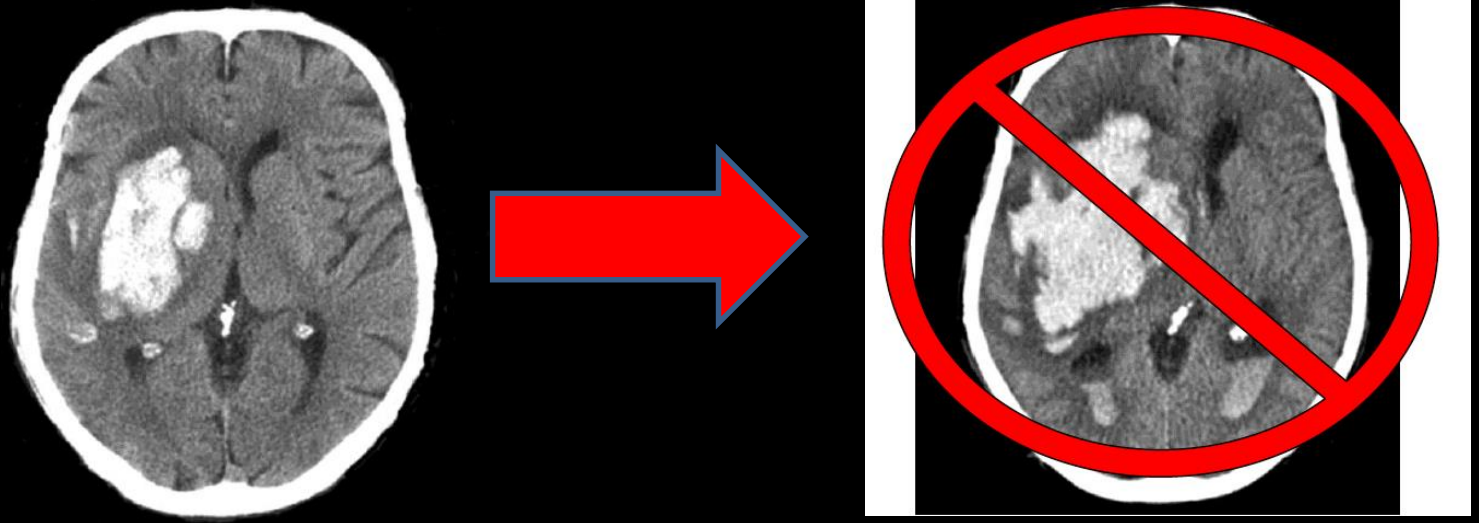
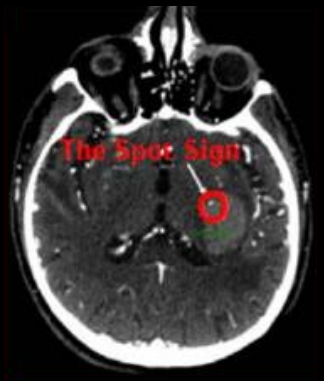
- Thrombolysis-WAKE UP
- Intra-arterial interventions – DEFUSE 3
- Haemorrhagic Stroke - TICH 2
- Secondary Prevention – CROMIS 2
- Secondary Prevention – NAVIGATE ESUS

Progression of haematoma





Anticoagulation
Large ICH volumes
Early Presentations
Spot Sign

Blood pressure lowering

Haemostatic agents

Haemostatic Options

Pro-coagulants: Factor VII a (SPOT-LIGHT)

Platelets (PATCH)

Prothrombin complex (INCH)

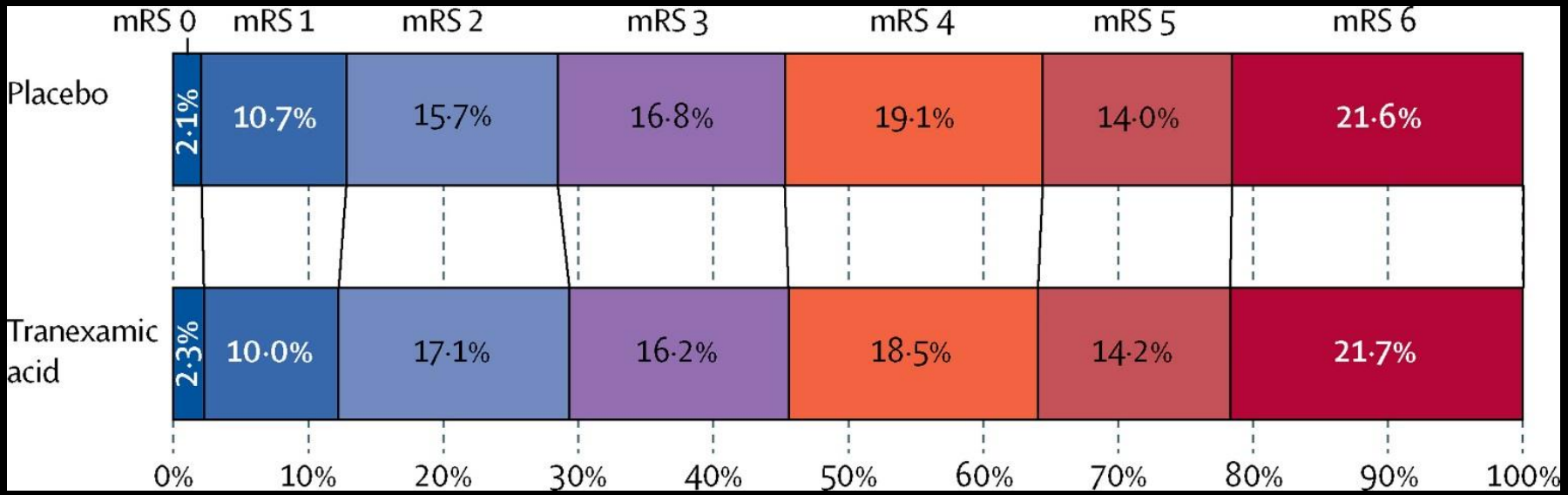
Anti-fibrinolytics: Tranexamic Acid (CRASH-2, TICH-2)

Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial

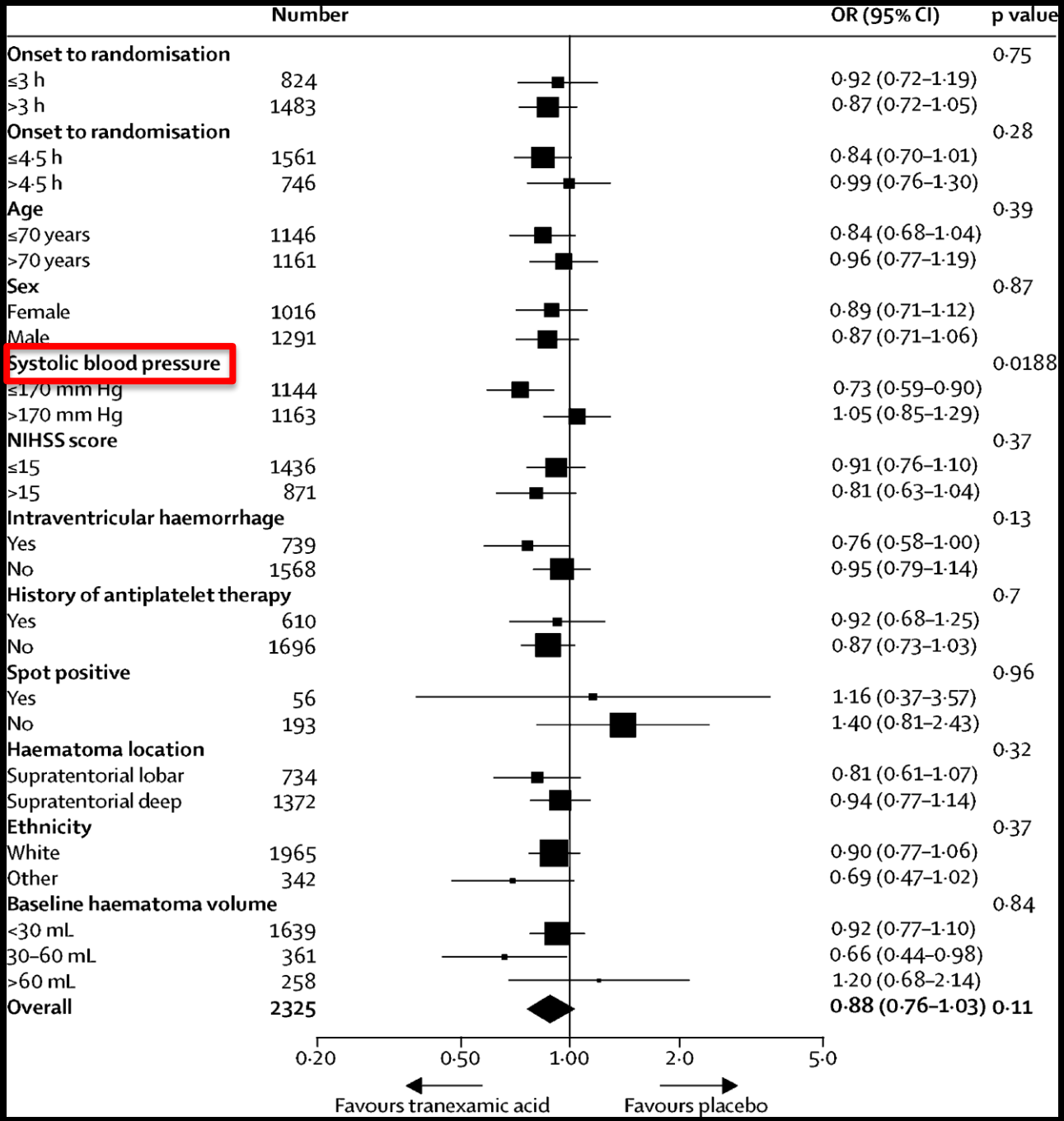
*Nikola Sprigg, Katie Flaherty, Jason P Appleton, Rustam Al-Shahi Salman, Daniel Bereczki, Maia Beridze, Hanne Christensen, Alfonso Ciccone, Ronan Collins, Anna Czlonkowska, Robert A Dineen, Lelia Duley, Juan Jose Egea-Guerrero, Timothy J England, Kailash Krishnan, Ann Charlotte Laska, Zhe Kang Law, Serefnur Ozturk, Stuart J Pocock, Ian Roberts, Thompson G Robinson, Christine Roffe, David Seiffge, Polly Scutt, Jegan Thanabalan, David Werring, David Whynes, Philip M Bath, for the TICH-2 Investigators**

