Rivaroxaban nel trattamento dell'ESUS (Embolic strokes of undetermined source): lo studio NAVIGATE ESUS

Distribution of ischaemic stroke subtypes in North American and European studies



-*TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification:* stroke of undetermined cause may refer to a stroke with incomplete workup, more than one potential cause, or indeed no determined etiology after investigations are complete.

-<u>ASCO calssification</u>: cause is completely unknown when stroke subtyping does not confer to atherosclerosis (A), small vessel disease (S), cardiac disease (C), or other cause (O).

Hart, Lancet Neurol 2014

Pathophysiologic classification of ischemic stroke



Ntaios, Circulation 2017

ESUS: Embolic strokes of undetermined source CRITERIA FOR DIAGNOSIS

- Stroke detected by CT or MRI that is not lacunar*
- Absence of extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischaemia
- No major-risk cardioembolic source of embolism (eg, permanent or paroxysmal atrial fibrillation, sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumours, mitral stenosis, recent <4 weeks myocardial infarction, left ventricular ejection fraction less than 30%, valvular vegetations, o infective endocarditis)
- No other specific cause of stroke identified (eg, arteritis, dissection, migraine/vasospasm, drug misuse)

*Lacunar defined as a subcortical infarct smaller than or equal to 1.5 cm (≤2.0 cm on MRI diffusion images) in largest dimension, and in the distribution of the small, penetrating cerebral arteries

ESUS: Embolic strokes of undetermined source PROPOSED DIAGNOSTIC ASSESSMENT

- Brain CT or MRI
- 12-lead ECG
- Precordial echocardiography
- Cardiac monitoring for ≥24 h with automated rhythm detection
- Imaging of both the extracranial and intracranial arteries supplying the area of brain ischaemia (catheter, MR, or CT angiography, or cervical duplex plus transcranial doppler ultrasonography)

ESUS: Embolic strokes of undetermined source STROKE RECURRENCE RISK



Patients with ESUS show a significantly higher rate of recurrent stroke than those of other subtypes

Modified from Bang et al. 2003

ESUS: Embolic strokes of undetermined source POTENTIAL CAUSES



ESUS: Embolic strokes of undetermined source TREATMENT

There are currently no established guidelines on the long-term treatment of ESUS; based on the studies summarized below, **guidelines** from the American Heart Association/American Stroke Association and the American College of Chest Physicians, **recommend antiplatelet therapy** (in the absence of sufficient data on NOACs) coupled with lifestyle modification and control of other risk factors such as hypertension, diabetes and dyslipidaemia.

ESUS: Embolic strokes of undetermined source TREATMENT

WARSS

- Multicenter double-blind study comparing ASA to Warfarin (goal INR 1.4-2.8)
- Primary endpoint (stroke or death within 2 years) was similar between the two groups (17.8% vs. 16.0%, p = 0.25).

Warfarin-Aspirin Recurrent Stroke Study Group, N Engl J Med 2001

WARSS



TABLE 3. ADVERSE EVENTS ACCORDING TO TREATMENT ASSIGNMENT.*

Event	WARFARIN (N=1103)	A SPIRIN (N=1103)	ODDS RATIO (95% CI)	P Valuet
	no.	(%)		
Death Related to hemorrhage	47 (4.3) 7 (0.6)	53 (4.8) 5 (0.4)	0.88(0.58-1.32) 1.40(0.42-5.13)	0.61 0.77
First hemorrhage ‡	our temperete			
Major	38 (3.4)	30 (2.7)	1.28(0.78 - 2.10)	0.39
Minor	261 (23.7)	188 (17.0)	1.51(1.22 - 1.87)	< 0.001

Warfarin-Aspirin Recurrent Stroke Study Group, N Engl J Med 2001

ORIGINAL ARTICLE

Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source

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Trial design

Prospective, randomized, double-blind, active-comparator, event-driven, superiority, phase III study

Patients with recent ischemic stroke and

- visualized by brain CT or MRI that is not lacunar (subcortical infarct≤1.5 cm)
- absence of cervical carotid atherosclerotic artery stenosis ≥ 50% or occlusion
- no atrial fibrillation after ≥ 24 hours cardiac rhythm monitoring
- no intra-cardiac thrombus on transthoracic echocardiography
- no other specific etiology for cause of stroke (eg, arteritis, dissection, migraine/ vasospasm, drug abuse)

Age ≥ 18 years (max 10% patients <60 years

Target RRR 30%; superiority w/ 90% power α=0.05 Enrollment ~24 months; minimum treatment ~12 months; study duration ~36 months Estimated mean treatment duration 18 - 24 months;



A total of **7213** participants were enrolled at 459 sites;

3609 patients were randomly assigned to receive *rivaroxaban* and 3604 to receive *aspirin*.

