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

Haemostatic options:
• Pro-coagulants - Factor VIIa
  Ongoing RCT: STOP-IT, SPOT-LIGHT
• Anti-fibrinolytics
  Ongoing RCT: TICH-2, STOP-AUST
• Platelets
  Ongoing RCT: PATCH
• ICH secondary to ICH
  Ongoing RCT: INCH

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

<table>
<thead>
<tr>
<th></th>
<th>Tranexamic acid (n=1161)</th>
<th>Placebo (n=1164)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong>, years</td>
<td>69.1 (13.7) [29–97]</td>
<td>68.7 (13.9) [20–101]</td>
</tr>
<tr>
<td>&gt;70</td>
<td>584 (50%)</td>
<td>580 (50%)</td>
</tr>
<tr>
<td><strong>Sex</strong>, male</td>
<td>642 (55%)</td>
<td>659 (57%)</td>
</tr>
<tr>
<td><strong>Ethnic origin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>986 (85%)</td>
<td>992 (85%)</td>
</tr>
<tr>
<td>Other</td>
<td>174 (15%)</td>
<td>172 (15%)</td>
</tr>
<tr>
<td><strong>Onset to randomisation</strong>, h</td>
<td>3.6 (2.6–5.1) [1.0–20.8]</td>
<td>3.7 (2.6–5.0) [0.8–8.0]</td>
</tr>
<tr>
<td>≤3</td>
<td>421 (36%)</td>
<td>412 (35%)</td>
</tr>
<tr>
<td>≤4.5</td>
<td>779 (67%)</td>
<td>796 (68%)</td>
</tr>
<tr>
<td><strong>History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous antiplatelet therapy*</td>
<td>316 (27%)</td>
<td>295 (25%)</td>
</tr>
<tr>
<td>Statin use prior to admission</td>
<td>319 (28%)</td>
<td>303 (26%)</td>
</tr>
<tr>
<td>Previous stroke or transient ischaemic attack</td>
<td>173 (15%)</td>
<td>156 (14%)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>110 (10%)</td>
<td>92 (8%)</td>
</tr>
<tr>
<td>Prestroke mRS</td>
<td>0 (0–1) [0–4]</td>
<td>0 (0–1) [0–4]</td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td>13 (2.2) [5.0–150]</td>
<td>14 (2.1) [5.0–150]</td>
</tr>
<tr>
<td><strong>NIHSS score</strong></td>
<td>13 (7.5) [0.0–41.0]</td>
<td>13 (7.5) [0.0–42.0]</td>
</tr>
<tr>
<td>Systolic blood pressure*, mm Hg</td>
<td>172 (27.5) [98.0–265]</td>
<td>174 (26.8) [99.0–265]</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>93 (18.4) [46.0–179]</td>
<td>94 (17.8) [35.5–162]</td>
</tr>
<tr>
<td><strong>Haematoma location</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supratentorial lobar</td>
<td>379 (33%)</td>
<td>359 (31%)</td>
</tr>
<tr>
<td>Supratentorial deep</td>
<td>675 (58%)</td>
<td>696 (60%)</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>73 (6%)</td>
<td>76 (7%)</td>
</tr>
<tr>
<td>Combination</td>
<td>34 (3%)</td>
<td>33 (3%)</td>
</tr>
<tr>
<td><strong>Intracerebral haematoma volume (mL)</strong></td>
<td>14.1 (5.9–32.4) [0.0–207]</td>
<td>12.5 (5.1–31.9) [0.0–163]</td>
</tr>
<tr>
<td>Intraventricular haemorrhage*</td>
<td>382 (33%)</td>
<td>363 (31%)</td>
</tr>
<tr>
<td>CT angiography done</td>
<td>121 (11%)</td>
<td>128 (11%)</td>
</tr>
<tr>
<td><strong>Spot positive</strong></td>
<td>24 (20%)</td>
<td>32 (25%)</td>
</tr>
<tr>
<td><strong>Spot negative</strong></td>
<td>97 (80%)</td>
<td>96 (75%)</td>
</tr>
</tbody>
</table>
### Results

<table>
<thead>
<tr>
<th>mRS 0</th>
<th>mRS 1</th>
<th>mRS 2</th>
<th>mRS 3</th>
<th>mRS 4</th>
<th>mRS 5</th>
<th>mRS 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.1%</td>
<td>10.7%</td>
<td>15.7%</td>
<td>16.8%</td>
<td>19.1%</td>
<td>14.0%</td>
<td>21.6%</td>
</tr>
<tr>
<td>Tranexamic acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.3%</td>
<td>10.0%</td>
<td>17.1%</td>
<td>16.2%</td>
<td>18.5%</td>
<td>14.2%</td>
<td>21.7%</td>
</tr>
</tbody>
</table>

