Age- and Sex-Specific Analysis of Patients with Embolic Stroke of Undetermined Source (ESUS)

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Embolic strokes of undetermined source: the case for a new clinical construct

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Cryptogenic (of unknown cause) ischaemic strokes are now thought to comprise about 25% of all ischaemic strokes. Advances in imaging techniques and improved understanding of stroke pathophysiology have prompted a reassessment of cryptogenic stroke. There is persuasive evidence that most cryptogenic strokes are thromboembolic. The thrombus is thought to originate from any of several well established potential embolic sources, including minor-risk or covert cardiac sources, veins via paradoxical embolism, and non-occlusive atherosclerotic plaques in the aortic arch, cervical, or cerebral arteries. Accordingly, we propose that embolic strokes of undetermined source are a therapeutically relevant entity, which are defined as a non-lacunar brain infarct without proximal arterial stenosis or cardioembolic sources, with a clear indication for anticoagulation. Because emboli consist mainly of thrombus, anticoagulants are likely to reduce recurrent brain ischaemia more effectively than are antiplatelet drugs. Randomised trials testing direct-acting oral anticoagulants for secondary prevention of embolic strokes of undetermined source are warranted.

• 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 source of cardioembolism.

• No other specific cause
ESUS are mild strokes

<table>
<thead>
<tr>
<th>Clinical and laboratory values</th>
<th>ESUS (n=275)</th>
<th>Large-artery atherosclerotic (n=497)</th>
<th>Cardioembolic (n=869)</th>
<th>Lacunar (n=622)</th>
<th>Undetermined other than ESUS (n=366)</th>
<th>Other determined (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>150 (130–160)</td>
<td>150 (140–170)</td>
<td>150 (130–170)</td>
<td>160 (140–180)</td>
<td>150 (135–170)</td>
<td>140 (120–150)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>85 (80–90)</td>
<td>90 (80–90)</td>
<td>85 (80–90)</td>
<td>90 (80–100)</td>
<td>84 (80–90)</td>
<td>80 (70–90)</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>109 (93–141)</td>
<td>111 (95–154)</td>
<td>118 (98–153)</td>
<td>105 (92–139)</td>
<td>116 (98–163)</td>
<td>100 (90–125)</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>5 (2–14)</td>
<td>5 (2–15)</td>
<td>13 (4–22)</td>
<td>2 (1–4)</td>
<td>8 (3–18)</td>
<td>4 (1–12)</td>
</tr>
</tbody>
</table>

ESUS: high recurrence risk

Is there any difference in characteristics and outcomes of ESUS patients among different age- and sex- groups?
ischemic stroke / TIA recurrence

- 1095 ESUS patients
- Mean age: 68 years
- 41% women
- Mean follow-up: 33 months
- Total follow-up: 3285 patient-years
<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Women</th>
<th>Men</th>
</tr>
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<tbody>
<tr>
<td><strong>All</strong> (n=451)</td>
<td></td>
<td></td>
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<tr>
<td><strong>&lt;60 years</strong> (n=117)</td>
<td></td>
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<tr>
<td><strong>60-80</strong> (n=235)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>&gt;80</strong> (n=99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All</strong> (n=644)</td>
<td></td>
<td></td>
</tr>
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<td></td>
</tr>
<tr>
<td><strong>60-80</strong> (n=350)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>&gt;80</strong> (n=57)</td>
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</tbody>
</table>

**Demographics**
- **Age (years)**:
  - Women: 72 (38-80), 46 (37-52), 72 (67-76), 84 (82-86), 65 (63-75)
  - Men: 47 (37.5-55), 70 (65-75), 84 (82-85)
- **Pre-stroke mNSS≤2**:
  - Women: 421 (94.4%), 116 (100%), 221 (95.3%), 84 (85.7%), 615 (96.1%)
  - Men: 229 (97.4%), 337 (96.8%), 49 (86.0%)
- **NIHSS score at admission**:
  - Women: 6 (1-12), 6 (2-12), 6 (2-13), 6 (3-12), 4 (2-9)
  - Men: 5 (2-9), 4 (2-8), 6 (3-14)
- **Follow-up (months)**:
  - Women: 25 (14-55), 24 (13-60), 31 (14-56), 24 (12-43), 33.5 (14-60)
  - Men: 35 (15-60), 33 (14-58), 24 (12.5-48.5)