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Table 1. Characteristics of the Patients at Trial Entry.*		
Characteristic	Rivaroxaban Group (N= 3609)	Aspirin Group (N=3604)
Age — yr	66.9±9.8	66.9±9.8
Male sex — no. (%)	2232 (62)	2204 (61)
Race — no. (%)†		
White only	2612 (72)	2604 (72)
Black only	51 (1)	60 (2)
Asian only	716 (20)	698 (19)
Other	230 (6)	242 (7)
Body-mass indect	27.1±4.9	27.3±5.1
Blood pressure — mm Hg		
Systolic	135.1±17.0	134.9±16.6
Diastolic	79.0±10.8	78.9±10.8
Statin use after randomization — no. (%)	2815 (78)	2789 (77)
Hypertension — no. (%)	2782 (77)	2803 (78)
Diabetes mellitus — no. (%)	889 (25)	917 (25)
Current tobacco use — no. (%)	756 (21)	728 (20)
Previous stroke or TIA — no. (%)	620 (17)	643 (18)
Geographic region — no. (%)		
United States or Canada	461 (13)	457 (13)
Latin America	372 (10)	374 (10)
Western Europe	1541 (43)	1540 (43)
Eastern Europe	560 (16)	558 (15)
East Asia	675 (19)	675 (19)
Qualifying stroke — no./total no. (%)		
Single acute lesion on imaging	3231/3606 (90)	3214/3602 (89)
Multiple lesions on imaging	375/3606 (10)	388/3602 (11)
Aspirin use before qualifying stroke — no. (%)	624 (17)	629 (17)
Median NIHSS score at randomization (IQR)	1 (0-2)	1 (0-2)
Median modified Rankin scale score at randomization (IQR)	1 (0-2)	1 (0-2)
Median time from qualifying stroke to randomization (IQR) — days	38.0 (15.0-89.0)	36.0 (14.0-86.5)
Intracranial vascular imaging — no. (%)	2821 (78)	2824 (78)
Cardiac rhythm monitoring ≥48 hr — no. (%)	1218 (34)	1217 (34)

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Table 2. Efficacy Outcomes.*					
Outcome	Rivaroxaban Group (N=3609)	Aspirin Group (N=3604)	Hazard Ratio (95% CI)†		
	no. of patients (annualized rate)				
Primary efficacy outcome: any recurrent stroke or systemic embolism	172 (5.1)	160 (4.8)	1.07 (0.87–1.33)		
Secondary efficacy outcomes					
Any recurrent stroke‡	171 (5.1)	158 (4.7)	1.08 (0.87-1.34)		
Ischemic stroke:	158 (4.7)	156 (4.7)	1.01 (0.81-1.26)		
Hemorrhagic stroke§	13 (0.4)	2 (0.1)	6.50 (1.47-28.8)		
Systemic embolism	1 (<0.1)	2 (0.1)	0.50 (0.05-5.51)		
Any recurrent stroke, myocardial infarction, death from cardiovascular causes, or systemic embolism¶	207 (6.2)	195 (5.8)	1.06 (0.87–1.29)		
Any disabling stroke	41 (1.2)	29 (0.8)	1.42 (0.88-2.28)		
Myocardial infarction	17 (0.5)	23 (0.7)	0.74 (0.39-1.38)		
Death from any cause	65 (1.9)	52 (1.5)	1.26 (0.87-1.81)		
Death from cardiovascular causes¶	34 (1.0)	23 (0.7)	1.48 (0.87–2.52)		

Figure 1. Cumulative Incidence of the Primary Efficacy Outcome and the Primary Safety Outcome, According to Treatment Assignment.

