NAVIGATE ESUS

An international, double-blind, phase III randomized trial

Main Results

Robert Hart on behalf of the
NAVIGATE ESUS Steering Committee
and Investigators

Sponsorship & Disclosures

NAVIGATE ESUS was sponsored by Bayer AG and Janssen LLC.

Disclosures: R. G. Hart (McMaster University)
Research support, honoraria and stipends from Bayer AG (rivaroxaban) for serving as the co-Principal Investigator of the NAVIGATE ESUS trial, for service on the Steering & Event Adjudication Committees of COMPASS / COMPASS MIND MRI trial, and for participation on advisory boards

Embolic Strokes of Undetermined Source (ESUS)

- Most cryptogenic strokes are embolic (cardioembolic, arteriogenic, paradoxic).
- Extensive diagnostic efforts to define the specific cause are expensive & not widely available; often one than one potential source is identified.
- For secondary prevention, anticoagulants may be more efficacious than antiplatelets for most embolic sources.
- ESUS criteria: Nonlacunar, cryptogenic ischemic stroke with open artery & no major-risk cardioembolic source.

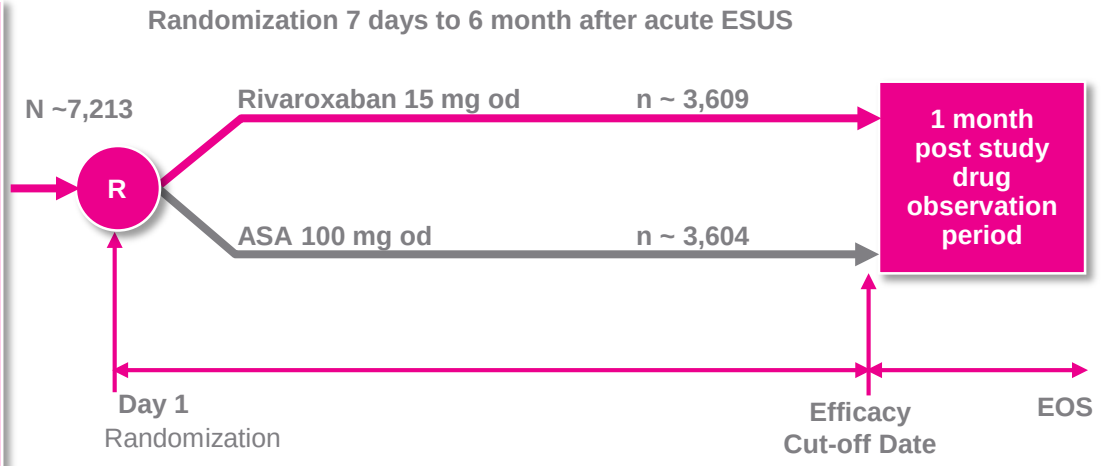
NAVIGATE ESUS Study Design

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

Patients with recent ischemic stroke and

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

Age ≥ 50 years

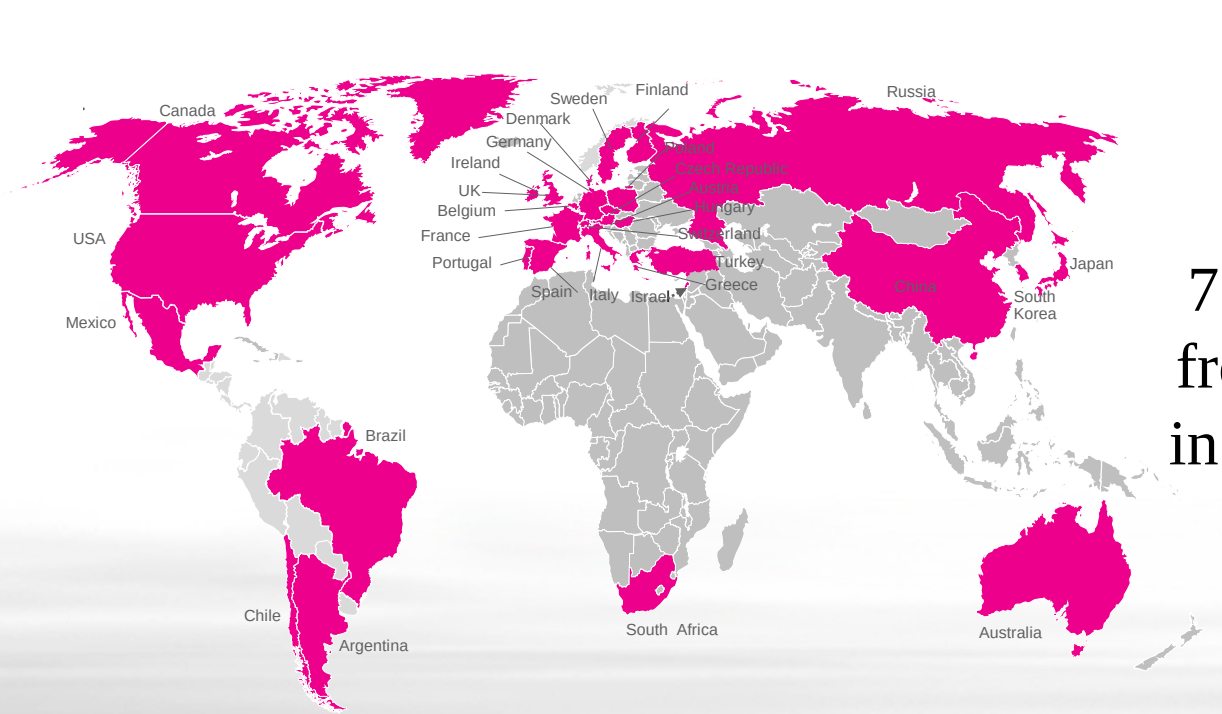


Primary efficacy endpoint: Stroke, systemic embolism (ITT)
Primary safety endpoint: ISTH major bleeding (ITT)

459 sites in 31 countries

Study halted on 5 October 2017 at the 2nd interim analysis based on recommendation by the DMC: *"In the absence of offsetting benefit, and little chance of showing benefit if the study were completed, there is a clear risk of excess bleeding."*

