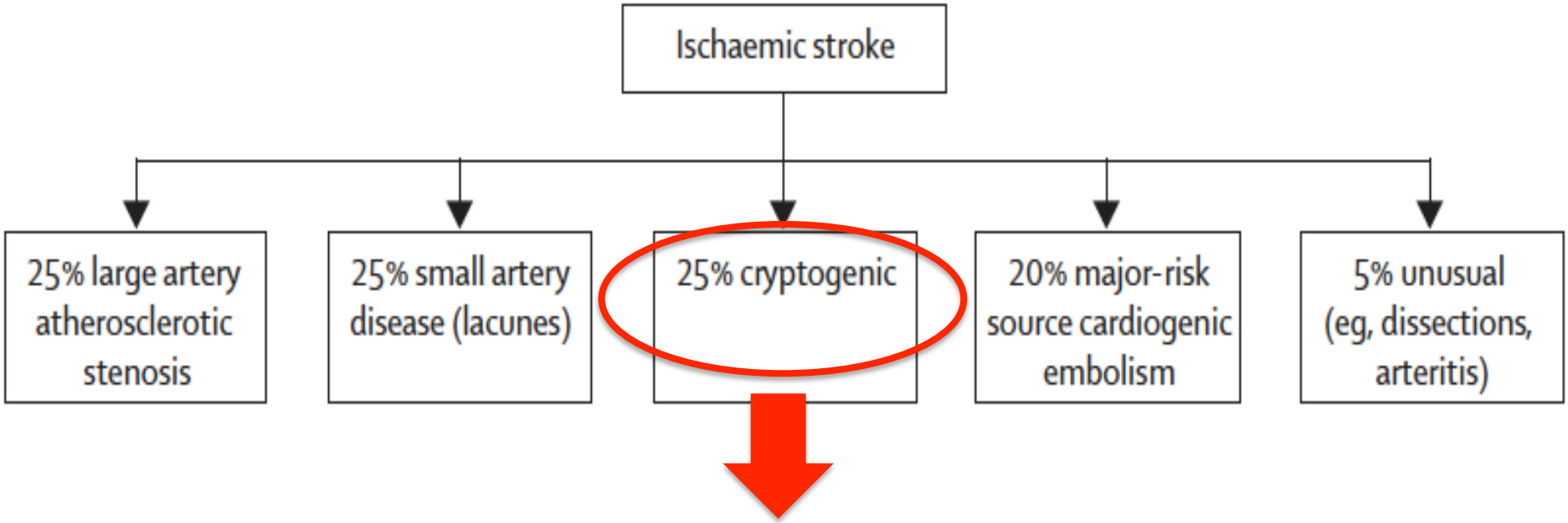
Rivaroxaban nel trattamento dell'ESUS (Embolic strokes of undetermined source): lo studio NAVIGATE ESUS