A Kaplan-Meier Curves for Time to Event in the Primary Efficacy Outcome



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Subgroup	Rivaroxaban	Aspirin	Hazard	Ratio (95% CI)		
· · · · · · · · · · · · · · · · · · ·	10. of patients with event/	total no. (annualized rate)		L .		
Overall	172/3609 (5.1)	160/3604 (4.8)	F		1.07 (0.87-1.33)	
Age						
<60 yr	43/861 (5.4)	25/855 (3.1)			1.73 (1.06-2.83)	
60-75 yr	90/2019 (4.8)	93/1993 (5.1)	⊢ ∎		0.94 (0.71-1.26)	There is four land and the four of the standard of the standard state
>75 yr	39/729 (5.7)	42/756 (5.8)		<u></u>	0.97 (0.63-1.51)	Figure 2. Exploratory Analyses of Treatment Effects
Sex						on the Primary Efficacy Outcome in Prespecified Subgroups
Male	122/2232 (5.8)	102/2204 (4.9)			1.17 (0.90-1.53)	on the Prinary Entracy Outcome in Prespective Subgroups.
Female	50/1377 (4.0)	58/1400 (4.5)	₽	<u>⊢</u> l	0.89 (0.61-1.29)	
Race						
White only	106/2612 (4.4)	114/2604 (4.7)	∎	F -I	0.93 (0.71-1.21)	
Black only	2/51 (3.9)	4/60 (7.9)		I	0.51 (0.09-2.83)	
Asian only	57/716 (8.3)	34/698 (5.0)		⊢ •−1	1.65 (1.08-2.52)	
Other	7/230 (3.5)	8/242 (3.9)		I	0.91 (0.33-2.51)	
Geographic region						
United States and Canada	27/461 (6.4)	15/457 (3.5)		⊢	1.82 (0.97-3.42)	
Latin America	12/372 (4.2)	10/374 (3.5)	► – – – – – – – – – – – – – – – – – – –		1.23 (0.53-2.85)	
Western Europe	56/1541 (3.7)	80/1540 (5.4)		ŧ	0.69 (0.49-0.97)	
Eastern Europe	24/560 (4.9)	22/558 (4.4)			1.10 (0.61-1.96)	
East Asia	53/675 (8.1)	33/675 (5.0)			1.61 (1.04-2.49)	
Body-mass index						
<25	65/1267 (5.5)	68/1233 (6.1)	⊢ ∎	<u>+-</u>	0.92 (0.65-1.29)	
≥25 to <30	76/1491 (5.5)	59/1484 (4.2)	ł		1.31 (0.93-1.84)	
≥30	31/839 (4.0)	33/868 (4.0)			0.97 (0.60-1.59)	
Weight						
<70 kg	68/1278 (5.8)	59/1257 (4.9)	H		1.16 (0.82-1.64)	
70-90 kg	79/1746 (4.9)	85/1733 (5.4)			0.92 (0.68-1.25)	
>90 kg	25/576 (4.6)	16/599 (2.9)	F		1.58 (0.84-2.96)	
Estimated GFR						
<50 ml/min	10/218 (4.8)	11/201 (5.9)			0.86 (0.36-2.02)	
50-80 ml/min	82/1773 (4.9)	97/1758 (5.8)		н. Н	0.83 (0.62-1.12)	
>80 ml/min	80/1617 (5.5)	52/1644 (3.5)		H--H	1.57 (1.11-2.23)	
Stroke or TIA before qualifying stroke		, , , ,				
Yes	52/620 (9.2)	51/643 (8.8)			1.05 (0.72-1.55)	
No	120/2989 (4.3)	109/2961 (3.9)			1.09 (0.84-1.42)	
Time from qualifying stroke to randomizatio	20					
<30 days	89/1566 (6.4)	81/1666 (5.4)	L		1 17 (0.87-1.59)	
>30 days to 3 mo	55/1158 (5.2)	48/1073 (4 9)			1.05 (0.72-1.57)	
3 mo	28/885 (3.2)	31/865 (3.6)			0.89 (0.53-1.48)	
Cardiac rhythm monitoring	201000 (0.21	54/665 (5.6)			0.05 (0.55-1.40)	
adk br	172/2390 /5 61	103/2382 (4.7)	L		1 10 /0 01 1 5/0	
>48 hr	50/1218 (4 3)	57/1217 (5.0)	٦ سال		0.87 (0.59-1.27)	
Unartanzion	50/1210 (4.5/	21/1221 (2.0)	-	1	0.07 (0.33-1.17)	
Ver	179/7792 /5 /0	121/2803 // 7\			1 07 /0 83 1 37	
No	AA 1877 15 71	30/801 /5 7)			1.00 (0.33-1.37)	
Dishatar mallitur	44/027 (2.7)	22/2022 (2.2)	-		1.02 [0.11-1.00]	
Var	54/880 /6 81	AC/017 /5 C)	1		1 21 /0 81 1 701	
No	118/2720 /4 (1	114/2687 (4.5)			1.07 (0.70 1.73)	
10	110/2/20 (4.0)	114/200/ (4.3)			1.02 [0.79-1.33]	
		0.1	0.25 0.5 1	0 2.0 3.0		DOI: 10 1056/NEIM1902696
		-	Divergelan	Aminin		DOI: 10.1020/ MEJM081002080
			Better	Better		

Table 3. Safety Outcomes.*					
Outcome	Rivaroxaban Group (N=3609)	Aspirin Group (N=3604)	Hazard Ratio (95% CI)†	P Value	
Primary safety outcome: ISTH major bleeding:	62 (1.8)	23 (0.7)	2.72 (1.68-4.39)	<0.001	
Secondary safety outcomes					
Life-threatening or fatal bleeding	35 (1.0)	15 (0.4)	2.34 (1.28-4.29)	0.004	
Clinically relevant nonmajor bleeding	118 (3.5)	79 (2.3)	1.51 (1.13-2.00)	0.004	
Symptomatic intracranial hemorrhage§	20 (0.6)	5 (0.1)	4.02 (1.51-10.7)	0.003	
Intracerebral hemorrhage	12 (0.3)	3 (0.1)	4.01 (1.13-14.2)	0.02	
Subarachnoid hemorrhage¶	5 (0.1)	1 (0.0)	5.03 (0.59-43.0)	0.10	
Subdural or epidural hematoma¶	3 (0.1)	2 (0.1)	1.51 (0.25–9.02)	0.65	

Conclusions

- Rivaroxaban was not superior to aspirin with regard to the prevention of recurrent stroke after an initial embolic stroke of undetermined source and was associated with a higher risk of bleeding.
- Ongoing randomized trials are testing alternative anticoagulants versus aspirin in similar groups of patients (ClinicalTrials.gov numbers, NCT02239120 and NCT02427126).