NAVIGATE ESUS Countries & National Leaders



7213 patients from 459 sites in 31 countries 2014-2017

Argentina: Sebastian Ameriso
Australia: Graeme Hankey
Austria: Wilfried Lang
Belgium: Raf Brouns
Brazil: Rubens José Gagliardi
Canada: Mike Sharma
Chile: Pablo Lavados
China: Yongjun Wang
Czech Republic: Robert Mikulik
Finland: Turgut Tatlisumak
France: Pierre Amarenco

Germany: Matthias Endres
Greece: George Ntaios
Hungary: Daniel Bereczki
Ireland: Martin O`Donnell
Israel: Natan Bornstein
Italy: Danilo Toni
Japan: Shinichiro Uchiyama
Mexico: Antonio Arauz
Poland: Anna Czlonkowska
Portugal: Luis Cunha
Russia: Nikolay Shamalov

South Africa: Mattys Basson
South Korea: Byung-Woo Yoon
Spain: Antoni Davalos
Sweden + Denmark; Arne Lindgren
Switzerland: Jens Eckstein
Turkey: Serefnur Öztürk
UK: Keith Muir
UK: Roland Veltkamp
USA: Scott Kasner

Baseline Characteristics

	Rivaroxaban (N=3609)	ASA (N=3604)
Age, years (mean)	66.9	66.9
Male sex	62 %	61%
Systolic Blood Pressure, mmHg (mean ± s.d.)	135 ± 17	135 ± 17
Statin use after randomization	78 %	77 %
Hypertension	77 %	78 %
Diabetes mellitus	25 %	25 %
Current tobacco use	21%	20%
Prior stroke or TIA	17 %	18 %
Geographic region • U.S.A. and Canada • Latin America • Europe • East Asia	 13 % 10% 59 % 19 %	 13 % 10 % 58 % 19 %
NIHSS score at randomization (median, IQR)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)
Intravenous tPA use	17 %	18 %
Time from qualifying stroke to randomization	38 d	36 d
Intracranial vascular imaging (any type)	78 %	78 %
Cardiac rhythm monitoring ≥48 hours	34 %	34 %

