Secondary prevention after ESUS

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Declaration of Interest

Nothing to declare
What is ESUS?

~85% of all strokes are ischaemic\(^1\)

~25% of these have no known cause\(^2\)

Previously termed ‘cryptogenic’:
~300,000 incident cases/year in North America and Europe

A subgroup of these are due to thromboembolism

New category proposed:

‘Embolic stroke of undetermined source’ (ESUS)\(^2\)

1. Andersen K et al. Stroke 2009;40:2068–72
Advances in imaging and improved understanding of stroke pathophysiology

Reassessment of ‘cryptogenic’ stroke

Non-lacunar brain infarct without large artery stenosis or cardioembolic sources

International Working Group of experts proposes new definition

More clinically useful, positively defined entity than cryptogenic stroke

Step-wise approach to diagnosis
76 years-old male, with vascular risk factors, who presents with fluctuating right-hand paresia and mild aphasia...

Embolic? YES  Cryptogenic? YES  ESUS? NO
Definitions of cryptogenic stroke vs ESUS

Cryptogenic stroke
- Diagnostic assessment incomplete
- Cause cannot be established due to ≥1 possible cause
- No cause found from assessment

ESUS if proven to be:
- NOT lacunar
  - NOT occlusive large atherosclerosis
  - NOT major cardioembolic source
NOT lacunar*

* Subcortical infarct <1.5mm on CT or <2mm on MRI
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- NOT occlusive large atherosclerosis

**NOT major cardioembolic source**
NOT major cardioembolic source
Infrequent stroke etiologies
Brain CT/MRI showing only embolic infarct (more than 1.5 cm)
MRA/ CTA of extra and intracranial vessels supplying the area of infarct with less than 50% atherosclerosis
Negative Trans Thoracic Echocardiography (No intracardiac thrombus, prosthetic valve, , mitral stenosis, atrial myxoma or other cardiac tumors, recent (<4 weeks) myocardial infarction, LVEF < 30%, no valvular vegetations, no infective Endocarditis)
No other specific cause of stroke like arteritis, dissection, migraine/vasospasm, drug abuse identified
Cardiac monitoring for ≥24 h with automated rhythm detection and no history of Permanent or paroxysmal atrial fibrillation,

- Consider Trans esophageal echocardiography
- Consider coagulopathy work-up
- Consider Metabolic or Genetic testing
- Consider Spinal Tap e.g. infection, vasculitis
- Consider further Imaging

- Long term Cardiac monitoring (minimum 30 days)
- D-Dimer, DVT screen, MRV of pelvic veins
- Lab Evaluation of hypercoagulable states (younger patients)
- Consideration of malignancy (older patients)

- Goal: Aortic arch atheroma, atrial valvulopathy, aortic valvulopathy, atrial/ventricular septal pathology
- Goal: Underlying surveillance of arrhythmias, in particular atrial fibrillation

- e.g. Fabry disease, Mitochondrial disease work-up, CADASIL, CARASIL, HERSN, Migrainous infarction, etc.
Covert AF
Non-AF auricular arrhythmias
Auricular dysfunction

Ventricular dysfunction
CHF

Paradoxal embolism

Non-stenosant atherosclerosis
### Vascular death, non-fatal stroke, non-fatal myocardial infarction or major bleeding complication

**Recurrent ischemic stroke**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Anticoagulation</th>
<th>Antiplatelet</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 INR 2.0 - 3.6</td>
<td>99/536</td>
<td>98/532</td>
<td>100.0 %</td>
<td>1000 %</td>
<td>1.00 [0.78, 1.29]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>536</td>
<td>532</td>
<td>100.0 %</td>
<td>1000 %</td>
<td>2.30 [1.58, 3.35]</td>
</tr>
<tr>
<td>Total events</td>
<td>99 (Anticoagulation), 98 (Antiplatelet)</td>
<td>100.0 %</td>
<td>1.00 [0.78, 1.29]</td>
<td>2.30 [1.58, 3.35]</td>
<td></td>
</tr>
</tbody>
</table>

**8 trials**

De Schryver ELM, Algra A, Kappelle LJ, van Gijn J, Koudstaal PJ
### Major bleeding complication