**OR: 0.88, 95% CI: (0.76-1.03)**
<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset to randomisation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3 h</td>
<td>824</td>
<td>0.92 (0.72-1.19)</td>
<td>0.75</td>
</tr>
<tr>
<td>&gt;3 h</td>
<td>1483</td>
<td>0.87 (0.72-1.05)</td>
<td>0.28</td>
</tr>
<tr>
<td>Onset to randomisation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤4.5 h</td>
<td>1561</td>
<td>0.84 (0.70-1.01)</td>
<td>0.67</td>
</tr>
<tr>
<td>&gt;4.5 h</td>
<td>746</td>
<td>0.99 (0.76-1.30)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤70 years</td>
<td>1146</td>
<td>0.84 (0.68-1.04)</td>
<td>0.39</td>
</tr>
<tr>
<td>&gt;70 years</td>
<td>1161</td>
<td>0.96 (0.77-1.19)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1016</td>
<td>0.89 (0.71-1.12)</td>
<td>0.87</td>
</tr>
<tr>
<td>Male</td>
<td>1291</td>
<td>0.87 (0.71-1.06)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤170 mm Hg</td>
<td>1144</td>
<td>0.73 (0.59-0.90)</td>
<td>0.0188</td>
</tr>
<tr>
<td>&gt;170 mm Hg</td>
<td>1163</td>
<td>1.05 (0.85-1.29)</td>
<td></td>
</tr>
<tr>
<td>NIHSS score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤15</td>
<td>1436</td>
<td>0.91 (0.76-1.10)</td>
<td>0.37</td>
</tr>
<tr>
<td>&gt;15</td>
<td>871</td>
<td>0.81 (0.63-1.04)</td>
<td></td>
</tr>
<tr>
<td>Intraventricular haemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>739</td>
<td>0.76 (0.58-1.00)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1568</td>
<td>0.95 (0.79-1.14)</td>
<td></td>
</tr>
<tr>
<td>History of antiplatelet therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>610</td>
<td>0.92 (0.68-1.25)</td>
<td>0.67</td>
</tr>
<tr>
<td>No</td>
<td>1696</td>
<td>0.87 (0.73-1.03)</td>
<td></td>
</tr>
<tr>
<td>Spot positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>56</td>
<td>1.16 (0.37-3.57)</td>
<td>0.96</td>
</tr>
<tr>
<td>No</td>
<td>193</td>
<td>1.40 (0.81-2.43)</td>
<td></td>
</tr>
<tr>
<td>Haematoma location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supratentorial lobar</td>
<td>734</td>
<td>0.81 (0.61-1.07)</td>
<td>0.32</td>
</tr>
<tr>
<td>Supratentorial deep</td>
<td>1372</td>
<td>0.94 (0.77-1.14)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1965</td>
<td>0.90 (0.77-1.06)</td>
<td>0.37</td>
</tr>
<tr>
<td>Other</td>
<td>342</td>
<td>0.69 (0.47-1.02)</td>
<td></td>
</tr>
<tr>
<td>Baseline haematoma volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 mL</td>
<td>1639</td>
<td>0.92 (0.77-1.10)</td>
<td>0.84</td>
</tr>
<tr>
<td>30–60 mL</td>
<td>361</td>
<td>0.66 (0.44-0.98)</td>
<td></td>
</tr>
<tr>
<td>&gt;60 mL</td>
<td>258</td>
<td>1.20 (0.68-2.14)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>2325</td>
<td>0.88 (0.76-1.03)</td>
<td>0.11</td>
</tr>
</tbody>
</table>
## Results

<table>
<thead>
<tr>
<th></th>
<th>TXA</th>
<th>Placebo</th>
<th>Effect Size</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haematoma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in volume from baseline to 24 h*, mL</td>
<td>3.72 (15.9)</td>
<td>4.90 (16.0)</td>
<td>MD -1.37 (-2.71 to -0.04)</td>
<td>0.0432</td>
</tr>
<tr>
<td>Participants with haematoma expansion†</td>
<td>265 (25%)</td>
<td>304 (29%)</td>
<td>Binary OR 0.80 (0.66 to 0.98)</td>
<td>0.0300</td>
</tr>
<tr>
<td><strong>Day 7</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death by day 7</td>
<td>101 (9%)</td>
<td>123 (11%)</td>
<td>Binary OR 0.73 (0.53 to 0.99)</td>
<td>0.0406</td>
</tr>
<tr>
<td>NIHSS day 7</td>
<td>10.13 (8.3)</td>
<td>10.29 (8.3)</td>
<td>MD -0.43 (-0.94 to 0.09)</td>
<td>0.10</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Table 8: CHA2DS2-VASc score and stroke rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Risk factors for stroke and thromboembolism in non-valvular AF</td>
</tr>
<tr>
<td><strong>Major</strong> risk factors</td>
</tr>
<tr>
<td>Previous stroke/TIA, or systemic embolism</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>(b) Risk factor-based approach expressed as a point-based scoring system, with the acronym CHA2DS2-VASc (Note: maximum score is 9 since age may contribute 0, 1, or 2 points)</td>
</tr>
<tr>
<td>Risk factor</td>
</tr>
<tr>
<td>Congestive heart failure/LV dysfunction</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Age ≥ 75</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Stroke/TIA/Thromboembolism</td>
</tr>
<tr>
<td>Vascular disease*</td>
</tr>
<tr>
<td>Age 65–74</td>
</tr>
<tr>
<td>Sex category (i.e., female sex)</td>
</tr>
</tbody>
</table>

