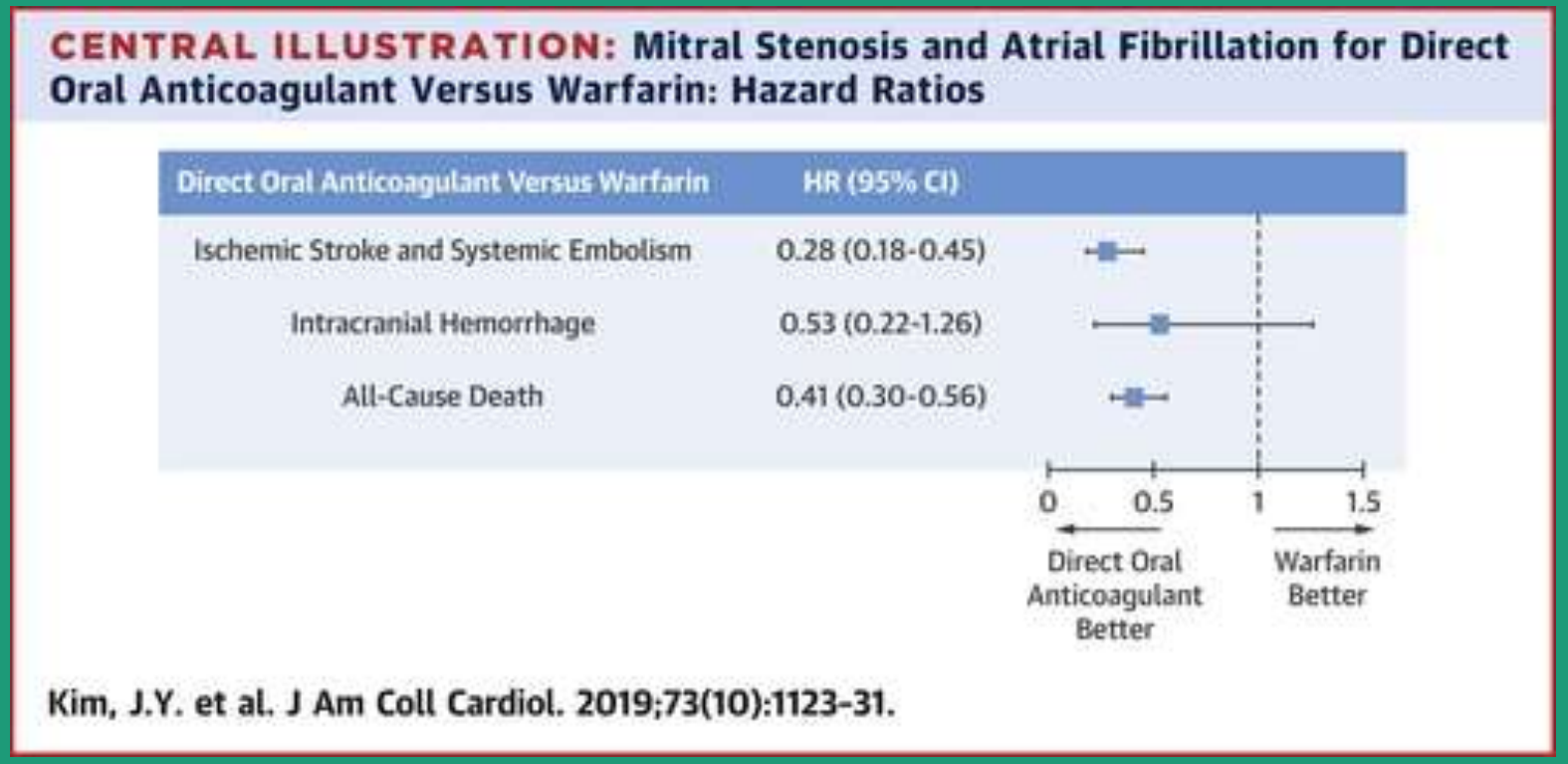
Utilizzo di rivaroxaban nei pazienti con stenosi mitralica: risultati del trial pilota RISE MS