Distribution of ischaemic stroke subtypes in North American and European studies

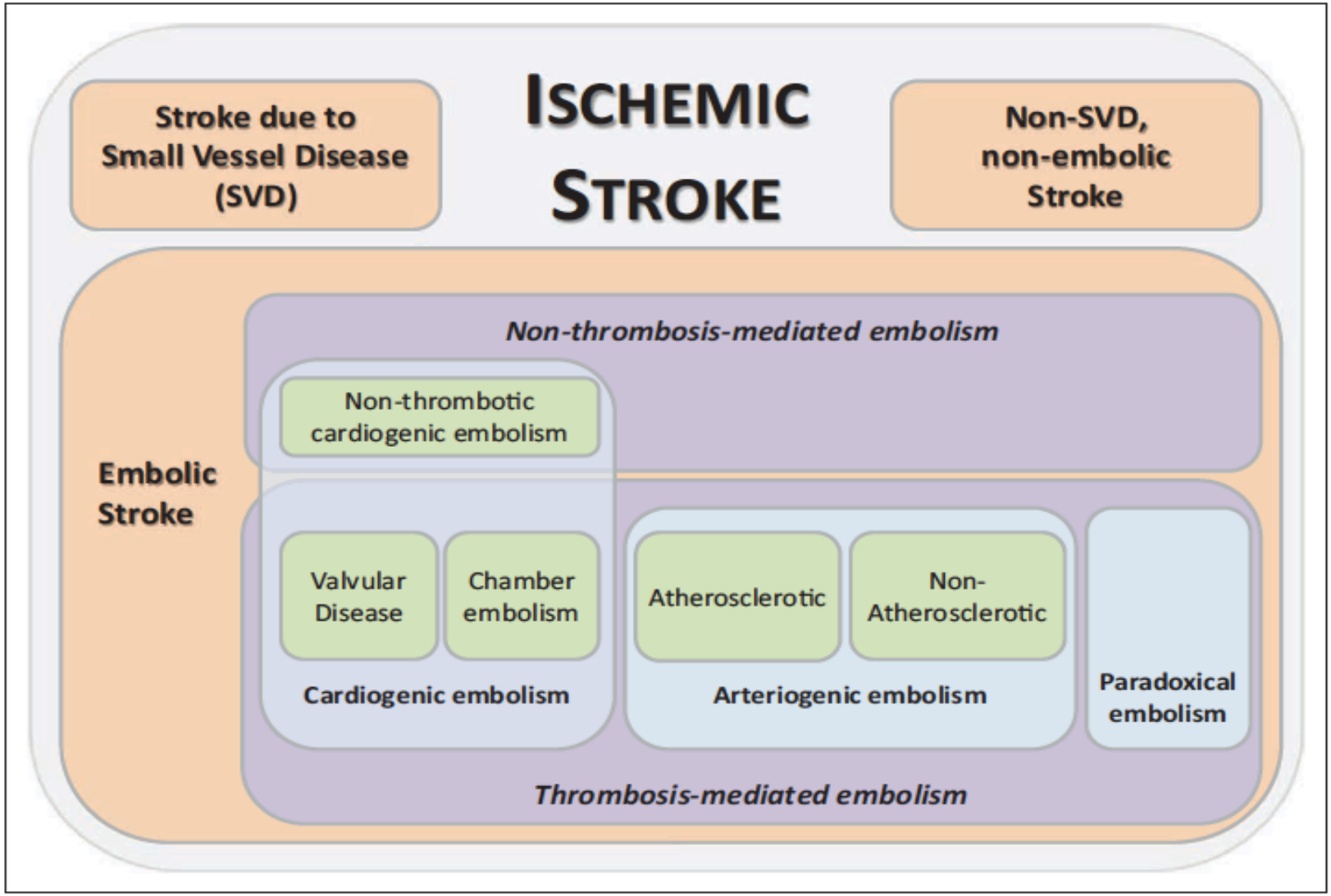


-*TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification:* stroke of undetermined cause may refer to a stroke with incomplete workup, more than one potential cause, or indeed no determined etiology after investigations are complete.

-*ASCO calssification*: 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

Hart, Lancet Neurol 2014

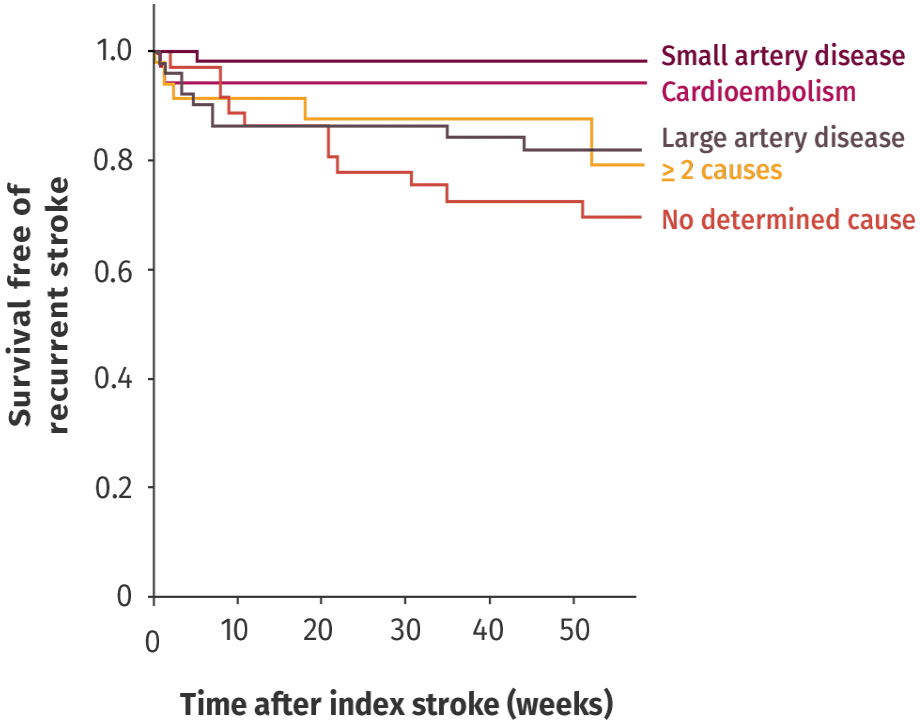
ESUS: Embolic strokes of undetermined source
PROPOSED DIAGNOSTIC ASSESSMENT