	Tranexamic acid (n=1161)	Placebo (n=1164)
Age*, years	69·1 (13·7) [29–97]	68·7 (13·9) [20–101]
>70	584 (50%)	580 (50%)
Sex*, male	642 (55%)	659 (57%)
Ethnic origin		
White	986 (85%)	992 (85%)
Other	174 (15%)	172 (15%)
Onset to randomisation*, h	3·6 (2·6–5·1) [1·0–20·8]	3·7 (2·6–5·0) [0·8–8·0]
≤3	421 (36%)	412 (35%)
≤4·5	779 (67%)	796 (68%)
History		
Previous antiplatelet therapy*	316 (27%)	295 (25%)
Statin use prior to admission	319 (28%)	303 (26%)
Previous stroke or transient ischaemic attack	173 (15%)	156 (14%)
Ischaemic heart disease	110 (10%)	92 (8%)
Prestroke mRS	0 (0–1) [0–4]	0 (0–1) [0–4]
Glasgow Coma Scale	13 (2·2) [5·0–150]	14 (2·1) [5·0–15·0]
NIHSS score*	13 (7·5) [0·0–41·0]	13 (7·5) [0·0–42·0]
Systolic blood pressure*, mm Hg	172 (27·5) [98·0–265]	174 (26·8) [99·0–265]
Diastolic blood pressure, mm Hg	93 (18·4) [46·0–179]	94 (17·8) [35·5–162]
Haematoma location		
Supratentorial lobar	379 (33%)	359 (31%)
Supratentorial deep	675 (58%)	696 (60%)
Infratentorial	73 (6%)	76 (7%)
Combination	34 (3%)	33 (3%)
ntracerebral haematoma volume (mL)	14·1 (5·9–32·4) [0·0–207]	12·5 (5·1–31·9) [0·0–163]
Intraventricular haemorrhage*	382 (33%)	363 (31%)
CT angiography done	121 (11%)	128 (11%)
Spot positive	24 (20%)	32 (25%)
Spot negative	97 (80%)	96 (75%)

Results



OR: 0.88, 95% CI: (0.76-1.03)


Number
OR (95% CI)
p value
Onset to randomisation
0·75
≤3 h
824
0·92 (0·72–1·19)
>3 h
1483
0·87 (0·72–1·05)
Onset to randomisation
0·28
≤4·5 h
1561
0·84 (0·70–1·01)
>4·5 h
746
0·99 (0·76–1·30)
Age
0·39
≤70 years
1146
0·84 (0·68–1·04)
>70 years
1161
0·96 (0·77–1·19)
Sex
0·87
Female
1016
0·89 (0·71–1·12)
Male
1291
0·87 (0·71–1·06)
Systolic blood pressure
0·0188
≤170 mm Hg
1144
0·73 (0·59–0·90)
>170 mm Hg
1163
1·05 (0·85–1·29)
NIHSS score
0·37
≤15
1436
0·91 (0·76–1·10)
>15
871
0·81 (0·63–1·04)
Intraventricular haemorrhage
0·13
Yes
739
0·76 (0·58–1·00)
No
1568
0·95 (0·79–1·14)
History of antiplatelet therapy
0·7
Yes
610
0·92 (0·68–1·25)
No
1696
0·87 (0·73–1·03)
Spot positive
0·96
Yes
56
1·16 (0·37–3·57)
No
193
1·40 (0·81–2·43)
Haematoma location
0·32
Supratentorial lobar
734
0·81 (0·61–1·07)
Supratentorial deep
1372
0·94 (0·77–1·14)
Ethnicity
0·37
White
1965
0·90 (0·77–1·06)
Other
342
0·69 (0·47–1·02)
Baseline haematoma volume
0·84
<30 mL
1639
0·92 (0·77–1·10)
30–60 mL
361
0·66 (0·44–0·98)
>60 mL
258
1·20 (0·68–2·14)
Overall
2325
0·88 (0·76–1·03)
0·11
0·20
0·50
1·00
2·0
5·0
Favours tranexamic acid
Favours placebo

Results

	TXA	Placebo		
Haematoma				
Change in volume from baseline to 24 h*, mL	3·72 (15·9)	4·90 (16·0)	MD −1·37 (−2·71 to −0·04)	0·0432
Participants with haematoma expansion†	265 (25%)	304 (29%)	Binary OR 0·80 (0·66 to 0·98)	0·0300
Day 7				
Death by day 7	101 (9%)	123 (11%)	Binary OR 0·73 (0·53 to 0·99)	0·0406
NIHSS day 7	10·13 (8·3)	10·29 (8·3)	MD −0·43 (−0·94 to 0·09)	0·10

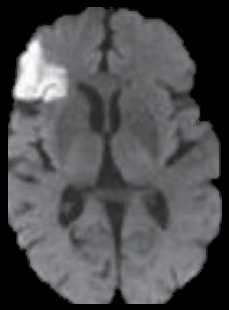
Summary

- There were no significant differences in functional status at 90 days after ICH in patients receiving tranexamic acid
- Reasons for findings
  - Tranexamic acid may not work?
  - Treatment effects overestimated
  - Heterogeneous population: dilutional effect
  - Timing < 3 hrs (rFVIIa)
- Subgroup analysis: Support for Blood pressure
  Haematoma Volume (30-60 ml)
- Future trials: Earlier (<3 hrs), effect on haematoma growth and focus of specific subgroups
- TICH-NOAC, DASH, STOP-AUST

- Thrombolysis-WAKE UP
- Intra-arterial interventions – DEFUSE 3
- Haemorrhagic Stroke - TICH 2
- Secondary Prevention – CROMIS 2
- Secondary Prevention – NAVIGATE ESUS

Treatment Dilemma

- Dilemma of anticoagulation in patients with AF
- Clinical risk scores are not perfect and do not differentiate between IS or ICH



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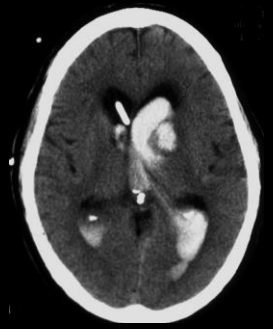


Table 8 CHA_2DS_2VASc score and stroke rate

(a) Risk factors for stroke and thrombo-embolism in non-valvular AF

'Major' risk factors	'Clinically relevant non-major' risk factors
Previous stroke, TIA, or systemic embolism Age ≥75 years	Heart failure or moderate to severe LV systolic dysfunction (e.g. LV EF ≤40%) Hypertension - Diabetes mellitus Female sex - Age 65–74 years Vascular disease[a]

(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc (Note: maximum score is 9 since age may contribute 0, 1, or 2 points)