Background

- Mitral stenosis (MS) is still a relevant disease entity, affecting about 33.4 million patients worldwide, especially in low- to middle-income countries.
- Three to 7.5% of affected patients are complicated by thromboembolic stroke as a consequence of highly prevalent atrial fibrillation (AF).
- Vitamin K antagonists use is complicated by a narrow therapeutic window requiring accurate titration and the need for constant monitoring, which appears largely impossible in affected populations.
- Patients with moderate-to-severe MS were systematically excluded from all pivotal large-scale RCTs testing non-vitamin K antagonist oral anticoagulants (NOACs) in patients with AF due to a perceived prohibitively high thromboembolic risk.
- Along with mechanical prosthetic valves, NOAC administration in patients with moderate-to-severe MS is currently contraindicated by major international guidelines.

Background

- 2,230 patients from the Health Insurance Review and Assessment Service (HIRA) database in the Republic of Korea



Short communication

RIvaroxaban in mitral stenosis (RISE MS): A pilot randomized clinical trial

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Methods

- RIvaroxaban in Mitral Stenosis (RISE MS) is an open-labeled, parallel-group, pilot registered RCT performed in Rajaie Cardiovascular Medical and Research Center, Tehran, Iran.
- Consecutive patients 18 to 75 years old with an echocardiographic diagnosis of moderate-to-severe MS and AF were randomly assigned to rivaroxaban 20 mg/day (15 mg/day in patients with creatinine clearance <50 mL/min) or warfarin.
- Each participant underwent baseline transesophageal echocardiog- raphy and brain magnetic resonance imaging at baseline and at 6- and 12-months after randomization.

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Endpoints

The primary outcome was a composite of symptomatic ischemic strokes and systemic embolic events during a 12-month follow-up.

The secondary (safety) outcomes were major and clinically relevant nonmajor bleeding according to the International Society on Thrombosis and Haemostasis classification.

All-cause mortality, the rate of development of high-thrombogenicity markers in the left atrial appendage (LAA) at 6 months, and silent cerebral ischemia at 12 months were exploratory outcomes.