- 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)

Hart, Lancet Neurol 2014

ESUS: Embolic strokes of undetermined source

STROKE RECURRENCE RISK

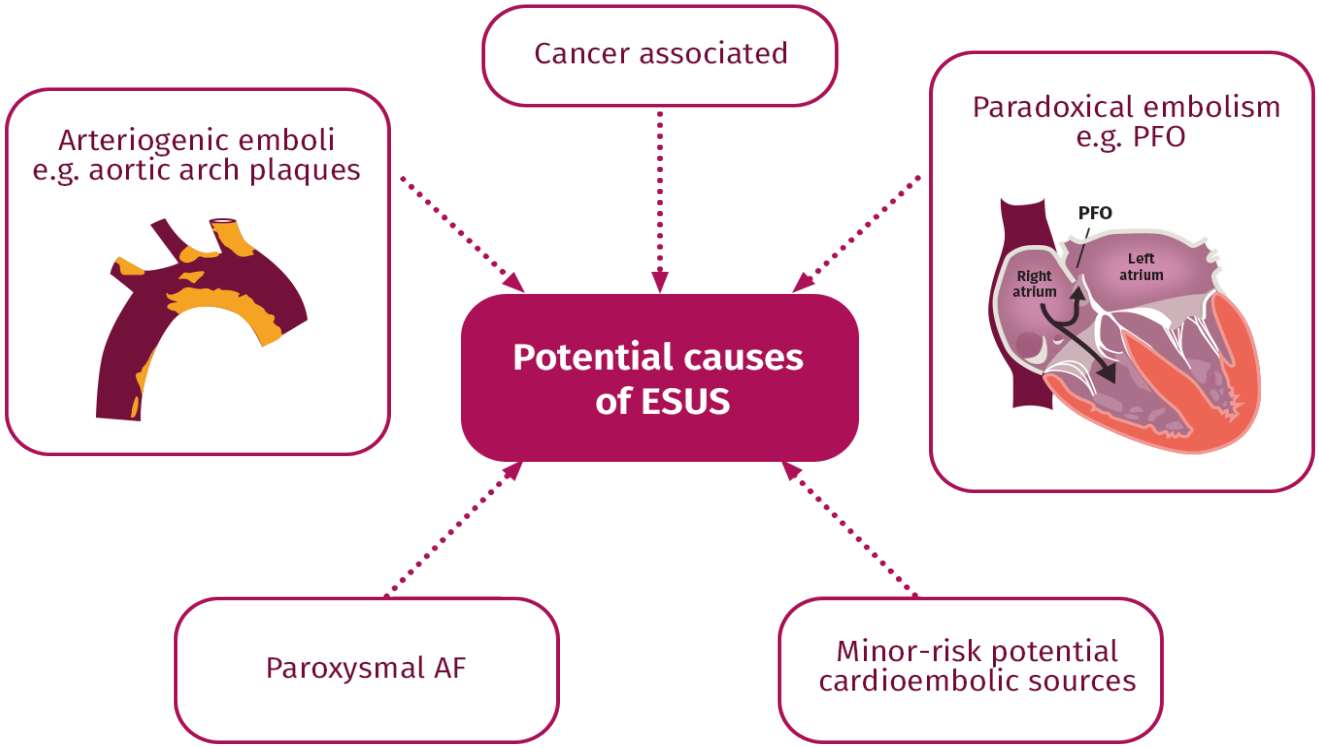


Patients with ESUS show a significantly higher rate of recurrent stroke than those of other subtypes

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.

