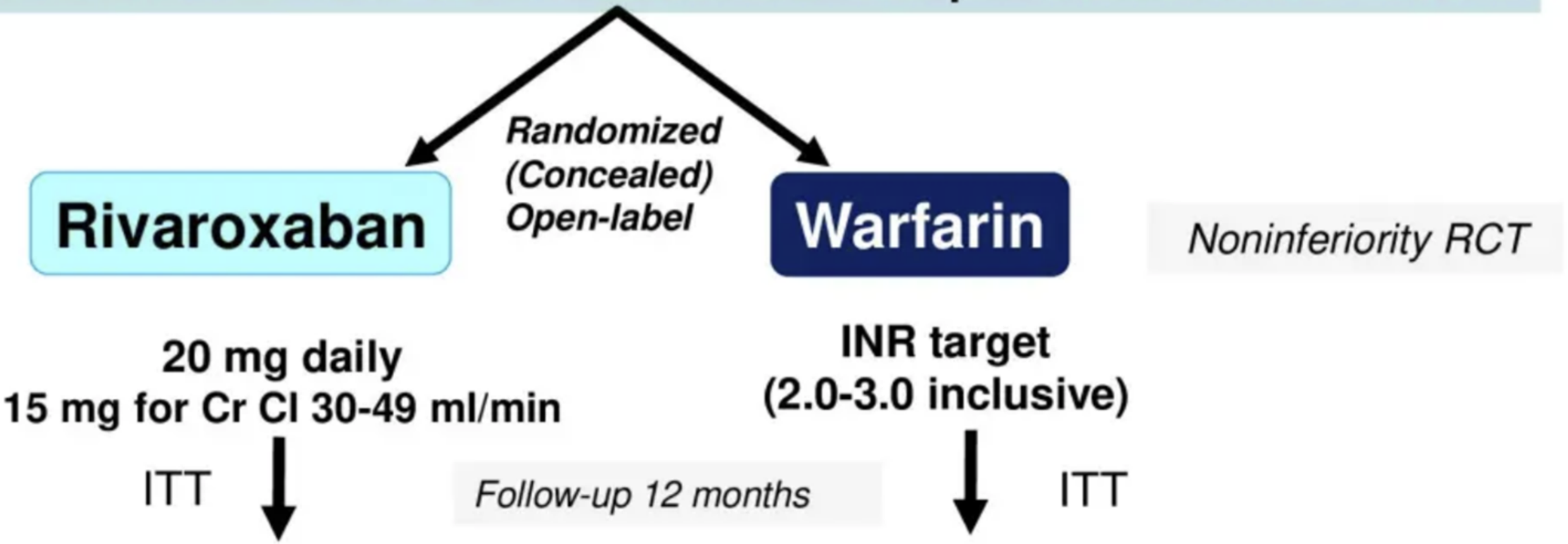
- 非劣效性设计的多中心随机双盲对照研究
  - 1005名植入生物二尖瓣的房颤或房扑患者
  - 随机分为利伐沙班20mg qd组和华法林组（INR：2.0-3.0
  - 12个月的随访。

- 研究的主要终点事件为随访期间的死亡、主要心血管不良事件和大出血事件。次要有效性终点事件为心源性死亡、栓塞事件（脑卒中、TIA、瓣膜血栓、静脉血栓、非CNS系统性栓塞）

- 次要安全性终点为各类出血事件。研究通过限制性平均生存时间（Restricted Mean Survival Time，RMST）对比两组的药物治疗疗效。

Study Design

Patients with atrial fibrillation or flutter and a bioprosthethic mitral valve



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.