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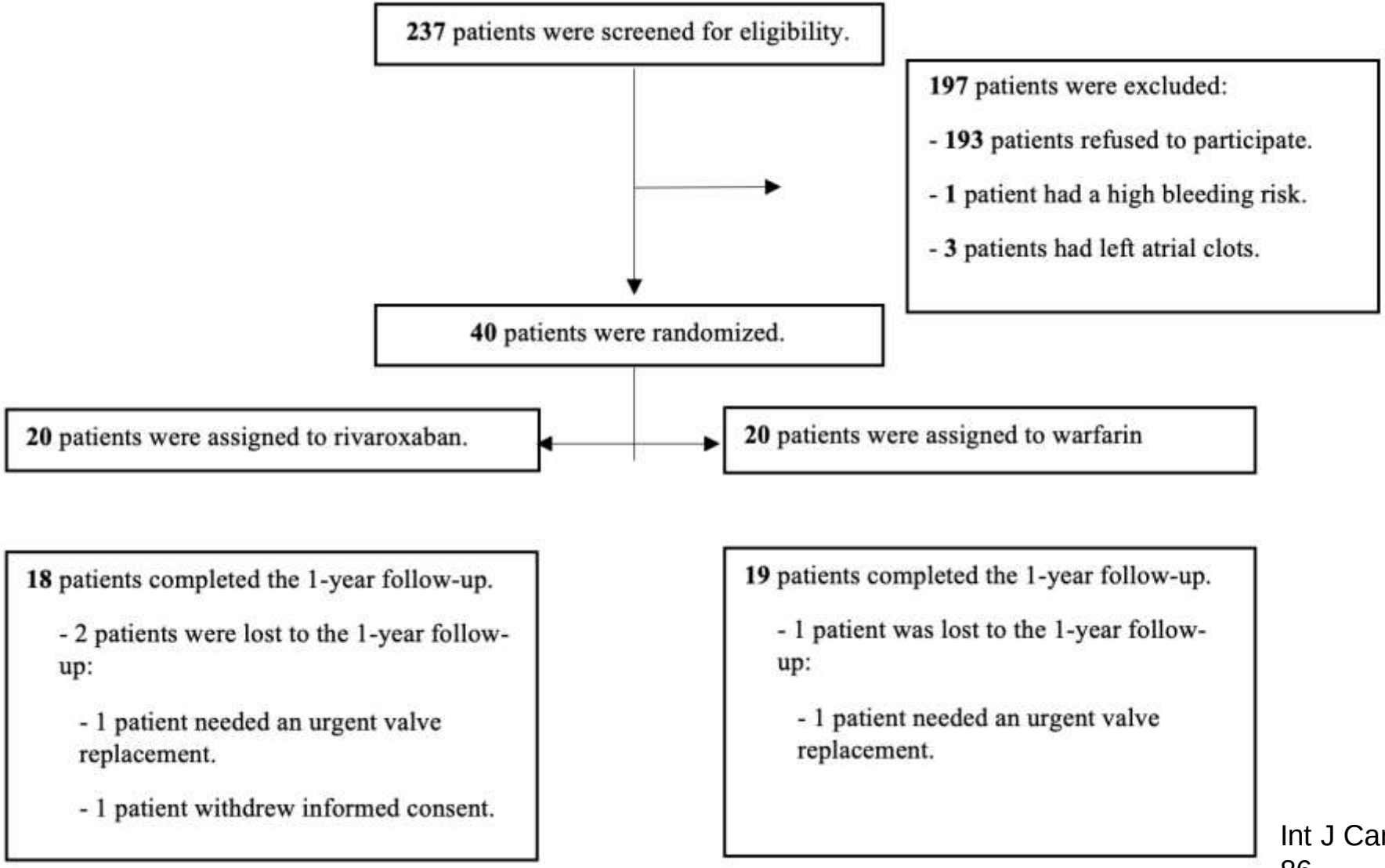
Study Flowchart



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Baseline characteristics

Characteristics	Rivaroxaban (n=20)	Warfarin (n=20)
Age— y	60 (46.5 , 64)	56 (51 , 65)
Sex		
Women — No. (%)	17 (85%)	14 (70%)
Men — No. (%)	3 (15%)	6 (30%)
Body mass index [b] — kg/m²	27.1 (22.7 , 29.4)	27.8 (22.2 , 30.6)
Current smokers— No. (%)	2 (10%)	2 (10%)
Coexisting Conditions— No. (%)		
Hypertension	5 (25%)	4 (20%)
Diabetes	3 (15%)	3 (15%)
Coronary artery disease	0 (0%)	3 (15%)
Heart failure	2 (10%)	3 (15%)

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Baseline characteristics

Characteristics	Rivaroxaban (n=20)	Warfarin (n=20)
Median laboratory Values at Baseline		
Creatinine—mg/dL	0.9 (0.9 , 1.1)	1.1 (0.9 , 1.2)
Hemoglobin level—g/dL	12.9 (12 , 13.5)	13.3 (12 , 14.7)
Platelet count—10^3/fL	246 (169 , 277)	200 (169 , 234)
Aspartate aminotransferase—units/L	16 (15 , 18)	23 (20, 30)
Alanine aminotransferase —units/L	13.5 (9 , 16)	28 (21 , 32)
Baseline Echocardiographic Index		
Mitral valve area (cm^2)	1.2 (1 , 1.4)	1.1 (0.9 , 1.4)
Pressure half time (ms)	165 (145 , 173)	164 (130 , 202)
Mitral valve mean gradient (mm Hg)	5.8 (4, 10)	7 (5, 10)
Pulmonary arterial pressure (mm Hg)	40 (32 , 55)	36.5 (30 , 42)

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One-year prespecified outcomes

