Embolic Stroke of Undetermined Source (ESUS)

O ρόλος του Καρδιολόγου στη διερεύνηση & αντιμετώπιση

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Disclosures

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ESUS agenda

• What is an ESUS?
• What can be the underlying cause of the ESUS?
• Why all this noise about ESUS?
• Anticoagulation or aspirin for ESUS?
ESUS agenda

• What is an ESUS?
Cryptogenic stroke

- Ischemic stroke
  - Large-artery atherosclerotic
  - Cardioembolic
  - Lacunar
  - Other/rare
  - Cryptogenic
ESUS vs. Cryptogenic stroke

Cryptogenic

- Not investigated
- Multiple causes
- Really cryptogenic (ESUS)
Embolic strokes of undetermined source: the case for a new clinical construct

Robert G Hart, Hans-Christoph Diener, Shelagh B Coutts, J Donald Easton, Christopher B Granger, Martin J O’Donnell, Ralph L Sacco, Stuart J Connolly, for the Cryptogenic Stroke/ESUS International Working Group

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.

ESUS agenda

• What is an ESUS?

• What can be the underlying cause of the ESUS?
## ESUS: Potential causes

### Covert Atrial Fibrillation
#### Cancer associated
- Covert non-bacterial thrombotic endocarditis
- Tumour emboli from occult cancer

#### Arteriogenic emboli
- Aortic arch atherosclerotic plaques
- Cerebral artery non-stenotic plaques with ulceration

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

### Minor-risk potential cardioembolic sources
#### Mitral or Aortic valve
- Myxomatous valvulopathy with prolapse
- Mitral annular calcification
- Aortic valve stenosis or Calcific aortic valve

#### Non-AF atrial dysrhythmias and stasis
- Atrial asystole and sick-sinus syndrome
- Atrial high-rate episodes
- Atrial appendage stasis with reduced flow velocities or spontaneous echodensities

#### Atrial structural abnormalities
- Atrial septal aneurysm or Chiari network

#### Left ventricle
- Moderate systolic or diastolic dysfunction (global or regional)
- Ventricular non-compaction or Endomyocardial fibrosis

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ESUS: Diagnostic criteria

- **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 cardiac source of embolism.**
  (permanent or paroxysmal AF, sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumours, mitral stenosis, recent (<4 weeks) MI, LVEF <30%, valvular vegetations or infective endocarditis)

- **No other specific cause** of stroke identified.

ESUS: Diagnostic algorithm

- Brain CT or MRI
- 12-lead ECG
- Precordial echocardiography
- Imaging of both extra- and intracranial arteries supplying the area of brain ischaemia
- Cardiac monitoring for ≥24 hours with automated rhythm detection

ESUS agenda

• What is an ESUS?

• What can be the underlying cause of the ESUS?

• Why all this noise about ESUS?
ESUS are frequent (17% of all ischaemic strokes)
ESUS: 5-year stroke recurrence

Risk of stroke recurrence (%)

- ESUS
- Cardioembolic
- Large-artery atherosclerotic
- Lacunar
- Undetermined other than ESUS
- Miscellaneous

Months

0 12 24 36 48 60

ESUS Strokes of Undetermined Source in the Athens Stroke Registry: An Outcome Analysis

George Ntaios, MD; Vassiliki Papapetrou, MD; Harisangis Milotos, MD; Konstantina Mavrofi, MD; Anastasia Vemete, MD; Fenti Koutsouhilis, MD; Elisabeth Markos, MD; Konstantinos Spigos, MD; Panagiotis Michou, MD; Konstantinos Vaznis, MD

Background and Purpose: Information about outcomes in Embolic Strokes of Undetermined Source (ESUS) patients is limited. This study was designed to analyze the outcomes of ESUS patients from a large single-center registry.

Methods: A prospective registry of all consecutive patients with ischemic stroke was performed at the Athens Medical Center. The patients were classified into six subtypes of embolic stroke. The primary outcome was 5-year overall survival. The data were analyzed using Kaplan-Meier survival analysis.

Results: A total of 778 patients were included in the study. The 5-year overall survival rate was 72.5% for ESUS, 79.7% for cardioembolic, 74.4% for large-artery atherosclerotic, 64.2% for lacunar, 71.6% for undetermined other than ESUS, and 78.8% for miscellaneous. The cumulative probability of stroke recurrence was 0.05, 0.12, 0.18, 0.24, 0.30, and 0.36 for ESUS, cardioembolic, large-artery atherosclerotic, lacunar, undetermined other than ESUS, and miscellaneous, respectively.

Conclusions: ESUS is a distinct entity with a lower risk of stroke recurrence compared to other subtypes of embolic stroke. The 5-year overall survival rate in ESUS is comparable to that of other embolic stroke subtypes.