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

研究结果

Baseline Characteristics

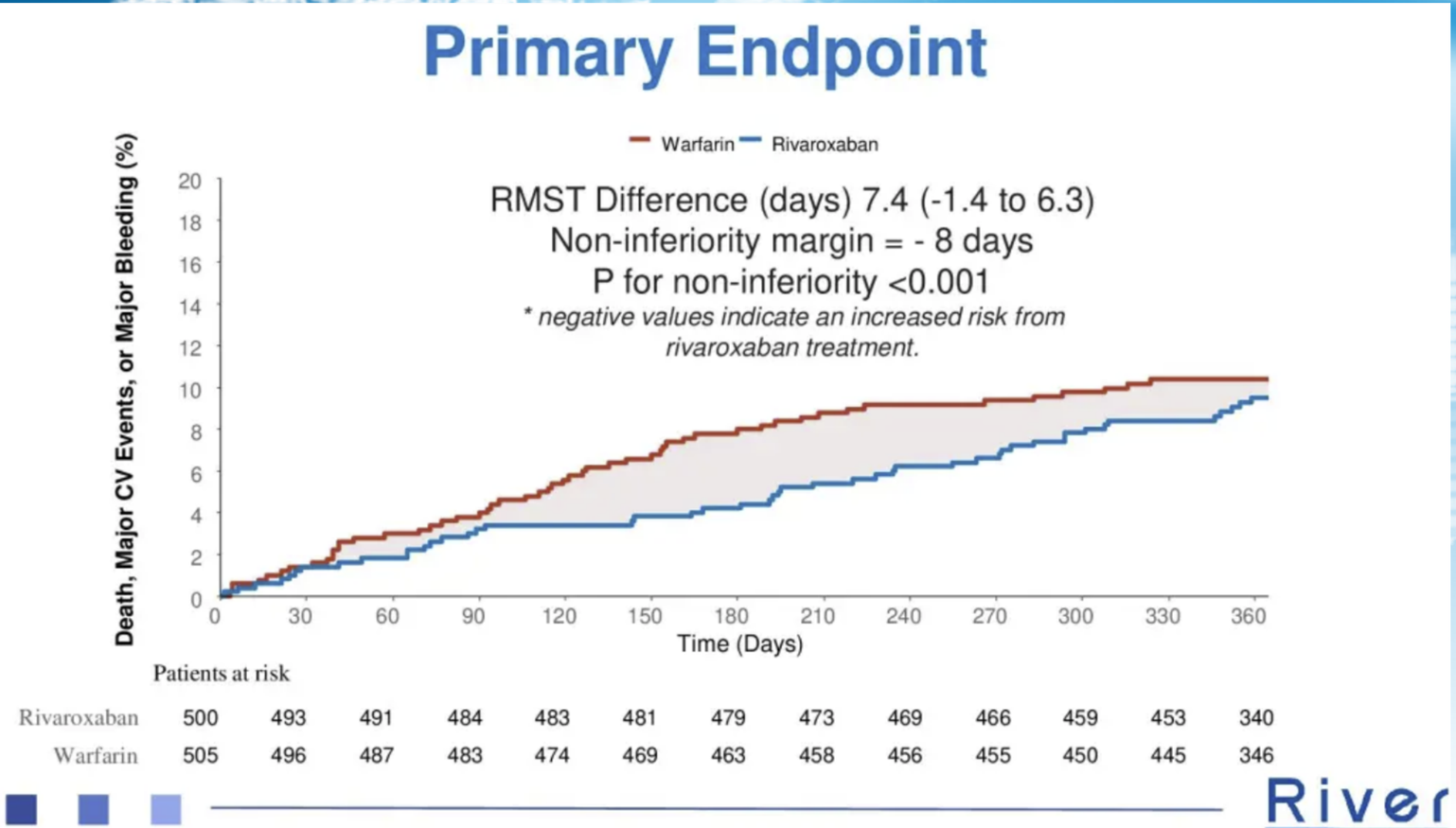
	Rivaroxaban (N=500)	Warfarin (N=505)
Age (y), mean ± SD	59 ±12.4	59.3 ± 11.8
Female sex (%)	62.2	58.6
Congestive Heart Failure (%)	40.4	37.2
Hypertension (%)	61.6	59.8
Diabetes Mellitus (%)	14.8	12.6
Prior Stroke/TIA (%)	15.0	15.3
Prior CAD (%)	21.2	19.1
CHA_2DS_2-VASc Score, mean ± SD	2.7 ± 1.5	2.5 ± 1.3
Atrial fibrillation (%)	96.0	95.3
Flutter (%)	4.0	4.7

研究结果

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

研究结果



- 主要终点事件方面达到了非劣效性终点，限制平均生存时间相差7.4天（非劣效性 P<0.001
- 利伐沙班和华法林治疗组1年内的复合终点事件的发生率分别为9.4%和10.3%。

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研究结果

Secondary Efficacy Endpoints

Endpoint	Rivaroxaban (N=500)	Warfarin (N=505)	HR (95% CI)	P value
CV mortality or thromboembolic events (%)	3.5	5.4	0.65 (0.35 –1.20)	0.17
Total Stroke (%)	0.6	2.5	0.25 (0.07–0.88)	0.03
CV Death (%)	2.3	2.7	0.85 (0.38–1.90)	0.69
All-cause Death (%)	4.1	4.1	1.01 (0.54–1.87)	0.98
Valve thrombosis (%)	1.0	0.6	1.68 (0.40–7.01)	0.48
Non-CNS embolism (%)	0.0	1.0	-	-

