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, paradoxical).
- Extensive diagnostic efforts to define the specific cause are expensive & not widely available, and often more than one potential source is identified.
- Hypothesis: 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

Randomization 7 days to 6 month after acute ESUS

N ~7,213
Rivaroxaban 15 mg od n ~ 3,609

ASA 100 mg od n ~ 3,604

1 month post study drug observation period

Day 1 Randomization
Efficacy Cut-off Date
EOS

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

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

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 Członkowska
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: Serefür Öztürk
UK: Keith Muir
UK: Roland Veltkamp
USA: Scott Kasner

7213 patients from 459 sites in 31 countries 2014-2017
## 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>
7,213 randomized

3609 assigned to rivaroxaban

3,552 vital status known
24 (0.7%) lost to follow up
33 (0.9%) withdrew consent

3604 assigned to aspirin

3,554 vital status known
17 (0.5%) lost to follow up
33 (0.9%) withdrew consent

Mean follow-up: 11 months
Atrial fibrillation identified in 3%

3609 analyzed

3604 analyzed
Figure 1a. Kaplan-Meier curves for time to first primary efficacy outcome

<table>
<thead>
<tr>
<th>Rivaroxaban</th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%/yr)</td>
<td>N (%/yr)</td>
</tr>
<tr>
<td>172 (5.1)</td>
<td>160 (4.8)</td>
</tr>
</tbody>
</table>

HR 1.1 (0.87 - 1.3)  
P = 0.52
# Efficacy Outcomes

<table>
<thead>
<tr>
<th>Primary outcome (all recurrent stroke or systemic embolism)</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>Primary outcome</td>
<td>172 (5.1)</td>
<td>160 (4.8)</td>
<td>1.1 (0.87-1.3)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

*Individual components included in the primary outcome*

<table>
<thead>
<tr>
<th>All recurrent stroke (ischemic, hemorrhagic, undefined)</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>All recurrent stroke</td>
<td>171 (5.1)</td>
<td>158 (4.7)</td>
<td>1.1 (0.87-1.3)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

| 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

<table>
<thead>
<tr>
<th>Event</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>All recurrent stroke, MI, CV death, systemic embolism</td>
<td>207 (6.2)</td>
<td>195 (5.8)</td>
<td>1.1 (0.87-1.3)</td>
<td>0.57</td>
</tr>
<tr>
<td>All disabling stroke</td>
<td>41 (1.2)</td>
<td>29 (0.8)</td>
<td>1.4 (0.88-2.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>Myocardial infarction (MI)</td>
<td>17 (0.5)</td>
<td>23 (0.7)</td>
<td>0.74 (0.39-1.4)</td>
<td>0.34</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>65 (1.9)</td>
<td>52 (1.5)</td>
<td>1.26 (0.87-1.8)</td>
<td>0.22</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>34 (1.0)</td>
<td>23 (0.7)</td>
<td>1.48 (0.87-2.5)</td>
<td>0.14</td>
</tr>
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</table>
Figure 1b. Kaplan-Meier curves for time to first major bleed

<table>
<thead>
<tr>
<th>Rivaroxaban</th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%/yr)</td>
<td>N (%/yr)</td>
</tr>
<tr>
<td>62 (1.8)</td>
<td>23 (0.7)</td>
</tr>
</tbody>
</table>

HR 2.7 (1.7-4.4)
P = <0.001

No. at risk:

<table>
<thead>
<tr>
<th>Aspirin</th>
<th>Rivaroxaban</th>
</tr>
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<tbody>
<tr>
<td>3604</td>
<td>3609</td>
</tr>
<tr>
<td>3254</td>
<td>3249</td>
</tr>
<tr>
<td>2918</td>
<td>2906</td>
</tr>
<tr>
<td>2597</td>
<td>2582</td>
</tr>
<tr>
<td>2231</td>
<td>2206</td>
</tr>
<tr>
<td>1939</td>
<td>1911</td>
</tr>
<tr>
<td>1637</td>
<td>1615</td>
</tr>
<tr>
<td>1371</td>
<td>1342</td>
</tr>
<tr>
<td>1083</td>
<td>1071</td>
</tr>
<tr>
<td>822</td>
<td>807</td>
</tr>
</tbody>
</table>
## Safety 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 safety outcome</strong>&lt;br&gt;(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>&lt;br&gt;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>
<tr>
<td>Subgroup</td>
<td>Rivaroxaban</td>
<td>Aspirin</td>
<td>Hazard Ratio (95% CI)</td>
<td></td>
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<tr>
<td>--------------------------------</td>
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<tr>
<td><strong>Overall</strong></td>
<td>172/3609 (5.1)</td>
<td>160/3604 (4.8)</td>
<td>1.07 (0.87–1.33)</td>
<td></td>
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<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;60 yr</td>
<td>43/861 (5.4)</td>
<td>25/815 (3.1)</td>
<td>1.73 (1.06–2.83)</td>
<td></td>
</tr>
<tr>
<td>60–75 yr</td>
<td>90/2019 (4.8)</td>
<td>91/1993 (5.1)</td>
<td>0.94 (0.71–1.26)</td>
<td></td>
</tr>
<tr>
<td>&gt;75 yr</td>
<td>39/729 (5.7)</td>
<td>42/756 (5.8)</td>
<td>0.97 (0.63–1.51)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>122/2232 (5.8)</td>
<td>102/2204 (4.9)</td>
<td>1.17 (0.90–1.53)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>50/1177 (4.0)</td>
<td>58/1400 (4.5)</td>
<td>0.89 (0.61–1.29)</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>White only</td>
<td>106/2612 (4.4)</td>
<td>114/2604 (4.7)</td>
<td>0.93 (0.71–1.21)</td>
<td></td>
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<tr>
<td>Black only</td>
<td>2/31 (3.9)</td>
<td>4/60 (7.9)</td>
<td>0.51 (0.09–2.83)</td>
<td></td>
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<tr>
<td>Asian only</td>
<td>57/716 (3.3)</td>
<td>34/698 (5.0)</td>
<td>1.63 (1.08–2.52)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7/230 (3.5)</td>
<td>8/242 (3.9)</td>
<td>0.91 (0.33–2.51)</td>
<td></td>
</tr>
<tr>
<td><strong>Geographic region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States and Canada</td>
<td>27/461 (6.4)</td>
<td>15/457 (3.5)</td>
<td>1.82 (0.97–3.42)</td>
<td></td>
</tr>
<tr>
<td>Latin America</td>
<td>12/372 (4.2)</td>
<td>10/374 (3.5)</td>
<td>1.23 (0.53–2.85)</td>
<td></td>
</tr>
<tr>
<td>Western Europe</td>
<td>56/1341 (3.7)</td>
<td>80/1340 (5.4)</td>
<td>0.69 (0.49–0.97)</td>
<td></td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>24/360 (4.9)</td>
<td>22/558 (4.4)</td>
<td>1.10 (0.61–1.96)</td>
<td></td>
</tr>
<tr>
<td>East Asia</td>
<td>53/675 (8.1)</td>
<td>33/675 (5.0)</td>
<td>1.61 (1.04–2.49)</td>
<td></td>
</tr>
<tr>
<td><strong>Body mass index</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;23</td>
<td>65/1267 (5.5)</td>
<td>68/1233 (6.1)</td>
<td>0.92 (0.65–1.29)</td>
<td></td>
</tr>
<tr>
<td>≥25 to &lt;30</td>
<td>76/1491 (5.5)</td>
<td>59/1484 (4.2)</td>
<td>1.31 (0.93–1.84)</td>
<td></td>
</tr>
<tr>
<td>≥30</td>
<td>31/819 (4.0)</td>
<td>31/868 (4.0)</td>
<td>0.97 (0.60–1.59)</td>
<td></td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70 kg</td>
<td>68/1278 (5.8)</td>
<td>59/1357 (4.9)</td>
<td>1.16 (0.82–1.64)</td>
<td></td>
</tr>
<tr>
<td>70–90 kg</td>
<td>79/1746 (4.9)</td>
<td>83/1733 (5.4)</td>
<td>0.92 (0.68–1.25)</td>
<td></td>
</tr>
<tr>
<td>&gt;90 kg</td>
<td>25/576 (4.6)</td>
<td>16/599 (2.9)</td>
<td>1.58 (0.84–2.96)</td>
<td></td>
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<tr>
<td><strong>Estimated GFR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 ml/min</td>
<td>10/218 (4.8)</td>
<td>11/201 (5.9)</td>
<td>0.86 (0.36–2.02)</td>
<td></td>
</tr>
<tr>
<td>50–80 ml/min</td>
<td>82/1773 (4.9)</td>
<td>97/1758 (5.8)</td>
<td>0.83 (0.62–1.21)</td>
<td></td>
</tr>
<tr>
<td>&gt;80 ml/min</td>
<td>80/1617 (5.5)</td>
<td>52/1644 (3.5)</td>
<td>1.57 (1.11–2.23)</td>
<td></td>
</tr>
<tr>
<td><strong>Stroke or TIA before qualifying stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>52/620 (8.2)</td>
<td>51/643 (8.8)</td>
<td>1.05 (0.72–1.55)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>120/2989 (4.3)</td>
<td>109/2961 (3.9)</td>
<td>1.09 (0.84–1.42)</td>
<td></td>
</tr>
<tr>
<td><strong>Time from qualifying stroke to randomization</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30 days</td>
<td>89/1566 (6.4)</td>
<td>81/1666 (5.4)</td>
<td>1.17 (0.87–1.59)</td>
<td></td>
</tr>
<tr>
<td>&gt;30 days to 3 mo</td>
<td>55/1158 (2.2)</td>
<td>45/1073 (4.9)</td>
<td>1.06 (0.72–1.57)</td>
<td></td>
</tr>
<tr>
<td>&gt;3 mo</td>
<td>28/885 (3.2)</td>
<td>31/865 (3.6)</td>
<td>0.89 (0.53–1.58)</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac rhythm monitoring</strong></td>
<td></td>
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</tr>
<tr>
<td>&lt;48 hr</td>
<td>122/2390 (5.6)</td>
<td>101/2382 (4.7)</td>
<td>1.19 (0.91–1.54)</td>
<td></td>
</tr>
<tr>
<td>≥48 hr</td>
<td>50/1218 (4.3)</td>
<td>57/1217 (5.0)</td>
<td>0.87 (0.59–1.37)</td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>128/2782 (5.0)</td>
<td>121/2803 (4.7)</td>
<td>1.07 (0.83–1.37)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>44/937 (5.7)</td>
<td>39/801 (5.2)</td>
<td>1.09 (0.71–1.68)</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>54/839 (6.8)</td>
<td>46/917 (5.6)</td>
<td>1.21 (0.81–1.87)</td>
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</tr>
<tr>
<td>No</td>
<td>118/2720 (4.6)</td>
<td>114/2687 (4.5)</td>
<td>1.02 (0.79–1.33)</td>
<td></td>
</tr>
</tbody>
</table>
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 100 mg/day, 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).