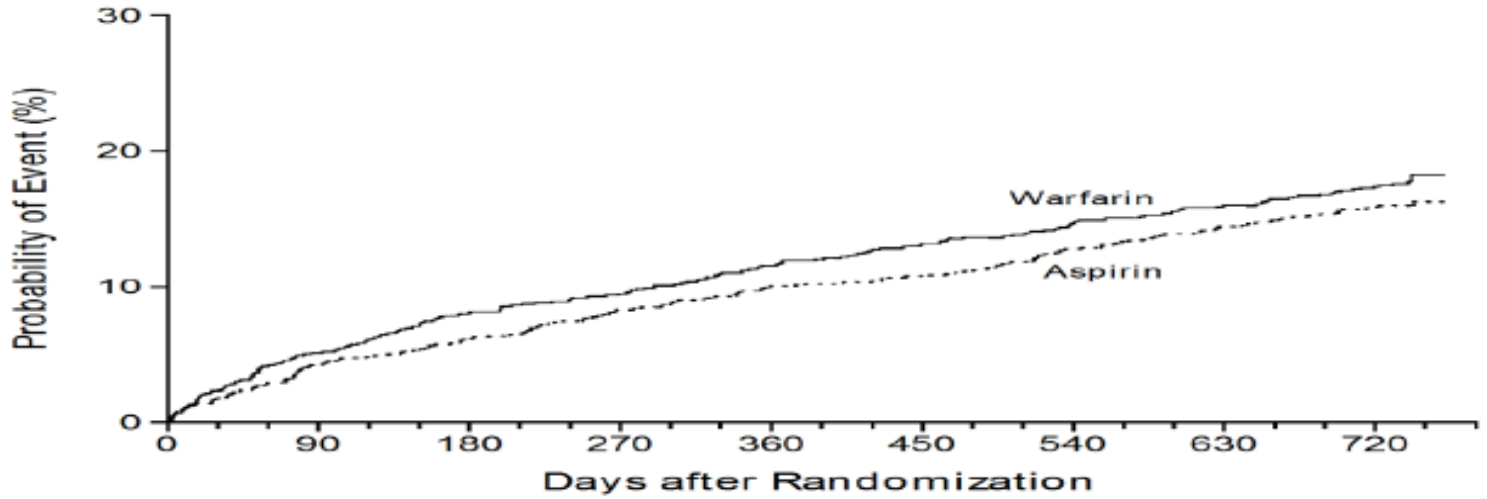
ESUS: Embolic strokes of undetermined source
TREATMENT

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



No. at Risk

Warfarin	1103	1047	1013	998	972	956	939	924	885
Aspirin	1103	1057	1032	1004	984	974	951	932	900

TABLE 3. ADVERSE EVENTS ACCORDING TO TREATMENT ASSIGNMENT.*

EVENT	WARFARIN (N=1103)	ASPIRIN (N=1103)	ODDS RATIO (95% CI)	P VALUE†
	no. (%)			
Death	47 (4.3)	53 (4.8)	0.88 (0.58–1.32)	0.61
Related to hemorrhage	7 (0.6)	5 (0.4)	1.40 (0.42–5.13)	0.77
First hemorrhage‡				
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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source