<p>| Table 10: Clinical characteristics comprising the HAS-BLED bleeding risk score |
|-------------------------------|-----------------|-------|</p>
<table>
<thead>
<tr>
<th>Letter</th>
<th>Clinical characteristic</th>
<th>Points awarded</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal renal and liver function (1 point each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>S</td>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>L</td>
<td>Liver INRs</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>Elderly (e.g., age &gt; 65 years)</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Drugs or alcohol (1 point each)</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

*Maximum 9 points
Cerebral Microbleeds

- Ischaemic stroke or TIA with atrial fibrillation
- MRI scan with blood-sensitive imaging shows cerebral microbleeds

A common clinical dilemma

Cerebral small vessel disease
- 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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with symptomatic intracranial haemorrhage (n=14)</th>
<th>Patients without symptomatic intracranial haemorrhage (n=1433)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years median (IQR)</td>
<td>79 (10)</td>
<td>76 (10)</td>
<td>0·32</td>
</tr>
<tr>
<td>Sex, female, n (%)</td>
<td>5 (36)</td>
<td>606 (42)</td>
<td>0·62</td>
</tr>
<tr>
<td>Hypertension n (%)</td>
<td>8 (57)</td>
<td>898 (64)</td>
<td>0·62</td>
</tr>
<tr>
<td>Hyperlipidaemia n (%)</td>
<td>8 (57)</td>
<td>653 (45)</td>
<td>0·36</td>
</tr>
<tr>
<td>Diabetes mellitus n (%)</td>
<td>6 (43)</td>
<td>236 (17)</td>
<td>0·0086</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>1 (7)</td>
<td>238 (17)</td>
<td>0·34</td>
</tr>
<tr>
<td>Previous ischaemic stroke n (%)</td>
<td>2 (15)</td>
<td>138 (10)</td>
<td>0·50</td>
</tr>
<tr>
<td>Previous intracerebral haemorrhage n (%)</td>
<td>0 (0)</td>
<td>8 (0·6)</td>
<td>1·00</td>
</tr>
<tr>
<td>Alcohol use &gt;14 units/week n (%)</td>
<td>1 (8)</td>
<td>212 (15)</td>
<td>0·50</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White n (%)</td>
<td>14 (100)</td>
<td>1356 (97)</td>
<td></td>
</tr>
<tr>
<td>Asian n (%)</td>
<td>0 (0)</td>
<td>29 (2)</td>
<td></td>
</tr>
<tr>
<td>Black n (%)</td>
<td>0 (0)</td>
<td>17 (1)</td>
<td></td>
</tr>
<tr>
<td>Platelet count median (IQR)</td>
<td>212 (167 to 225)</td>
<td>220 (185 to 264)</td>
<td>0·25</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc score median (IQR)</td>
<td>6 (4 to 6)</td>
<td>5 (4 to 6)</td>
<td>0·23</td>
</tr>
<tr>
<td>HAS-BLED score median (IQR)</td>
<td>2 (2 to 3)</td>
<td>3 (2 to 3)</td>
<td>0·14</td>
</tr>
<tr>
<td>Anticoagulation started n (%)</td>
<td>14 (100)</td>
<td>1385 (97)</td>
<td>0·49</td>
</tr>
<tr>
<td>DOAC use n (%)</td>
<td>2 (14)</td>
<td>510 (37)</td>
<td>0·081</td>
</tr>
<tr>
<td>Concurrent antiplatelets n (%)</td>
<td>1 (7)</td>
<td>56 (4)</td>
<td>0·54</td>
</tr>
<tr>
<td>Poor therapeutic time in range n (%)</td>
<td>0 (0)</td>
<td>133/862 (15)</td>
<td>0·145</td>
</tr>
<tr>
<td>Total white matter hyperintensity (ARWMC) score median (IQR)</td>
<td>1·5 (0 to 5)</td>
<td>1 (0 to 3)</td>
<td>0·97</td>
</tr>
<tr>
<td>CMB presence n (%)</td>
<td>7 (50)</td>
<td>297 (21)</td>
<td>0·0075</td>
</tr>
<tr>
<td>CMB median (IQR)</td>
<td>0·5 (0 to 3)</td>
<td>0 (0 to 0)</td>
<td>0·0036</td>
</tr>
<tr>
<td>CMB range</td>
<td>0 to 12</td>
<td>0 to 107</td>
<td>N/A</td>
</tr>
<tr>
<td>cSS presence n (%)</td>
<td>1 (7)</td>
<td>4 (0·3)</td>
<td>&lt;0·0001</td>
</tr>
</tbody>
</table>
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)
Intracranial haemorrhage rate