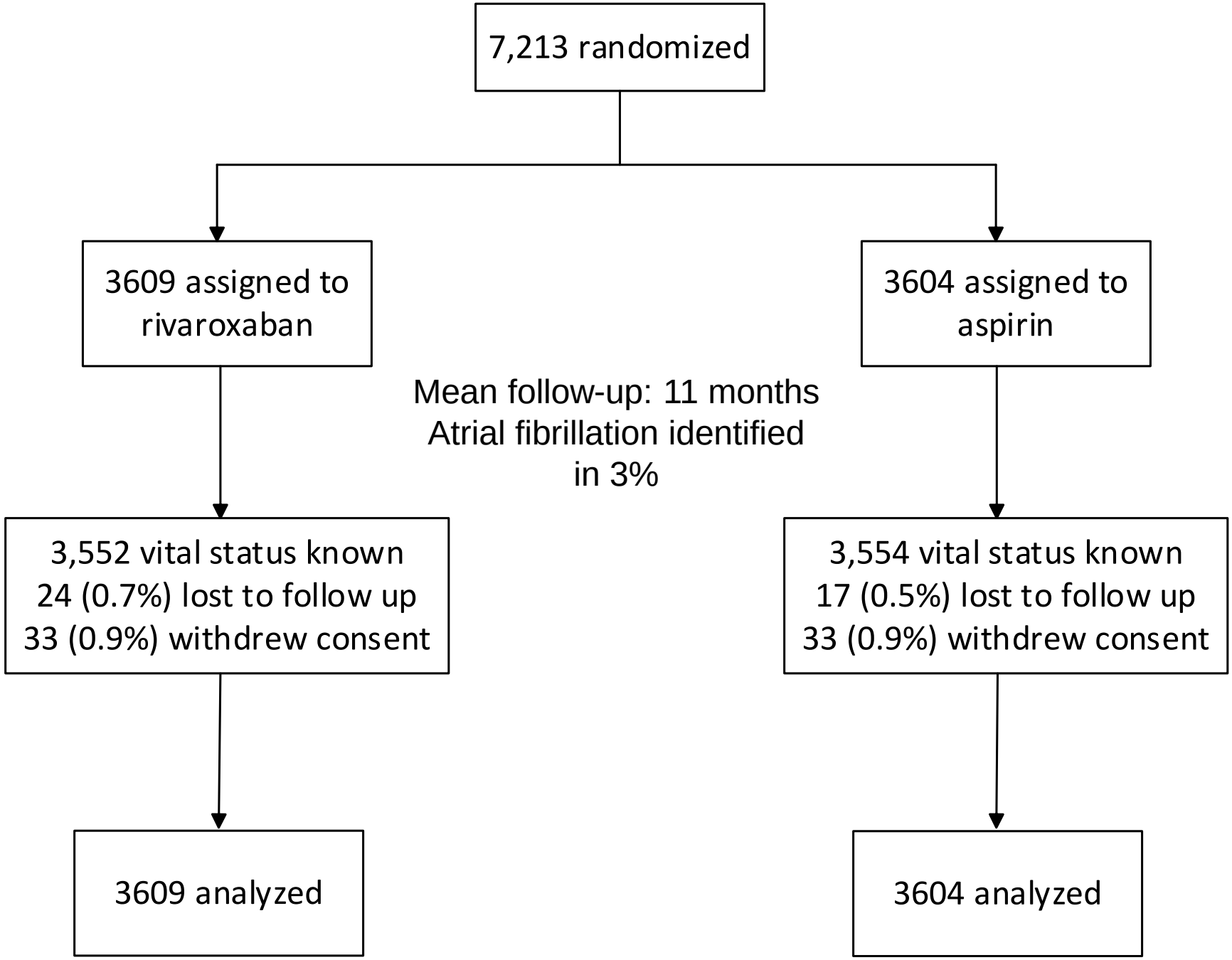