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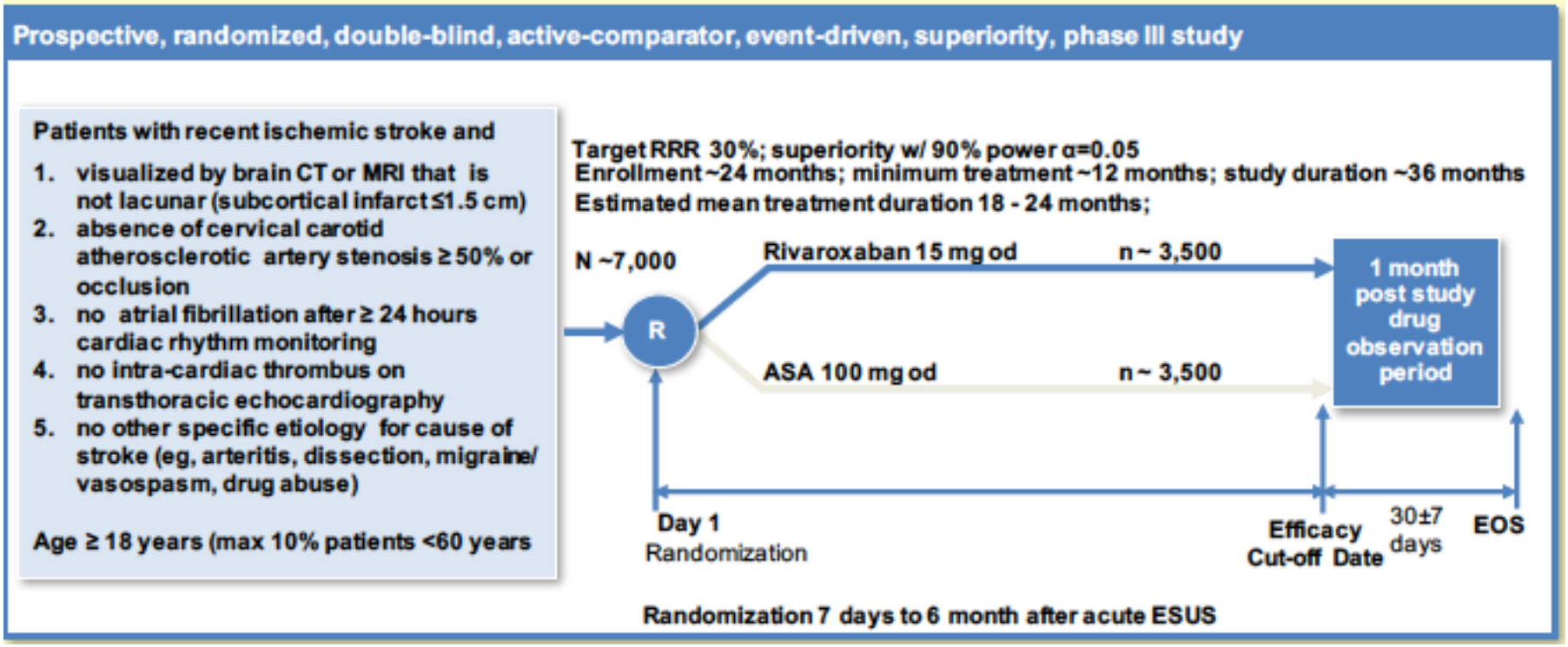
Trial design



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 index‡	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)