Keywords: embolic stroke, undetermined source, ESUS, mortality, stroke recurrence.
ESUS: 90% are treated with antiplatelets

<table>
<thead>
<tr>
<th>Study</th>
<th>n/ Mean Follow-Up (y)</th>
<th>Mean Age, y</th>
<th>Antithrombotic Therapy</th>
<th>AF During Follow-Up†</th>
<th>Stroke (Est Annualized Rate)†</th>
<th>Stroke, MI, Vascular Death (Est Annualized Rate)</th>
<th>Total Mortality (Est Annualized Rate)</th>
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<tr>
<td>Ntaios et al&lt;sup&gt;13,26&lt;/sup&gt;‡</td>
<td>275 (3.2)</td>
<td>68</td>
<td>74% APT only, 22% OAC</td>
<td>80 (29%)</td>
<td>6.8%/y</td>
<td>9.0%/y§</td>
<td>8.2%/y</td>
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<td>Li et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td>189 (1)</td>
<td>65</td>
<td>NR</td>
<td>NR</td>
<td>~5%/y</td>
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<td>Putaala et al&lt;sup&gt;11&lt;/sup&gt;‡</td>
<td>46 (1.8)</td>
<td>62</td>
<td>85% APT, 11% OAC</td>
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<td>1.3%/y</td>
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<td>Ntaios et al&lt;sup&gt;24&lt;/sup&gt;‡</td>
<td>1095 (3.0)</td>
<td>68</td>
<td>87% APT only, 12% OAC</td>
<td>NR</td>
<td>4.8%/y†</td>
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<td>Masina et al&lt;sup&gt;12&lt;/sup&gt;†</td>
<td>84 (2.1)</td>
<td>73</td>
<td>99% APT</td>
<td>NR</td>
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<td>Ueno et al&lt;sup&gt;22&lt;/sup&gt;#</td>
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<td>5.0%/y**</td>
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<td>Arauz et al&lt;sup&gt;23&lt;/sup&gt;‡‡</td>
<td>149 (2.3)</td>
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<td>87% APT, 12% OAC</td>
<td>…</td>
<td>4.0%/y</td>
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<tr>
<td>Pooled – weighted average‡, †‡</td>
<td>1605 (2.7)</td>
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<td>86% APT, 13% OAC</td>
<td>…</td>
<td>4.5%/y</td>
<td>…</td>
<td>3.9%/y</td>
</tr>
</tbody>
</table>
ESUS agenda

• What is an ESUS?
• What can be the underlying cause of the ESUS?
• Why all this noise about ESUS?
• Anticoagulation or aspirin for ESUS?
Rivaroxaban 15 mg once daily

Aspirin 100 mg once daily
Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source

Hazard ratio, 1.07 (95% CI, 0.87–1.33)

- Rivaroxaban
- Aspirin
NAVIGATE-ESUS: safety outcome

Hazard ratio, 2.72 (95% CI, 1.68–4.39)

Rivaroxaban

Aspirin

0.03
0.02
0.01
0.00

0 60 120 180 240 300 360 420 480 540
RESPECT-ESUS

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Dabigatran Etxilate for Secondary Stroke Prevention In Patients With Embolic Stroke of Undetermined Source (RE-SPECT ESUS)

This study is currently recruiting participants. (see Contacts and Locations)
Verified January 2015 by Boehringer Ingelheim

Sponsor:
Boehringer Ingelheim

Information provided by (Responsible Party):
Boehringer Ingelheim

ClinicalTrials.gov Identifier:
NCT02239120

First received: September 10, 2014
Last updated: January 22, 2015
Last verified: January 2015

History of Changes

Dabigatran 150/110 mg twice daily

ESUS

Aspirin 100 mg once daily
ESUS & atrial myopathy

Apixaban 5 mg twice daily

Aspirin 81 mg once daily

- P-wave terminal force >5000 mVms in V1
- NTproBNP > 250 pg/mL
- Left atrial diameter index ≥3 cm/m²

The AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke randomized trial: Rationale and methods

ESUS agenda & take-home messages

• What is an ESUS?
  An ischemic stroke without an identifiable cause despite recommended work-up

• What can be the underlying cause of the ESUS?
  Too many causes, many from the heart

• Why all this noise about ESUS?
  17% of all ischemic strokes, with a significant recurrence risk (4.5-5.0% annually)

• Anticoagulation or aspirin for ESUS?
  Aspirin
Η Ελληνική Οργανώση Εγχειρολόγων ιατρικής εκδόσεως Αίγινας

ΑΓΓΕΙΑΚΑ ΕΓΚΕΦΑΛΙΚΑ ΕΠΕΙΣΟΔΙΑ

Hellenic Stroke Organization

ΠΑΝΕΛΛΗΝΙΟ ΣΥΝΕΔΡΙΟ 2019

7-9 ΜΑΡΤΙΟΥ 2019 ΑΘΗΝΑ

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