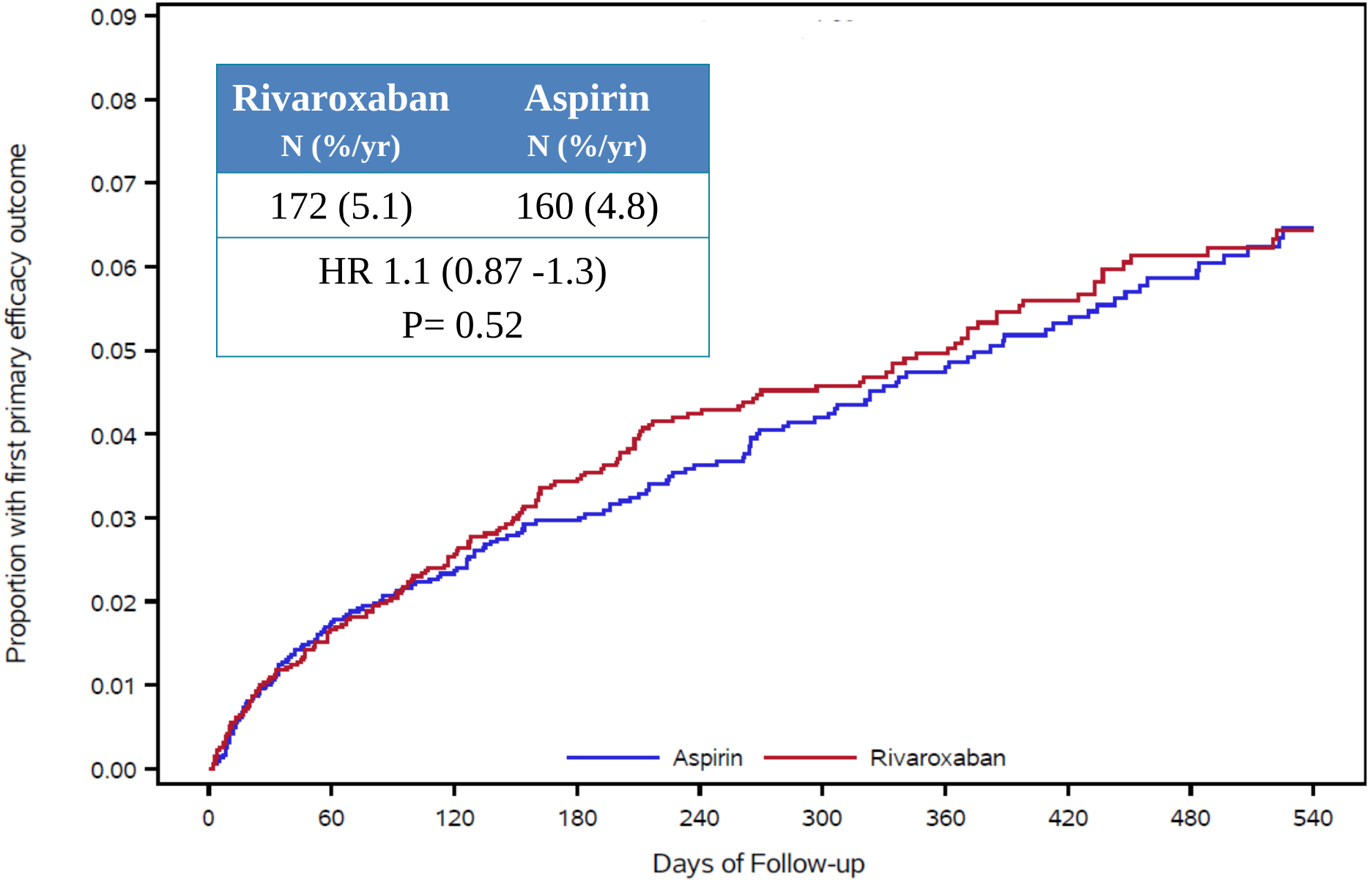