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1

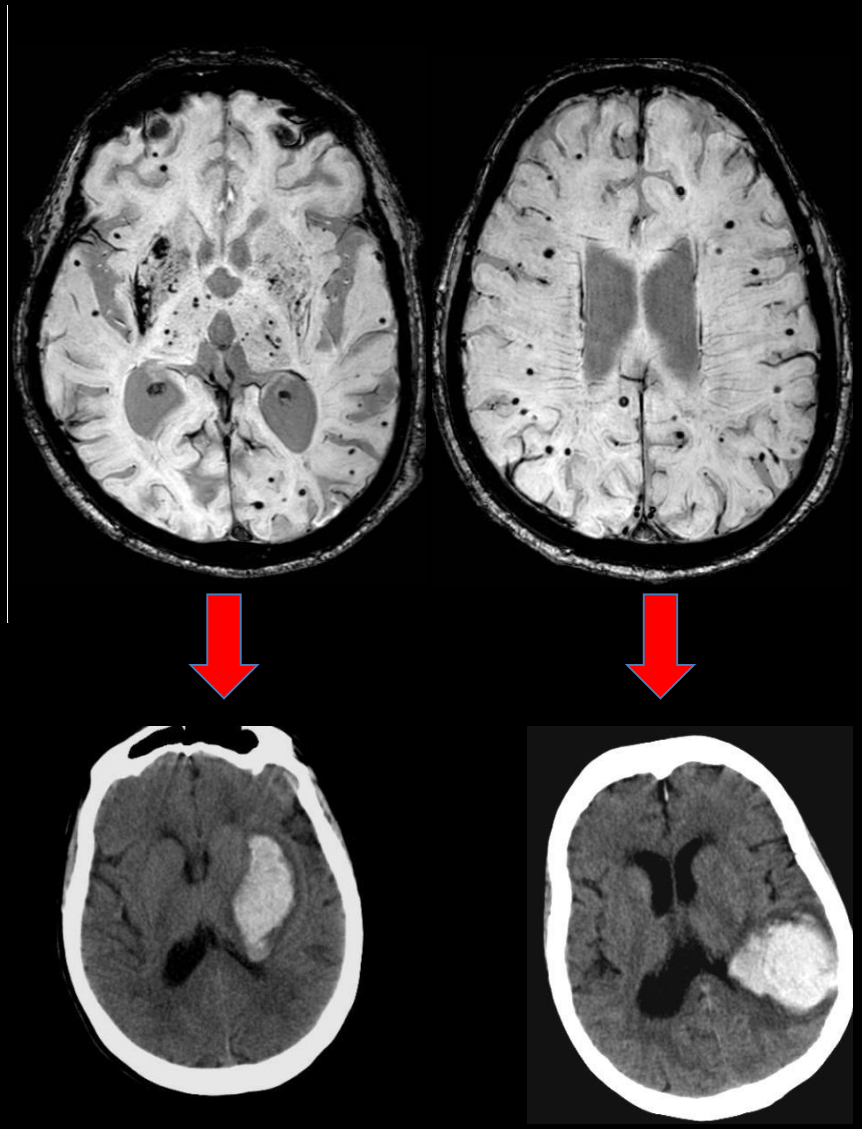
vs

Table 10 Clinical characteristics comprising the HAS-BLED bleeding risk score

Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

Cerebral Microbleeds

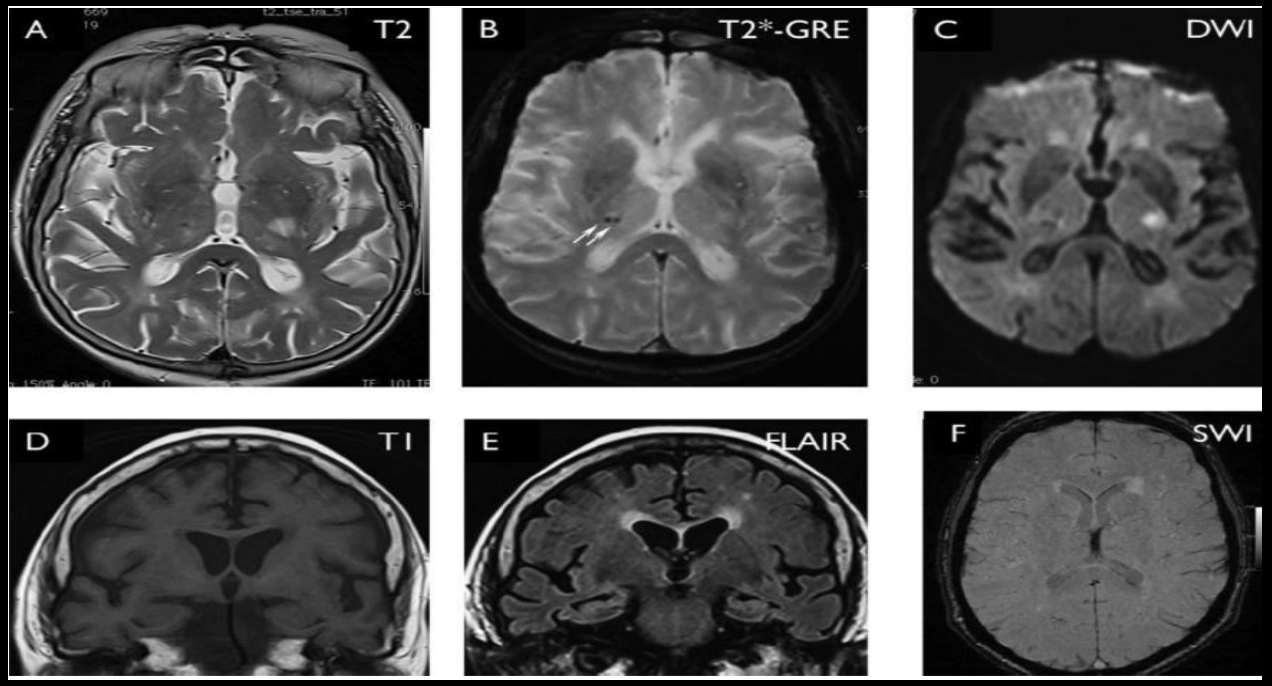
Hypertensive arteriopathy



Cerebral amyloid angiopathy

Cerebral microbleeds and intracranial haemorrhage risk in patients anticoagulated for atrial fibrillation after acute ischaemic stroke or transient ischaemic attack (CROMIS-2): a multicentre observational cohort study

