How Can We Properly Manage Patients With Stroke of Undetermined Origin?

: Spotlight on Embolic Stroke of Undetermined Source (ESUS)

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Hallym University College of Medicine
How Can We Properly Manage Patients With Stroke of Undetermined Origin?

1. Stroke of Undetermined Origin;
   Cryptogenic stroke vs. Embolic Stroke of Undetermined Source (ESUS)

2. Tailoring Diagnostic Strategy in Embolic Stroke of Undetermined Source

3. Tailoring Therapeutic Strategy in Embolic Stroke of Undetermined Source
Agenda

01. Stroke of Undetermined Origin vs. Cryptogenic stroke vs. Embolic Stroke of Undetermined Source (ESUS)

02. Tailoring Diagnostic Strategy in Embolic Stroke of Undetermined Source

03. Tailoring Therapeutic Strategy in Embolic Stroke of Undetermined Source
Cryptogenic Stroke and ESUS

**Stroke of Undetermined Origin**

![Figure 1: Distribution of ischaemic stroke subtypes in North American and European studies](image)

The distribution in Asian and African populations differs from that in North American and European populations.

LAA, large artery atherosclerosis; SVO, small vessel occlusion; UDE, undetermined of etiology; CE, cardioembolism; ODE, other determined of etiology

Adams HP, Jr et al. Stroke 24:35-41, 1993
Stroke of Undetermined Origin

Cryptogenic Stroke?

Brain infarct *not* attributed to a definite source of large-vessel atherosclerosis (LAA), cardioembolism (CE), or small-vessel disease (SVO).

- **Stroke with incomplete evaluation**
- **Two or more competing cause**
- **Really Cryptogenic stroke**

No determined etiology after extensive cardiac, vascular, hematologic, and serologic evaluation.

LAA, large artery atherosclerosis; SVO, small vessel occlusion; UDE, undetermined of etiology; CE, cardioembolism; ODE, other determined of etiology

The Concepts of ESUS

- Cryptogenic stroke ≠ ESUS
- a subset of cryptogenic stroke with embolic source
  - embolic stroke for which the etiology of embolism remains unidentified despite thorough investigations ruling out established cardiac and vascular sources
- as a potential subgroup of ischemic stroke patients with more benefit from anticoagulation
- as the basis for future RCT for secondary prevention

**Embolic Stroke of Undetermined Source (ESUS):**
Proposed Criteria by the Cryptogenic Stroke/ESUS International Working Group in 2014

ESUS based on established criteria

Proposed diagnostic criteria by the Cryptogenic Stroke/ESUS International Working Group

**Diagnostic Criteria**

✔ **Non-lacunar ischemic stroke** detected by CT or MRI
  
  - Lacunar defined as subcortical infarct ≤1.5cm (≤2.0cm on DWI) in largest dimension, and in distribution of small, penetrating cerebral arteries

  ➔ To exclude lacunar infarction (SVO) !!!

✔ **Absence** of extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying territory

  ➔ To exclude LAA !!!

✔ **No major-risk cardioembolic source of embolism**

  - Major-risk CE: *permanent* or *paroxysmal* AF, sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumor, mitral stenosis, recent MI within past 4 weeks, LVEF < 30%, valvular vegetations or infectious endocarditis

  ➔ To exclude CE (definite) !!!

✔ **No other specific cause** of stroke identified

  - e.g. arteritis, dissection, migraine/vasospasm, drug misuse

  ➔ To exclude ODE !!!
ESUS based on established criteria

Proposed diagnostic criteria by the Cryptogenic Stroke/ESUS International Working Group

**Diagnostic Criteria**

- Non-lacunar ischemic stroke
  - Lacunar defined as subcortical infarct ≤1.5cm in largest dimension, and in distribution of small, penetrating cerebral arteries
  - To exclude lacunar infarction (SVO) !!!

- Absence of extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying territory
  - To exclude LAA !!!

- No major-risk cardioembolic source
  - Major-risk CE: permanent or paroxysmal AF, sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumor, mitral stenosis, recent MI within past 4 weeks, LVEF < 30%, valvular vegetations or infectious endocarditis
  - To exclude CE (definite) !!!

- No other specific cause of stroke identified
  - e.g. arteritis, dissection, migraine/vasospasm, drug misuse
  - To exclude ODE !!!