7,213 randomized
3609 assigned to rivaroxaban
3604 assigned to aspirin
Mean follow-up: 11 months
Atrial fibrillation identified in 3%
3,552 vital status known
24 (0.7%) lost to follow up
33 (0.9%) withdrew consent
3,554 vital status known
17 (0.5%) lost to follow up
33 (0.9%) withdrew consent
3609 analyzed
3604 analyzed

Figure 1a. Kaplan-Meier curves for time to first primary efficacy outcome



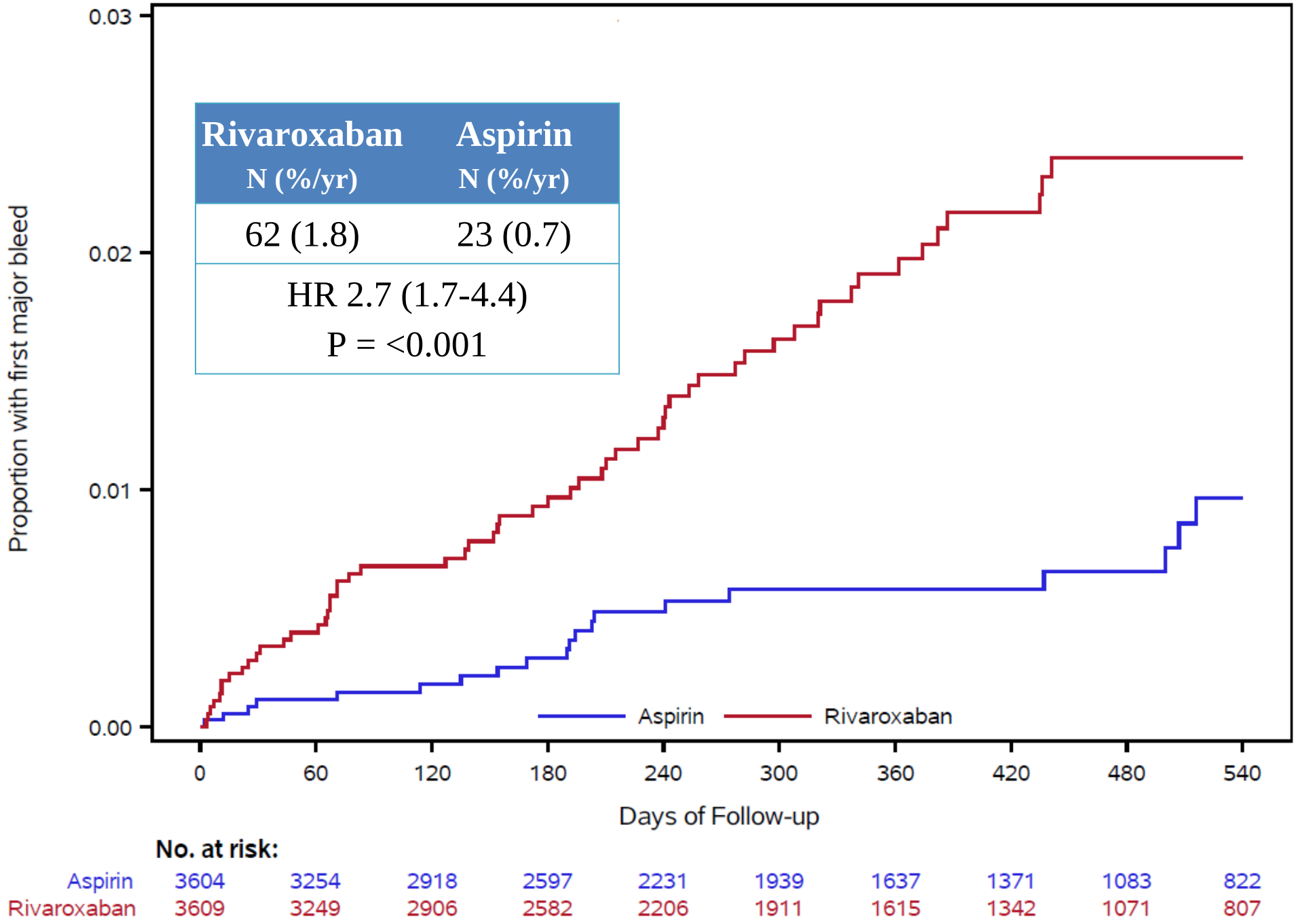
Efficacy Outcomes

	Rivaroxaban N=3609 n (%/year)	ASA N=3604 n (%/year)	HR (95% CI)	p-value
Primary outcome (all recurrent stroke or systemic embolism)	172 (5.1)	160 (4.8)	1.1 (0.87-1.3)	0.52
Individual components included in the primary outcome				
All recurrent stroke (ischemic, hemorrhagic, undefined)	171 (5.1)	158 (4.7)	1.1 (0.87-1.3)	0.48
Ischemic stroke	158 (4.7)	156 (4.7)	1.0 (0.81-1.3)	0.92
Hemorrhagic stroke	13 (0.4)	2 (0.1)	6.5 (1.5-28)	0.01