*Duncan Wilson, Gareth Ambler, Clare Shakeshaft, Martin M Brown, Andreas Charidimou, Rustam Al-Shahi Salman, Gregory Y H Lip, Hannah Cohen, Gargi Banerjee, Henry Houlden, Mark J White, Tarek A Yousry, Kirsty Harkness, Enrico Flossmann, Nigel Smyth, Louise J Shaw, Elizabeth Warburton, Keith W Muir, Hans Rolf Jäger, David J Werring, on behalf of the CROMIS-2 collaborators**



Results

Variable		Patients with symptomatic intracranial haemorrhage (n=14)	Patients without symptomatic intracranial haemorrhage (n=1433)	p value
Age, years median (IQR)		79 (10)	76 (10)	0·32
Sex, female, n (%)		5 (36)	606 (42)	0·62
Hypertension n (%)		8 (57)	898 (64)	0·62
Hyperlipidaemia n (%)		8 (57)	653 (45)	0·36
Diabetes mellitus n (%)		**6 (43)**	**236 (17)**	**0·0086**
Ischaemic heart disease		1 (7)	238 (17)	0·34
Previous ischaemic stroke n (%)		2 (15)	138 (10)	0·50
Previous intracerebral haemorrhage n (%)		0 (0)	8 (0·6)	1·00
Alcohol use >14 units/week n (%)		1 (8)	212 (15)	0·50
Ethnicity	White n (%)	14 (100)	1356 (97)	
	Asian n (%)	0 (0)	29 (2)	
	Black n (%)	0 (0)	17 (1)	
Platelet count median (IQR)		212 (167 to 225)	220 (185 to 264)	0.25
CHA_2DS_2VASc score median (IQR)		6 (4 to 6)	5 (4 to 6)	0·23
HAS-BLED score median (IQR)		2 (2 to 3)	3 (2 to 3)	0·14
Anticoagulation started n (%)		14 (100)	1385(97)	0.49
DOAC use n (%)		**2 (14)**	**510 (37)**	**0·081**
Concurrent antiplatelets n (%)		1 (7)	56 (4)	0.54
Poor therapeutic time in range n (%)		0 (0)	133/862 (15)	0.145
Total white matter hyperintensity (ARWMC) score median (IQR)		1·5 (0 to 5)	1 (0 to 3)	0·97
CMB presence n (%) **CMB median (IQR)** **CMB range**		**7 (50)** **0.5 (0 to 3)** 0 to 12	**297 (21)** **0 (0 to 0)** 0 to 107	**0·0075** **0·0036** N/A
cSS presence n (%)		**1 (7)**	**4 (0·3)**	<0·0001