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Anticoagulation</th>
<th>Antiplatelet</th>
<th>Risk Ratio M.H.Fixed (95% CI)</th>
<th>Weight</th>
<th>Risk Ratio M.H.Fixed (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 INR 1.4 - 2.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WARSS 2001</td>
<td>38/1103</td>
<td>30/1103</td>
<td>1.27 [0.79, 2.03]</td>
<td>100.0 %</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1103</strong></td>
<td><strong>1103</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 INR 2.0 - 3.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESPRIT 2007</td>
<td>45/536</td>
<td>18/532</td>
<td>2.48 [1.46, 4.23]</td>
<td>57.5 %</td>
<td></td>
</tr>
<tr>
<td>Garde 1983</td>
<td>8/114</td>
<td>4/127</td>
<td>2.23 [0.69, 7.20]</td>
<td>12.0 %</td>
<td></td>
</tr>
<tr>
<td>Olsson 1980</td>
<td>7/68</td>
<td>3/67</td>
<td>2.30 [0.62, 8.52]</td>
<td>9.6 %</td>
<td></td>
</tr>
<tr>
<td>SWAT 1998</td>
<td>0/59</td>
<td>6/58</td>
<td>0.08 [0.00, 1.31]</td>
<td>20.9 %</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>777</strong></td>
<td><strong>784</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 INR 3.0 - 4.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPIRIT 1997</td>
<td>53/651</td>
<td>6/665</td>
<td>9.02 [3.91, 20.84]</td>
<td>100.0 %</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>651</strong></td>
<td><strong>665</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 38 (Anticoagulation), 30 (Antiplatelet)

Heterogeneity: not applicable

Test for overall effect: Z = 0.98 (P = 0.33)

Total events: 60 (Anticoagulation), 31 (Antiplatelet)

Heterogeneity: Chi² = 5.92, df = 3 (P = 0.12), I² = 49%

Test for overall effect: Z = 3.07 (P = 0.0021)

Total events: 53 (Anticoagulation), 6 (Antiplatelet)

Heterogeneity: not applicable

Test for overall effect: Z = 5.15 (P = 0.00001)
Risk Stratification for Recurrence and Mortality in Embolic Stroke of Undetermined Source

Results—One hundred fifty-nine (5.6%) ischemic stroke/TIA recurrences and 148 (5.2%) deaths occurred in 1095 patients (median age, 68 years) followed-up for a median of 31 months. Compared with CHADS, score 0, CHA₂DS₂-VASc scores were higher for each risk factor.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>CHADS₂ (Maximum score, 6)</th>
<th>CHA₂DS₂-VASc (Maximum score, 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>N/A</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74</td>
<td>N/A</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Female sex</td>
<td>N/A</td>
<td>1</td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>
Covert AF and stroke risk

- **24h**: 3.8%
- **48%**: 6.4%
- **7 days**: 9%
- **3 w- 6 mo**: 15%
• High clinical suspicion of cardioembolism
• Low risk of bleeding
• High recurrent risk (CHADS-VASC)
• High probability of AF:
  • Dilated atrium,
  • chicken wing appendage
  • BNP, troponin
  • Frequent extrasist
For how long?

• Depends on availability and type of long-term ECG monitoring

• 3 weeks to 3 months... to ≥ 1 year...

• If no AF detected.....switch to antiplatelet?
ESUS-RCT

• NAVIGATE ESUS
  • Rivaroxaban vs AAS

• RE-SPECT ESUS
  • Dabigatran vs AAS

• ITTACUS
  • Apixaban vs AAS
NAVIGATE-ESUS: SECONDARY PREVENTION OF STROKE IN PATIENTS WITH A RECENT ESUS


Supported by BAYER

Principal Investigator at BMC: Viken Babikian, MD

Study duration: 18+ months

Study drugs: Rivaroxaban 15mg vs aspirin 100mg QD

ClinicalTrials.gov Identifier: NCT02313909

Recruitment Status: Terminated (Study halted early due to no efficacy improvement over aspirin at an interim analysis and very little chance of showing overall benefit if study were completed)

First Posted: December 10, 2014

Last Update Posted: October 23, 2017
Thanks for your attention...