**Minimum assessment of ESUS**

1. Brain CT or MRI
2. 12-lead ECG
3. Precordial echocardiography (TTE)
4. Cardiac monitoring for ≥24 h with automated rhythm detection (telemetry not sufficient)
5. Imaging of extra and intracranial arteries

## Burden of ESUS

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>Mean age (years)</th>
<th>Criteria for cryptogenic stroke</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Besancon Stroke Registry (2000)</td>
<td>1776</td>
<td>71</td>
<td>Study specific</td>
<td>18%†</td>
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<tr>
<td>Athens Stroke Registry (2000)</td>
<td>885</td>
<td>70</td>
<td>Not specified</td>
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<td>German Stroke Data Bank (2001)</td>
<td>5017</td>
<td>66</td>
<td>Modified TOAST criteria</td>
<td>23%</td>
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<td>WARSS (2001)</td>
<td>2206</td>
<td>63</td>
<td>TOAST criteria</td>
<td>26%</td>
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<td>Erlangen Study (2001)</td>
<td>583</td>
<td>73</td>
<td>TOAST criteria</td>
<td>32%</td>
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<td>Ankara (2002)</td>
<td>264</td>
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<td>33%</td>
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<td>Suwon (2003)</td>
<td>204</td>
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<td>TULIPS (Japan) (2004)</td>
<td>831</td>
<td>72</td>
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<td>Penugia (2006)</td>
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<td>PRoFESS (2008)</td>
<td>20,332</td>
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<td>TOAST criteria</td>
<td>16%‡</td>
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<td>Bern (2008)</td>
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<td>TOAST criteria</td>
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<td>Buenos Aires (2010)</td>
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<tr>
<td>ASTRAL (2010)</td>
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<td>73</td>
<td>Modified TOAST criteria</td>
<td>12%§</td>
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<td>North Dublin (2010)</td>
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<td>Causative Classification System</td>
<td>26%</td>
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<td>VITALOPS (2010)</td>
<td>8164</td>
<td>63</td>
<td>Study specific†</td>
<td>14%</td>
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<td>PERFORM (2011)</td>
<td>19,100</td>
<td>67</td>
<td>Study specific‡</td>
<td>22%</td>
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<td>Mannheim Stroke Center (2012)</td>
<td>103</td>
<td>69</td>
<td>TOAST criteria</td>
<td>30%</td>
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<td>Hebi, China (2012)</td>
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<td>16%</td>
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<td>Barcelona (2012)</td>
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<td>32%</td>
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<td>Santiago de Compostela (2013)</td>
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<td>NR</td>
<td>TOAST criteria</td>
<td>35%</td>
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<tr>
<td>Bavaria (2013)</td>
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<td>NR</td>
<td>TOAST criteria</td>
<td>17%</td>
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ESUS and Stroke recurrence risk in Athens Stroke Registry; 5-year stroke recurrence

<table>
<thead>
<tr>
<th></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>
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<tbody>
<tr>
<td>Risk of stroke recurrence (%)</td>
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<td>0</td>
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<td>12</td>
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<td>24</td>
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<td>36</td>
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<td>48</td>
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<td>60</td>
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</tbody>
</table>

Recurrent stroke: about 7% at 30 days and about 12-15% at 1 year, and about 20% at 2-3 years

Log-rank test: 30.9, < 0.0001

ESUS and Stroke recurrence risk in Korea

<table>
<thead>
<tr>
<th>No determined (ESUS) (n=37)</th>
<th>Large-artery disease (n=56)</th>
<th>Cardioembolism (n=62)</th>
<th>small artery disease (n=27)</th>
<th>Two or more causes (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30%</td>
<td>16%</td>
<td>2%</td>
<td>14%</td>
<td>16%</td>
</tr>
</tbody>
</table>

$P < 0.001$

Potential Causes of ESUS

- **Cancer associated**
  - Tumor emboli from occult cancer

- **Paradoxical embolism**
  - Patent foramen ovale
  - Atrial septal defect
  - Pulmonary arteriovenous fistula

- **Minor-risk potential CE sources**
  - Mitral valve
  - Aortic valve
  - Non-AF atrial dysrhythmias & stasis
  - Atrial structural abnormalities (ASA)
  - Left ventricle

- **Others**
  - Hypercoagulable disease
  - Migraine, Fabry disease, hyper-homocysteinmeia

- **Covert AF**

- **Arteriogenic emboli**
  - Aortic arch atherosclerotic plaque
  - Cerebral artery non-stenotic plaque with ulceration

Potential causes of ESUS in the Athens Stroke registry

- **Arteriogenic emboli 23.9%**
  - Aortic arch atherosclerotic plaque 3.3%
  - Cerebral artery non-stenotic plaque with ulceration 10.6%

- **Covert AF 29.3%**
  - AF detected on stroke recurrence 11%
  - AF detected on monitoring during f/u 18.3%