Results

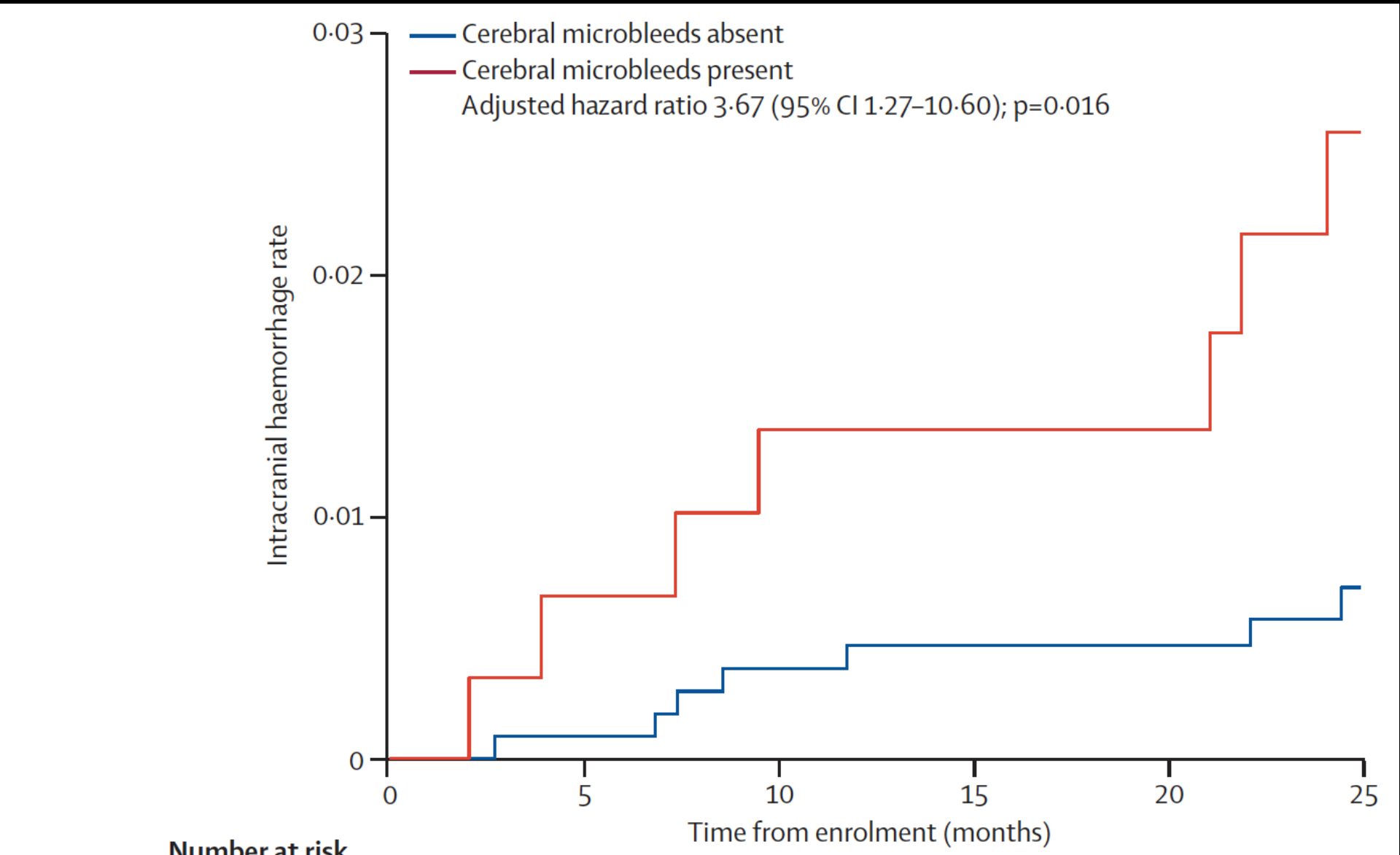
Primary Outcome

The symptomatic intracranial event rates were:

10 per 1000 patient years (95% CI: 4-20) in CMBs

3 per 1000 patient years (95% CI: 1-5) without CMB

The **absolute rate** increase associated with CBMs were **7 per 1000 patient years** (95% CI: 3-15)



Number at risk

Cerebral microbleeds absent	1143	1095	1057	969	935	679
Cerebral microbleeds present	304	292	283	261	261	180

Results

Secondary Outcome

There were 56 recurrent ischaemic stroke during 3312 patient years of follow up

Recurrent ischaemic rates were:

24 per 1000 patient years (95% CI: 14-39) in CMBs

15 **per 1000 patient years** (95% CI: 11-20) without CMB

The **absolute rate** increase associated with CBMs were 9 **per 1000 patient years** (95% CI: 3-15)

Presence of CMBs were not associated with recurrent ischaemic stroke in analysis

Results

Prediction models for intracranial haemorrhage

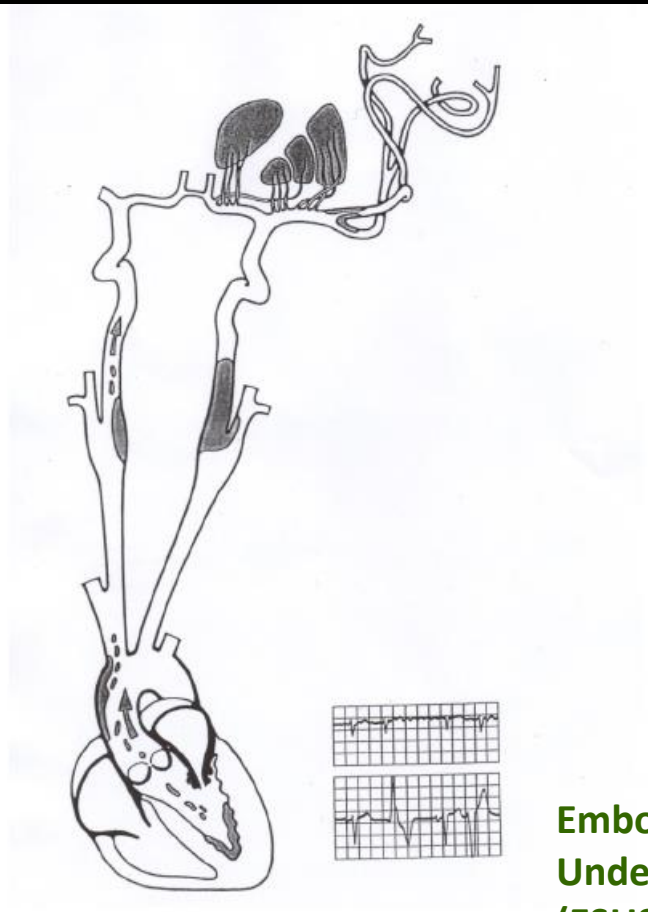
HASBLED only	C-Index 0.41
Model 1: HASBLED + CMBs	C-Index 0.66
Model 2: HASBLED + CMBs + DOAC + DBM	C-Index 0.74

Summary

- CMBs were associated with increased hazard of symptomatic intracranial haemorrhage but not recurrent ischaemic stroke
- However in patients CMBs, the absolute number of symptomatic intracranial haemorrhage was lower than recurrent ischaemic stroke
- Unclear whether there is a microbleed burden threshold where intracranial haemorrhage exceeds ischaemic stroke
- Including CMB presence as neuroimaging biomarker improves the predictive value of HASBLED score based on clinical data alone
- Large collaborative studies are required to validate these findings, as well as these risk scores (CMBs burden) and to identify which patients may be at risk from harm rather than benefit with anticoagulation

- Thrombolysis-WAKE UP
- Intra-arterial interventions – DEFUSE 3
- Haemorrhagic Stroke - TICH 2
- Secondary Prevention – CROMIS 2
- Secondary Prevention – NAVIGATE ESUS