- 次要终点方面，华法林组的总脑卒中事件发生率高于利伐沙班组（0.6% vs 2.4%; HR 0.25, 95% CI 0.07-0.88），而利伐沙班组的其余各个终点事件（包括出血事件发生率）与华法林组无明显差异

研究结果

Bleeding Events

Endpoint	Rivaroxaban (N=500)	Warfarin (N=505)	HR (95% CI)	P value
Major (%)	1.5	2.7	0.54 (0.21–1.35)	0.18
Intracranial bleeding (%)	0.0	0.9	-	-
Fatal bleeding (%)	0.0	0.4	-	-
Clinically Relevant non major (%)	5.1	4.9	1.05 (0.60 –1.87)	0.85
Minor (%)	8.0	10.8	0.75 (0.49 –1.15)	0.18
Total (%)	14.7	18.0	0.83 (0.59 –1.15)	0.25

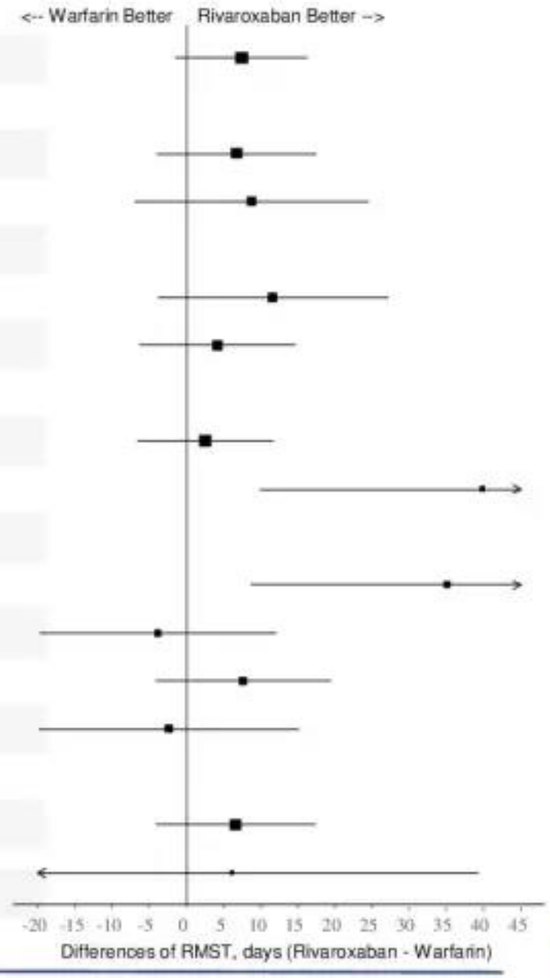
Bleeding events defined by the ROCKET-AF trial criteria

主要出血事件发生率利伐沙班组为1.4%，华法林组为2.6%（HR 0.54，95%CI 0.21-1.35），利伐沙班组无颅内出血或致死性出血，华法林组各5例和2例。

研究结果

Subgroup Analysis

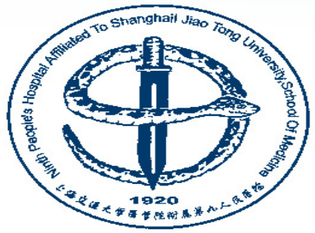
	Rivaroxaban		Warfarin	
	No./Total No.(%)	RMST [95% CI]	No./Total No.(%)	RMST [95% CI]
All	47/500 (9.4%)	347.5 [341.8 to 353.1]	52/505 (10.3%)	340.1 [333.2 to 346.9]
Age				
< 65	28/321 (8.7%)	349.0 [342.1 to 355.8]	30/329 (9.1%)	342.2 [334.0 to 350.5]
≥ 65	19/179 (10.6%)	344.8 [335.0 to 354.7]	22/176 (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/min)				
≥ 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]



结论

- 在植入人工生物二尖瓣的房颤或房扑患者中，利伐沙班的疗效不劣于华法林。
- 研究结果中利伐沙班组脑卒中发生率显著降低，但是因为事件的数量小，置信区间宽，且缺乏对多种混杂因素的校正，因此这一结果需谨慎解读。
- 本研究的结果填补了关于植入人工生物二尖瓣的房颤或房扑患者最佳抗凝治疗的空白

谢 谢



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