- **Cancer associated, 1.2%**

- **Paradoxical embolism**
  - Patent foramen ovale 4.0%
  - Atrial septal defect 1.1%
  - Pulmonary arteriovenous fistula 0%

- **Minor-risk potential CE sources**
  - Mitral valve 4.7%
  - Aortic valve 5.5%
  - Non-AF atrial dysrhythmias & stasis 5.9%
  - **Atrial structural abnormalities (ASA) 3.6%**
  - **Left ventricle 20.2%**

Potential causes of ESUS in Korea

- Acute ischemic stroke (N=3981)
- Cryptogenic embolic stroke (n=321, 8%)
- Cardioembolic, other than PAF (n=241)
- Incomplete evaluation (n=230)
- Large artery disease (n=1295)
- Cardioembolic stroke (n=693)
- Small artery occlusion (n=674)
- Others (n=186)
- Extensive work-ups
- History taking, ECG, brain MRI + MRA

TOAST classification

- Undetermined etiology (n=368, 9.2%)
- PFO (n=153)
- Aortic arch atheroma (n=40)
- PAF (n=128)

Agenda.

01. Stroke of Undetermined Origin; Cryptogenic stroke vs. Embolic Stroke of Undetermined Source (ESUS)

02. Tailoring Diagnostic Strategy in Embolic Stroke of Undetermined Source

02. Tailoring Therapeutic Strategy in Embolic Stroke of Undetermined Source
Challenges in the Diagnosis of ESUS

Potential causes of ESUS

- Arteriogenic emboli 23.9%
  - Aortic arch atherosclerotic plaque 3.3%
  - Cerebral artery non-stenotic plaque with ulceration 10.6%
- Covert AF 29.3%
  - AF detected on stroke recurrence 11%
  - AF detected on monitoring during I/u 18.3%
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- Minor-risk potential CE sources
  - Mitral valve 4.7%
  - Aortic valve 5.5%
  - Non-AF atrial dysrythmias & stasis 5.9%
  - Atrial structural abnormalities (ASA) 3.6%
  - Left ventricle 20.2%

Advanced Vascular Imaging
- Carotid plaque MRI imaging
- High-resolution (HR) wall MRI (vessel wall imaging)

Advanced Monitoring for Covert AF Detection
- Longer monitoring (more than 24-h) or
- Implantable loop recorder (LRP)
- TEE, Coronary CT angiography (CTA), and Cardiac MRI for left atrial appendage thrombus


Bang OY et al. Stroke 45:1186, 2014
Diagnostic strategy of ESUS

Advanced Monitoring for Covert AF Detection

Two Post-stroke prolonged monitoring trials of AF

Event Monitor Belt for Recording AF after a Cerebral Ischemic Event (EMBRACE)\(^1\)

Ambulatory 30-d ECG vs. conventional 24-h monitoring

EMBRACE-AF 15 % detection

Cryptogenic Stroke and Underlying Atrial Fibrillation (CRYSTAL-AF)\(^2\)

Insertable cardiac monitor (ICM) vs. control group

CRystal-AF trial 8.9 % within 6 m., 30% within 36 m.

- Patients with AF detected (%)
- Duration of ECG monitoring

- Atrial Fibrillation Detected (% of patients)
- Months since Randomization

Hazard ratio, 8.8 (95% CI, 3.5–22.2) P<0.001 by log-rank test

Challenges in the Diagnosis of ESUS

Paradoxical or Aortogenic Embolic Source Evaluation
- PFO study: TEE, TCD monitoring
- AAA: TEE, Coronary CT angiography (CCTA)

Tests for Coagulopathy and Cancer Screening
- D-dimer
- Cancer work up

Figure 6. Changes in stroke subtypes with application of advanced diagnostic techniques. *Either intracranial or extracranial vessels. †Intracranial vessels.

Bang OY et al. Stroke 45:1186, 2014
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Warfarin-Aspirin Recurrent Stroke study (WARSS)

- Multicenter double-blind study comparing ASA to Warfarin (goal INR 1.4-2.8)

**Primary outcome (stroke or death within 2 years)**

![Graph showing the probability of event over time for Warfarin and Aspirin]

**Subgroup analyses for primary outcome**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Number</th>
<th>Warfarin</th>
<th>Aspirin</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptogenic</td>
<td>576</td>
<td>15.0</td>
<td>16.5</td>
<td>0.92</td>
<td>0.61-1.39</td>
<td>0.68</td>
</tr>
<tr>
<td>Lacunar</td>
<td>1237</td>
<td>17.1</td>
<td>15.2</td>
<td>1.15</td>
<td>0.88-1.52</td>
<td>0.31</td>
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<tr>
<td>Large artery</td>
<td>259</td>
<td>18.8</td>
<td>15.7</td>
<td>1.12</td>
<td>0.67-2.22</td>
<td>0.51</td>
</tr>
<tr>
<td>Other</td>
<td>63</td>
<td>36.7</td>
<td>21.2</td>
<td>1.99</td>
<td>0.77-5.15</td>
<td>0.15</td>
</tr>
</tbody>
</table>