Embolic Stroke of Undetermined Source



Microangiopathic infarcts
20-25 %

Macroangiopathy
20-25 %

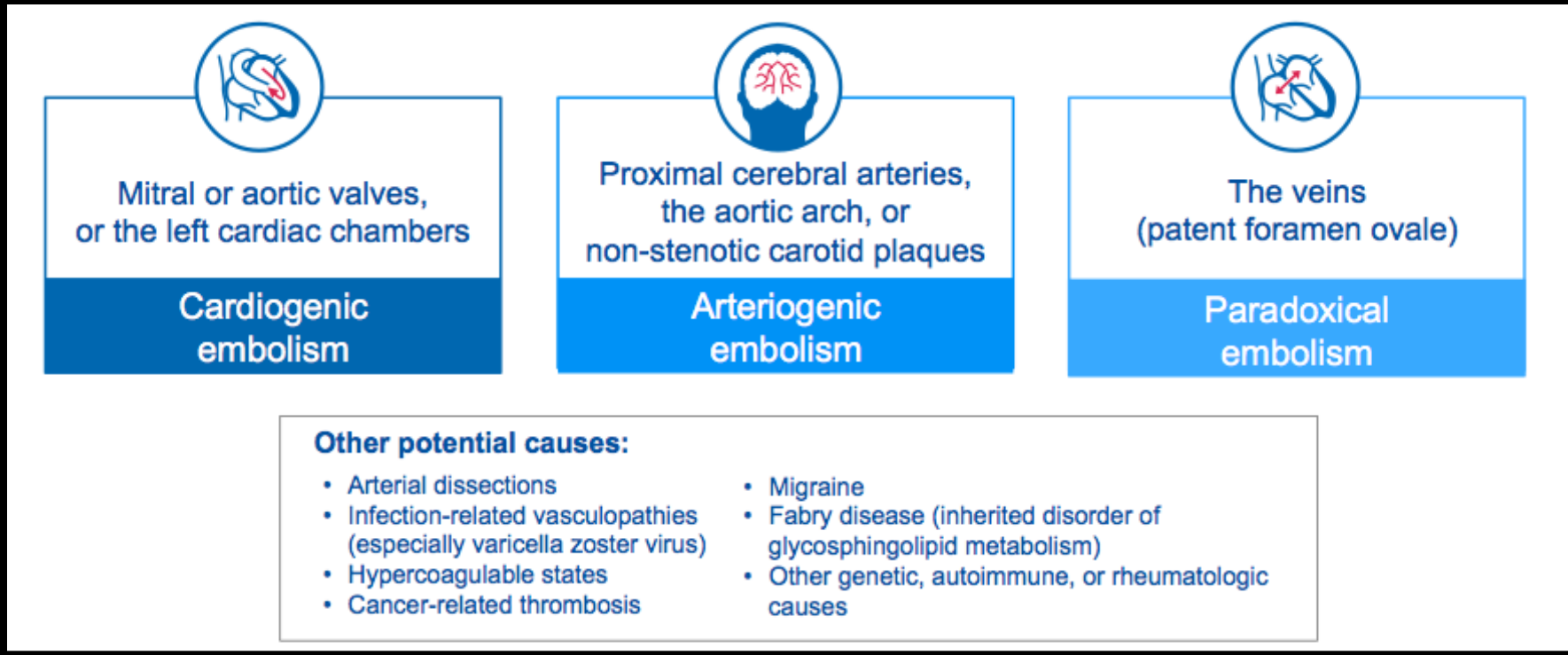
Cardiogenic embolism
25 %

Cryptogenic stroke
20-25 %

Embolic Stroke Of Undetermined Source (ESUS)

→ **non detected paroxysmal AF?**

Potential Causes of ESUS



ORIGINAL ARTICLE

Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source

R.G. Hart, M. Sharma, H. Mundl, S.E. Kasner, S.I. Bangdiwala, S.D. Berkowitz, B. Swaminathan, P. Lavados, Y. Wang, Y. Wang, A. Davalos, N. Shamalov, R. Mikulik, L. Cunha, A. Lindgren, A. Arauz, W. Lang, A. Czlonkowska, J. Eckstein, R.J. Gagliardi, P. Amarenco, S.F. Ameriso, T. Tatlisumak, R. Veltkamp, G.J. Hankey, D. Toni, D. Bereczki, S. Uchiyama, G. Ntaios, B.-W. Yoon, R. Brouns, M. Endres, K.W. Muir, N. Bornstein, S. Ozturk, M.J. O'Donnell, M.M. De Vries Basson, G. Pare, C. Pater, B. Kirsch, P. Sheridan, G. Peters, J.I. Weitz, W.F. Peacock, A. Shoamanesh, O.R. Benavente, C. Joyner, E. Themeles, and S.J. Connolly, for the NAVIGATE ESUS Investigators*

NAVIGATE ESUS Study Design

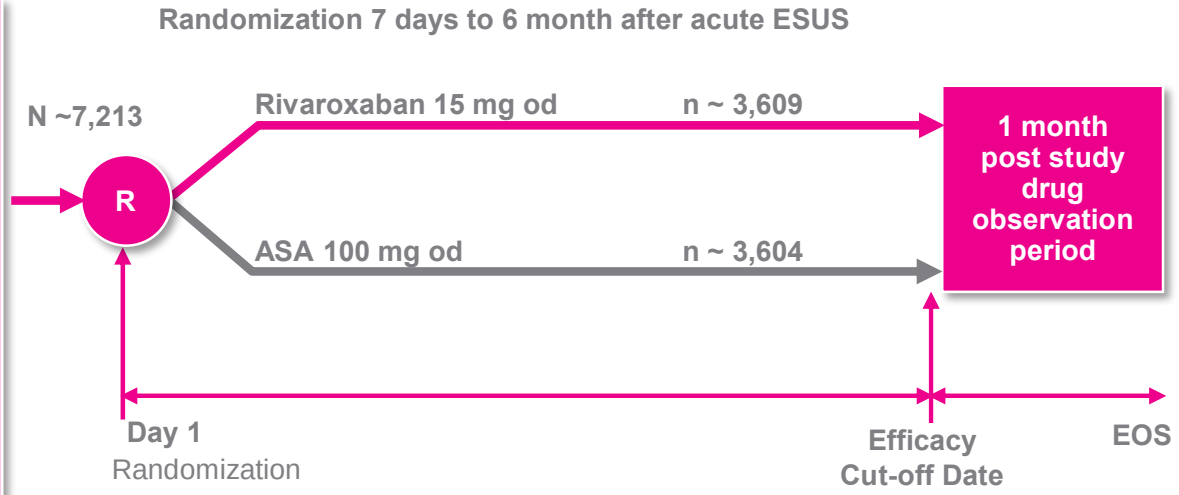
Prospective, randomized, double-blind, active-comparator, event-driven, superiority, phase III study