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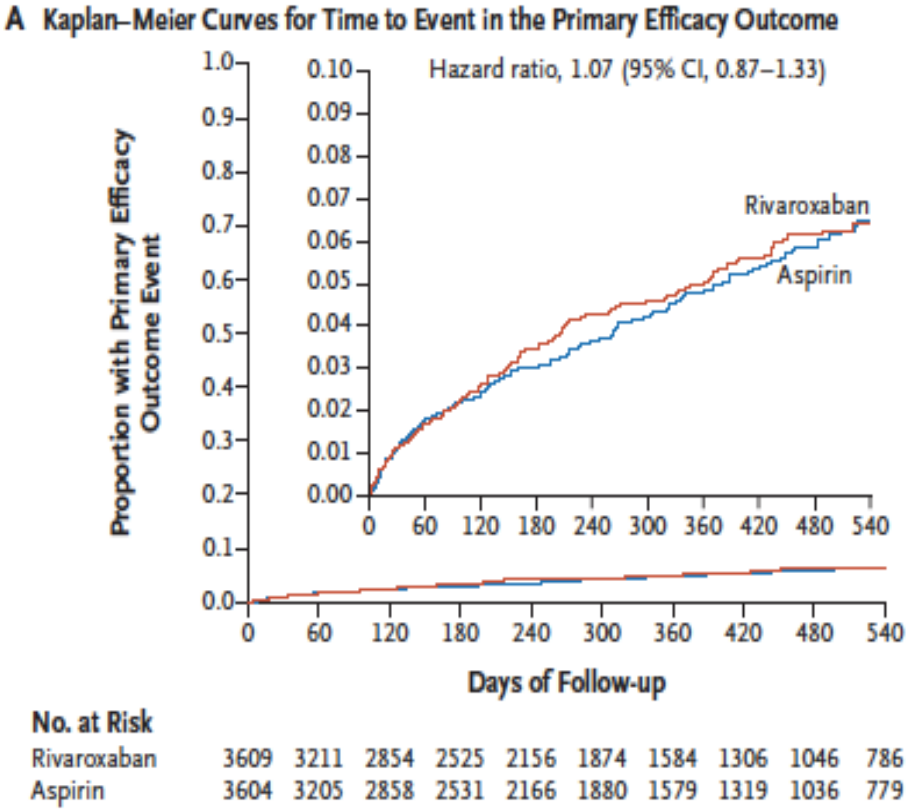
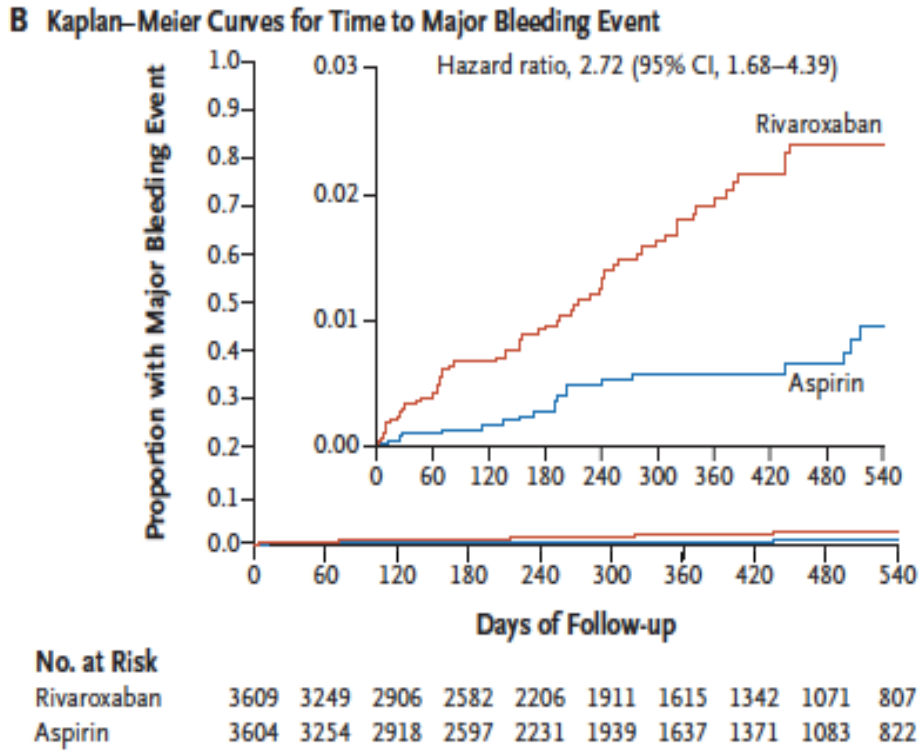
Figure 1. Cumulative Incidence of the Primary Efficacy Outcome and the Primary Safety Outcome, According to Treatment Assignment.