Cerebral microbleeds absent
Cerebral microbleeds present

Adjusted hazard ratio 3.67 (95% CI 1.27-10.60); p=0.016

Number at risk
Cerebral microbleeds absent 1143
Cerebral microbleeds present 304

Time from enrolment (months)
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 Underdetermined Source (ESUS)

non detected paroxysmal AF?
Potential Causes of ESUS

**Cardiogenic embolism**
- Mitral or aortic valves, or the left cardiac chambers

**Arteriogenic embolism**
- Proximal cerebral arteries, the aortic arch, or non-stenotic carotid plaques

**Paradoxical embolism**
- The veins (patent foramen ovale)

**Other potential causes:**
- Arterial dissections
- Infection-related vasculopathies (especially varicella zoster virus)
- Hypercoagulable states
- Cancer-related thrombosis
- Migraine
- Fabry disease (inherited disorder of glycosphingolipid metabolism)
- Other genetic, autoimmune, or rheumatologic causes
Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source

Patients with recent ischemic stroke and
1. visualized by brain CT or MRI that is
2. absence of cervical carotid
atherosclerotic artery stenosis > 50% or
occlusion
3. no atrial
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)

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

NAVIGATE ESUS Study Design
Prospective, randomized, double-blind, active-comparator, event-driven, superiority, phase III study

Randomization 7 days to 6 month after acute ESUS

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

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

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban N=3609 n (%/year)</th>
<th>ASA N=3604 n (%/year)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td>172 (5.1)</td>
<td>160 (4.8)</td>
<td>1.1 (0.87-1.3)</td>
<td>0.52</td>
</tr>
<tr>
<td>Individual components included in the primary outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All recurrent stroke (ischemic, hemorrhagic, undefined)</td>
<td>171 (5.1)</td>
<td>158 (4.7)</td>
<td>1.1 (0.87-1.3)</td>
<td>0.48</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>158 (4.7)</td>
<td>156 (4.7)</td>
<td>1.0 (0.81-1.3)</td>
<td>0.92</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>13 (0.4)</td>
<td>2 (0.1)</td>
<td>6.5 (1.5-28)</td>
<td>0.01</td>
</tr>
<tr>
<td>Safety Outcomes</td>
<td>Rivaroxaban N=3609 n (%/year)</td>
<td>ASA N=3604 n (%/year)</td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>--------------------------------</td>
<td>-----------------------</td>
<td>----------------------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>Primary safety outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ISTH major bleeding)</td>
<td>62 (1.8)</td>
<td>23 (0.7)</td>
<td>2.7 (1.7-4.4)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Secondary safety outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life-threatening/fatal bleeding</td>
<td>35 (1.0)</td>
<td>15 (0.4)</td>
<td>2.3 (1.3-4.3)</td>
<td>0.006</td>
</tr>
<tr>
<td>Clinically-relevant non-major bleeding</td>
<td>118 (3.5)</td>
<td>79 (2.3)</td>
<td>1.5 (1.1-2.0)</td>
<td>0.005</td>
</tr>
<tr>
<td>Symptomatic intracranial hemorrhage</td>
<td>20 (0.6)</td>
<td>5 (0.1)</td>
<td>4.0 (1.5-11)</td>
<td>0.005</td>
</tr>
<tr>
<td>- intracerebral</td>
<td>12 (0.3)</td>
<td>3 (0.1)</td>
<td>4.0 (1.1-14)</td>
<td>0.03</td>
</tr>
<tr>
<td>- subarachnoid</td>
<td>5 (0.1)</td>
<td>1 (0.0)</td>
<td>5.0 (0.5-43)</td>
<td>0.10</td>
</tr>
<tr>
<td>- subdural/epidural</td>
<td>3 (0.1)</td>
<td>2 (0.1)</td>
<td>1.5 (0.3-9.0)</td>
<td>0.65</td>
</tr>
</tbody>
</table>
**Rivaroxaban**

N (%/yr)

62 (1.8)

**Aspirin**

N (%/yr)

23 (0.7)

HR 2.7 (1.7-4.4)

P = <0.001

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