Secondary Efficacy Outcomes

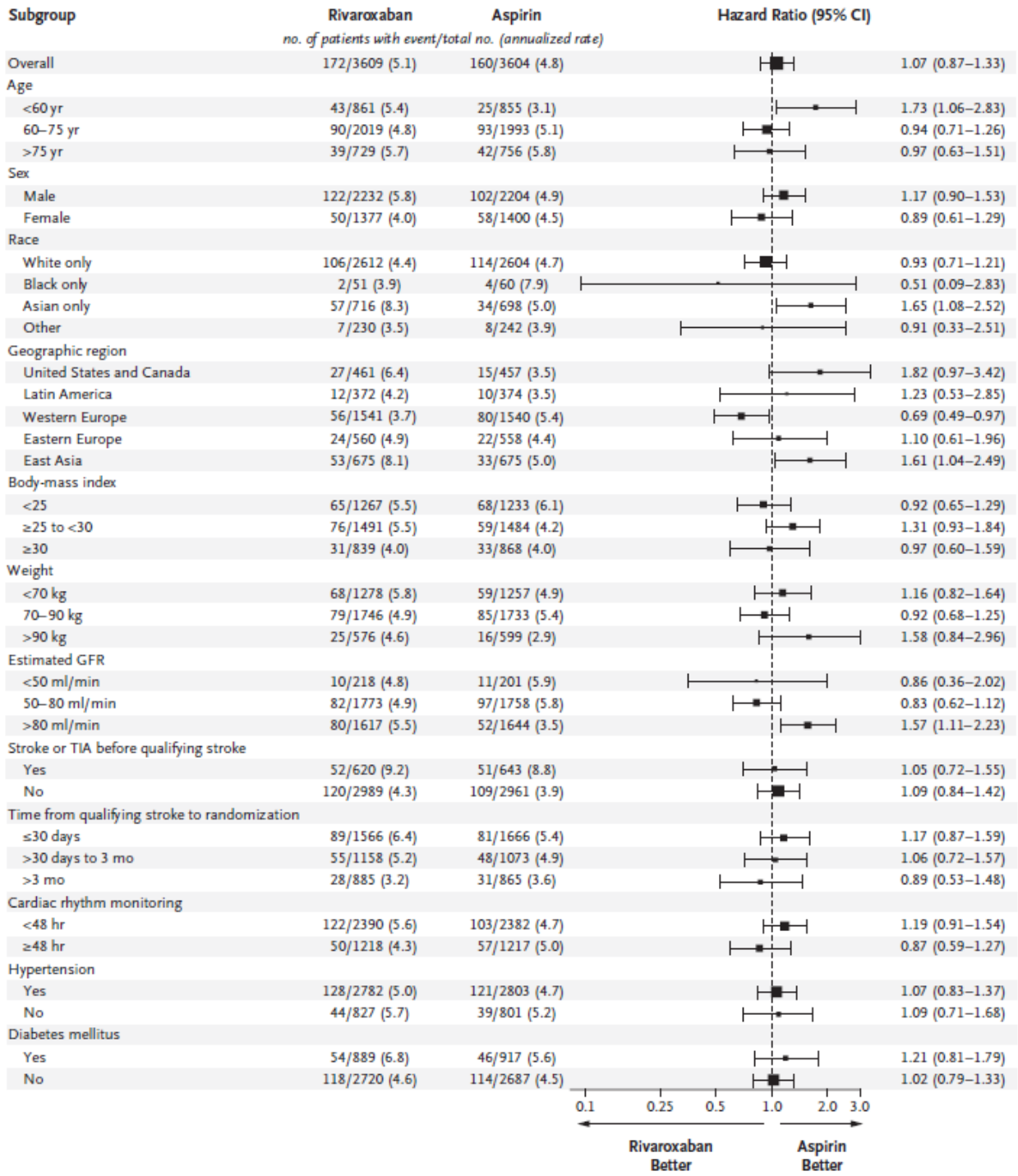
	Rivaroxaban N=3609 n (%/year)	ASA N=3604 n (%/year)	HR (95% CI)	p-value
All recurrent stroke, MI, CV death, systemic embolism	207 (6.2)	195 (5.8)	1.1 (0.87-1.3)	0.57
All disabling stroke	41 (1.2)	29 (0.8)	1.4 (0.88-2.3)	0.15
Myocardial infarction (MI)	17 (0.5)	23 (0.7)	0.74 (0.39-1.4)	0.34
All-cause mortality	65 (1.9)	52 (1.5)	1.26 (0.87-1.8)	0.22
Cardiovascular death	34 (1.0)	23 (0.7)	1.48 (0.87-2.5)	0.14