Patients with recent ischemic stroke and

1. visualized by brain CT or MRI that is [illegible]
2. absence of cervical carotid atherosclerotic artery stenosis > 50% or occlusion
3. no atrial [illegible] 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)

[illegible] 50 years

459 sites in 31 countries



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

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		
❿U.S.A. and Canada	13 %	13 %
❿Latin America	10%	10 %
❿Europe	59 %	58 %
❿East Asia	19 %	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 %
[illegible]	34 %	34 %

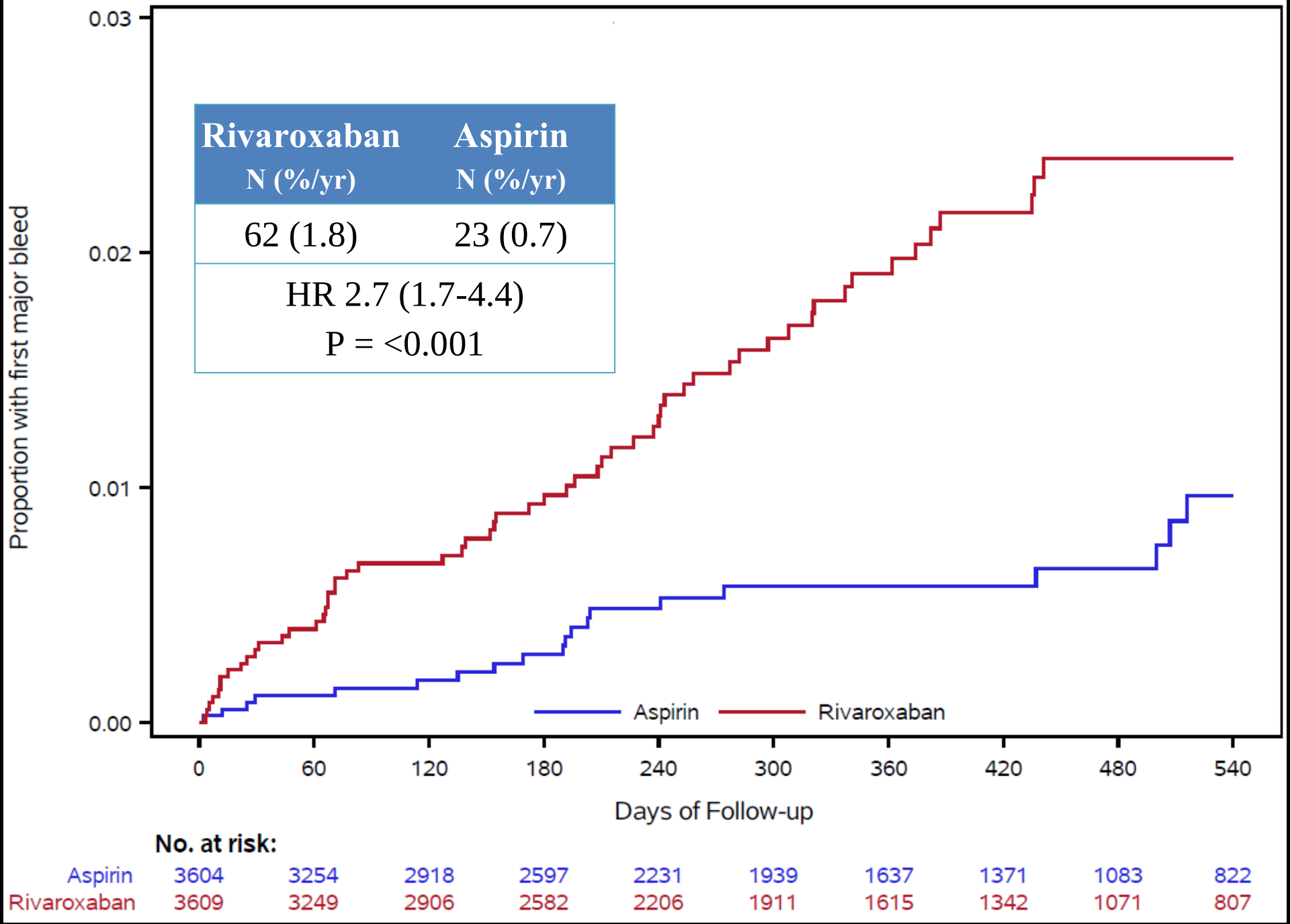
Efficacy Outcomes

	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

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

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



Summary

- No reduction in recurrent stroke by rivaroxaban 15 mg vs aspirin 100mg and major bleeding increased
- Stopped early with 74% of planned primary events but still had power to detect 13% benefit for rivaroxaban
- High rate of recurrent stroke 5% (year) with either treatment

- Why was NAVIGATE ESUS negative?
  - Dosing (15 mg vs 20 mg)
  - Drug (Rivaroxaban had the least favourable safety data)
  - Time to randomisation (> 7 days)
  - Did the ESUS criteria define embolic stroke accurately
  - Heterogeneous nature of embolic sources

- Future trials: Dosing, Covert AF, PFO, Arterogenic embolic., safety endpoints,
- ARCADIA and ATTICUS (Apixaban), RE-SPECT ESUS (Dabigatran)

Conclusions

- Huge strides made in stroke management in recent years and a productive year in 2018
- Key interventions will highlight what needs to be developed as part of the National Plan
- Exciting developments in hyper-acute treatments (thrombectomy) which will alter stroke landscape
- Still lots of unanswered questions and stroke burden still remains high