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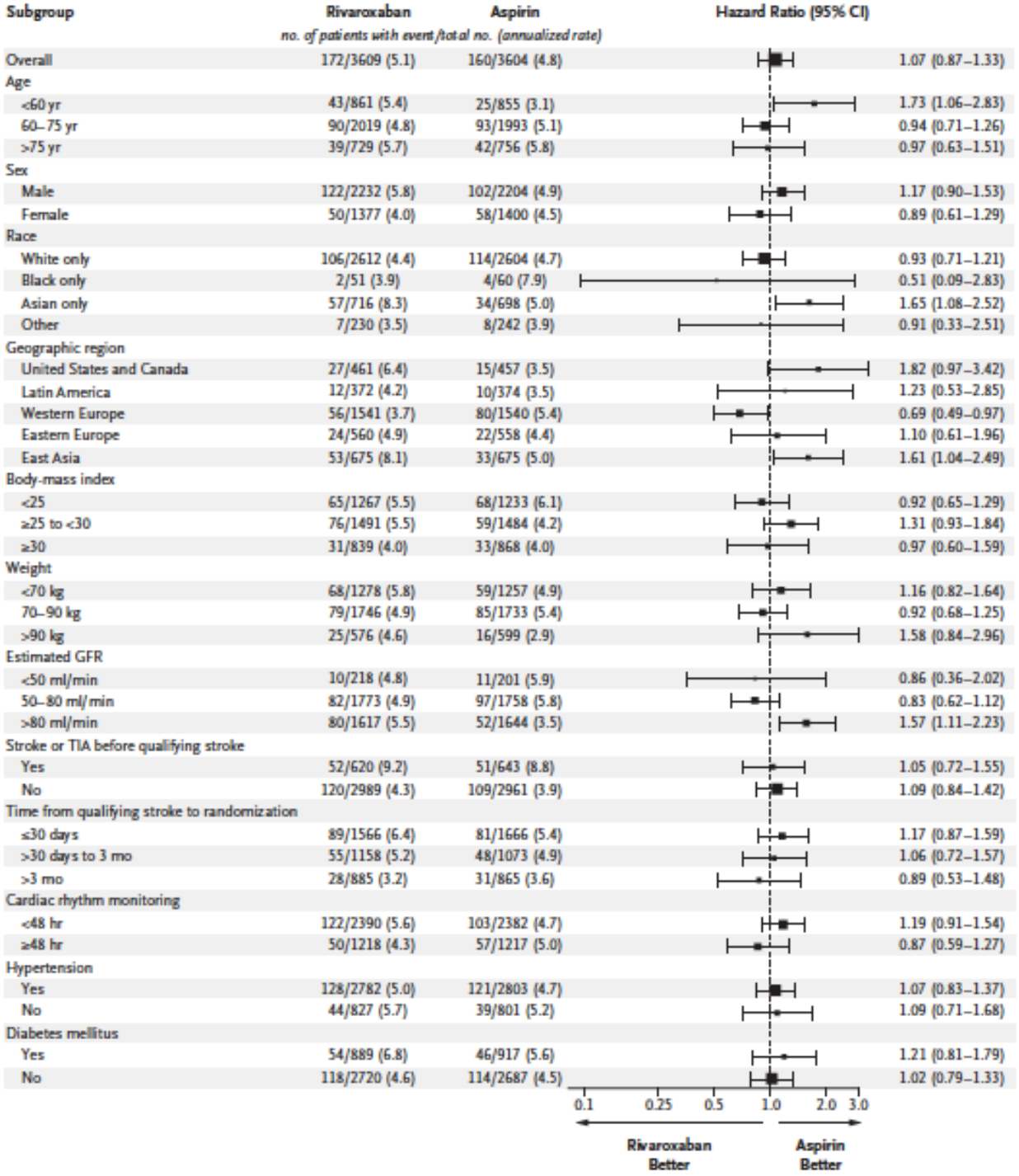

Figure 2. Exploratory Analyses of Treatment Effects on the Primary Efficacy Outcome in Prespecified Subgroups.

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Table 3. Safety Outcomes.*

Outcome	Rivaroxaban Group (N=3609)	Aspirin Group (N=3604)	Hazard Ratio (95% CI)†	P Value
	no. of patients (annualized rate)			
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

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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).

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