Figure 1b. Kaplan-Meier curves for time to first major bleed



Safety Outcomes

	Rivaroxaban N=3609 n (%/year)	ASA N=3604 n (%/year)	HR (95% CI)	p-value
Primary safety outcome (ISTH major bleeding)	62 (1.8)	23 (0.7)	2.7 (1.7-4.4)	0.001
Secondary safety outcomes				
Life-threatening/fatal bleeding	35 (1.0)	15 (0.4)	2.3 (1.3-4.3)	0.006
Clinically-relevant non-major bleeding	118 (3.5)	79 (2.3)	1.5 (1.1-2.0)	0.005
Symptomatic intracranial hemorrhage	20 (0.6)	5 (0.1)	4.0 (1.5-11)	0.005
- intracerebral	12 (0.3)	3 (0.1)	4.0 (1.1-14)	0.03
- subarachnoid	5 (0.1)	1 (0.0)	5.0 (0.5-43)	0.10
- subdural/epidural	3 (0.1)	2 (0.1)	1.5 (0.3-9.0)	0.65


Subgroup
Rivaroxaban
Aspirin
Hazard Ratio (95% CI)
no. of patients with event/total no. (annualized rate)
Overall 172/3609 (5.1) 160/3604 (4.8) 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)
>75 yr 39/729 (5.7) 42/756 (5.8) 0.97 (0.63–1.51)
Sex
Male 122/2232 (5.8) 102/2204 (4.9) 1.17 (0.90–1.53)
Female 50/1377 (4.0) 58/1400 (4.5) 0.89 (0.61–1.29)
Race
White only 106/2612 (4.4) 114/2604 (4.7) 0.93 (0.71–1.21)
Black only 2/51 (3.9) 4/60 (7.9) 0.51 (0.09–2.83)
Asian only 57/716 (8.3) 34/698 (5.0) 1.65 (1.08–2.52)
Other 7/230 (3.5) 8/242 (3.9) 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) 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) 0.92 (0.65–1.29)
≥25 to <30 76/1491 (5.5) 59/1484 (4.2) 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) 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) 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) 0.83 (0.62–1.12)
>80 ml/min 80/1617 (5.5) 52/1644 (3.5) 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 randomization
≤30 days 89/1566 (6.4) 81/1666 (5.4) 1.17 (0.87–1.59)
>30 days to 3 mo 55/1158 (5.2) 48/1073 (4.9) 1.06 (0.72–1.57)
>3 mo 28/885 (3.2) 31/865 (3.6) 0.89 (0.53–1.48)
Cardiac rhythm monitoring
<48 hr 122/2390 (5.6) 103/2382 (4.7) 1.19 (0.91–1.54)
≥48 hr 50/1218 (4.3) 57/1217 (5.0) 0.87 (0.59–1.27)
Hypertension
Yes 128/2782 (5.0) 121/2803 (4.7) 1.07 (0.83–1.37)
No 44/827 (5.7) 39/801 (5.2) 1.09 (0.71–1.68)
Diabetes mellitus
Yes 54/889 (6.8) 46/917 (5.6) 1.21 (0.81–1.79)
No 118/2720 (4.6) 114/2687 (4.5) 1.02 (0.79–1.33)
0.1
0.25
0.5
1.0
2.0
3.0
Rivaroxaban Better
Aspirin Better

NAVIGATE ESUS Main Results- I

- Rigorously-conducted, hypothesis-testing phase III international randomized trial.
- No reduction in recurrent stroke by rivaroxaban 15 mg daily vs. aspirin, and major bleeding was increased.
- Stopped early with 74% of planned primary events, but adequate power to exclude >13% stroke reduction by rivaroxaban.
- High rate of recurrent stroke (~5%/yr) with either treatment.

NAVIGATE ESUS Main Results - II

- "A beautiful hypothesis slain by ugly facts."*
- Why was NAVIGATE ESUS negative?
  - Did ESUS criteria define embolic strokes?
  - Heterogeneous embolic sources with different composition of emboli did not respond better to factor Xa inhibition?
- Ongoing randomized trials will clarify if the high stroke recurrence rates in ESUS patients can be reduced by alternative anticoagulants.

* Adapted from Thomas Huxley; address to British Association for Advancement of Science (1870).