**Acute treatment**
- **Antiplatelets only**:
  - Women: 368 (81.6%), 102 (87.2%), 185 (84.1%), 87 (87.9%), 547 (84.9%)
  - Men: 198 (84.6%), 299 (85.4%), 50 (87.7%)
- **Intravenous thrombolysis**:
  - Women: 75 (16.6%), 12 (10.3%), 51 (21.7%), 12 (12.1%), 90 (14.0%)
  - Men: 35 (14.8%), 48 (13.7%), 7 (12.3%)
- **Acute endovascular (pure)**
  - Women: 3 (0.7%), 1 (0.9%), 2 (0.9%), 0 (0.0%), 3 (0.5%)
  - Men: 2 (0.8%), 1 (0.3%), 0 (0.0%)
- **Bridging**
  - Women: 4 (0.9%), 2 (1.7%), 2 (0.9%), 0 (0.0%), 4 (0.6%)
  - Men: 2 (0.8%), 2 (0.6%), 0 (0.0%)

**Treatment on discharge**
- **No antithrombotic**:
  - Women: 4 (0.9%), 0 (0.0%), 3 (1.3%), 1 (1.0%), 7 (1.1%)
  - Men: 1 (0.4%), 4 (1.2%), 2 (3.6%)
- **Antiplatelet(s)**
  - Women: 387 (88.2%), 94 (84.7%), 202 (87.4%), 91 (93.8%), 550 (86.9%)
  - Men: 198 (84.6%), 299 (87.2%), 53 (94.6%)
- **Oral anticoagulant**
  - Women: 45 (10.3%), 16 (14.4%), 24 (10.4%), 5 (5.2%), 58 (9.2%)
  - Men: 30 (12.8%), 28 (8.2%), 0 (0.0%)
- **Antiplatelet(s) and oral anticoagulant**
  - Women: 3 (0.7%), 1 (0.9%), 2 (0.9%), 0 (0.0%), 18 (2.8%)
  - Men: 5 (2.1%), 12 (3.5%), 1 (1.8%)

**Outcome**
- **Ischemic stroke / TIA recurrence**
  - Women: 70 (15.5%), 8 (6.8%), 39 (16.6%), 23 (23.2%), 89 (13.8%)
  - Men: 21 (8.9%), 59 (16.9%), 9 (15.8%)
- **All-cause death**
  - Women: 69 (15.3%), 5 (4.3%), 33 (14.0%), 31 (31.3%), 79 (12.3%)
  - Men: 7 (3.0%), 56 (16.0%), 16 (28.1%)
Women: recurrence & death rates

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Number of Patients (n)</th>
<th>Ischaemic Stroke/TIA Recurrence (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60 years</td>
<td>117</td>
<td>3.4</td>
<td>2.2</td>
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<td>60-80 years</td>
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<td>6.4</td>
<td>5.4</td>
</tr>
<tr>
<td>&gt;80 years</td>
<td>99</td>
<td>11.6</td>
<td>15.7</td>
</tr>
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Annualized event rate (%)
Men: recurrence & death rates

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Number of Patients (n)</th>
<th>Ischaemic Stroke/TIA recurrence (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60 years</td>
<td>237</td>
<td>3.0</td>
<td>1.0</td>
</tr>
<tr>
<td>60-80 years</td>
<td>350</td>
<td>6.1</td>
<td>5.8</td>
</tr>
<tr>
<td>&gt;80 years</td>
<td>57</td>
<td>7.9</td>
<td>14</td>
</tr>
</tbody>
</table>
Risk of stroke recurrence

- Women (vs. men): 1.15 (0.84-1.58)
- 60-80 years (vs. <60 years): 1.90 (1.21-2.98)
- >80 years (vs. <60 years): 2.71 (1.57-4.70)
Risk of stroke recurrence

- Women (vs. men): 1.15 (0.84-1.58)
- 60-80 years (vs. <60 years): 1.90 (1.21-2.98)
- >80 years (vs. <60 years): 2.71 (1.57-4.70)
Risk of death

- Women (vs. men): 1.34 (0.97-1.86)
- 60-80 years (vs. <60 years): 4.43 (2.33-8.43)
- >80 years (vs. <60 years): 8.01 (3.98-16.1)
Cumulative probability of recurrence/death
Cumulative probability of recurrence/death
Large population size (>1000 patients).

Long follow-up (>3,000 patient-years).

Standardized definition of ESUS patients.

Multiple analyses performed.

Retrospective analysis.
Take-home messages

✓ The higher the age, the more recurrences and deaths.

✓ No important difference among sex groups.