NO. AT RISK

Warfarin: 1103, 1047, 1013, 998, 972, 956, 939, 924, 885

Aspirin: 1103, 1057, 1032, 1004, 984, 974, 951, 932, 900

WASS sub-analysis: cryptogenic stroke

In 569 patients Cryptogenic stroke subgroup of WASS

• Interaction (Treatment * HTN) P=0.02

Exploratory Analyses

<table>
<thead>
<tr>
<th></th>
<th>Hypertension (N=152 WAR, 158 ASA)</th>
<th>No hypertension (N=127 WAR, 132 ASA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin RR=1.32</td>
<td>21.1%</td>
<td>7.9%</td>
</tr>
<tr>
<td>P=0.29</td>
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<tr>
<td>Warfarin RR=0.45</td>
<td>16.5%</td>
<td>16.7%</td>
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<td>P=0.04</td>
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</table>

Treatment strategy of ESUS

WARSS/APASS: Effect of warfarin vs aspirin on recurrent stroke/death among those with elevated NT-proBNP

**NT-proBNP > 750 pg/ml**

- (n=49)

- HR = 1.30 (95% CI 0.12-0.84)
- P = 0.02

**NT-proBNP ≤ 750 pg/ml**

- (n=979)

- HR = 1.21 (95% CI 0.87-1.69)
- P = 0.24

Interaction (Treatment * NT-proBNP) P = 0.01

The potential for DOAC usage in ESUS

Ongoing trials with DOACs in patients with ESUS

<table>
<thead>
<tr>
<th>Intervention Comparison</th>
<th>Study design</th>
<th>Inclusion</th>
<th>Estimated enrolment</th>
<th>NOAC dosing</th>
<th>Information</th>
</tr>
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<tbody>
<tr>
<td><strong>ATTICUS</strong></td>
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<tr>
<td>Apixaban vs Aspirin</td>
<td>Open-label, phase III RCT in Germany</td>
<td>With ESUS and ≥1 suggestive risk factor for cardiac embolism</td>
<td>500 patients</td>
<td>Apixaban 5mg bid</td>
<td>ClinicalTrials.gov: NCT02427126</td>
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<tr>
<td><strong>RE-SPECT ESUS</strong></td>
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<tr>
<td>Dabigatran vs Aspirin</td>
<td>Double-blind, phase III, international RCT</td>
<td>Up to 3 m before randomization</td>
<td>6000 patients</td>
<td>Dabigatran 110mg or 150mg bid</td>
<td>ClinicalTrials.gov: NCT02239120 Diener HC et al. 2015</td>
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<td><strong>NAVIGATE ESUS</strong></td>
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<tr>
<td>Rivaroxaban vs Aspirin</td>
<td>Double-blind, Double-dummy, phase III, international RCT</td>
<td>7 d to 6 m before randomization</td>
<td>7000 patients</td>
<td>Rivaroxaban 15 mg od</td>
<td>ClinicalTrials.gov: NCT02313909</td>
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</table>
Current Paradigm

Current treatment guideline of ESUS (2014 AHA/ASA)

ESUS

- atrial fibrillation
  - warfarin
- No atrial fibrillation
  - aspirin

The Potential treatment of ESUS

ESUS

- PFO
  - aspirin or PFO closer
- Atrial Fibrillation
  - aspirin or OAC closer
- NOAC trials for non-AF
- Aortic arch atheroma or non-stenosing atheroma
  - Statin, short term DAPT

CCTA, coronary CT angiography; HR-MRI, high-resolution MRI; OAC, oral anticoagulant; DAPT, dual antiplatelet
Conclusions

• Most cryptogenic strokes are embolic (cardiogenic, arteriogenic, paradoxical).
• ESUS (embolic strokes of undetermined source) is a new, clinically useful construct for future RCTS.
• Extensive diagnostic efforts to define the specific cause are often futile and may be unnecessary.
• No specific preventive strategies but, for secondary prevention of ESUS, anticoagulants are likely to be more efficacious than antiplatelet drugs
• Ongoing trials for the secondary prevention of ESUS (NOAC vs. ASA)
How Can We Properly Manage Patients With Stroke of Undetermined Origin?

THANKS FOR YOUR ATTENTION !!!