Outcome, N (%)	N (%)	
	Rivaroxaban ($n = 18$)	Warfarin ($n = 19$)
Primary outcome		
Composite of symptomatic ischemic strokes and systemic embolic events during a 12-month follow-up	0	0
Secondary outcomes		
Major bleeding[1]	0	0
Clinically relevant nonmajor bleeding	1	0
Exploratory outcomes		
Increased thrombogenicity in the left atrial appendage at 6 months[2]	3/11 (27.2)	3/11 (27.2)
Silent cerebral ischemia at 12 months[3]	2/15 (13.3)	3/17 (17.6)

Increased risk of left atrial appendage thrombogenicity, assessed by TEE, was defined as a decrease in left atrial appendage velocity to below 20 cm/s accompanied by transformation to a severe smoke-like pattern in the left atrial appendage.

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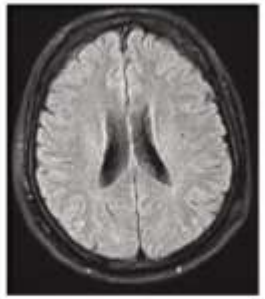
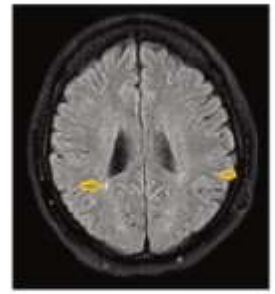
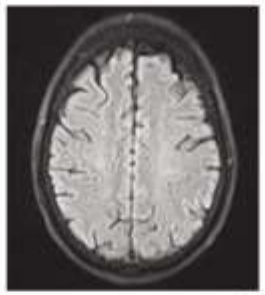
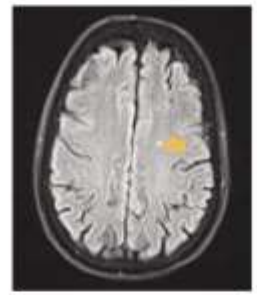
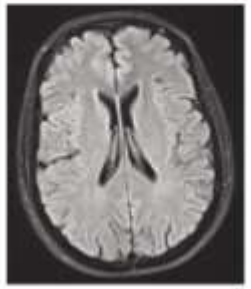
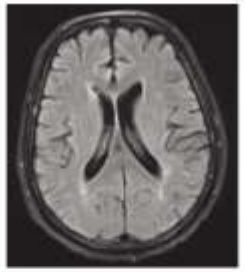
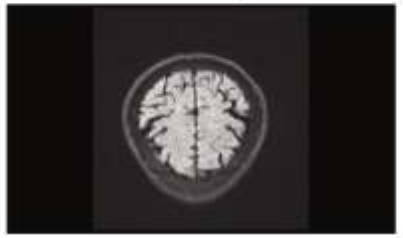
Graphical and detailed description of patients with silent brain ischemia.

Patients	Baseline brain MRI	12-Month brain MRI	Comment
1			New abnormal high T2 signals and white matter lesions in the right periventricular and left subcortical regions (yellow arrows)
2			New abnormal high T2 signals and white matter lesions at the left centrum semiovale (yellow arrow)
3			Multiple abnormal high T2 signals and white matter lesions in the left subcortical regions (yellow arrows)
4			Progression of diffuse periventricular high T2 signal intensities and white matter lesions around both lateral ventricles (change from Fazekas 2 to Fazekas 3 scales) (yellow arrows)
5			Multiple abnormal high T2 signals and white matter lesions in the right subcortical region (yellow arrow)

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Limitations

The small study size renders it underpowered for its primary outcome.

The participation in the foreseen imaging examinations was far from desirable, mainly due to the fear of COVID-19 contamination in imaging centers.

Out of 237 patients screened for this trial, 193 patients rejected trial participation mainly on advice by their primary care physicians, highlighting a problem of recruitment difficulty in future similar studies and the possible occurrence of selection bias by which more severe cases at higher risk for stroke are excluded.

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Conclusions

The results of the present pilot RCT together with previous observational experience suggest similar efficacy and safety for the NOACs – in this specific case rivaroxaban – in comparison with warfarin in AF with MS.

The performance of larger RCTs that can conclusively prove NOAC value in this setting is eagerly awaited.

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