True cryptogenic stroke

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Astra Zeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Gore, Pfizer, sanofi aventis

Adjunct member of steering committee of International Stroke Genetics Consortium

National leader for NAVIGATE-ESUS trial, representing Denmark and Sweden
Definitions cryptogenic stroke 1(2)

- Cryptogenic = of unknown origin
- 10-40% of all ischemic strokes
- No generally accepted definition
- Extensive definitions – also include:
  - more than one cause
  - incomplete evaluation

Definitions cryptogenic stroke 2(2)

More circumspect definitions are more common:

”Completely unknown cause”

”Truly unknown cryptogenic”

”Highly cryptogenic”
Cryptogenic stroke

ESUS

Intermediate findings
Minor cardiac sources
Carotid artery stenosis <50%
Migraine
Hypertension, other risk factors
Genetic disorders

True ESUS*

Lacunar

Intermediate findings
Hypertension, other risk factors
Plaque at origin of penetrating artery
Genetic disorders

True cryptogenic Lacunar

ICH

Intermediate findings
Hypertension
Vascular malformation
Genetic disorders

True cryptogenic ICH

ESUS = embolic stroke of undetermined source
*presuming that cryptogenic clots cannot evolve “in situ” in cerebral vessels

Lindgren A. Nordic Stroke, Århus 25 Aug 2017
Standardised methods for establishing **ischemic** cryptogenic stroke

1. TOAST

2. CCS causative classification of stroke

3. A-S-C-O

4. ESUS = embolic stroke of undetermined source
1. TOAST cryptogenic/undetermined

Based on:
- Clinical features
- Brain imaging
- Cardiac imaging
- Duplex
- Angiography
- Lab tests

No exact description of the above

<table>
<thead>
<tr>
<th>TABLE 1. TOAST Classification of Subtypes of Acute Ischemic Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large-artery atherosclerosis (embolus/thrombosis)*</td>
</tr>
<tr>
<td>Cardioembolism (high-risk/medium-risk)*</td>
</tr>
<tr>
<td>Small-vessel occlusion (lacune)*</td>
</tr>
<tr>
<td>Stroke of other determined etiology*</td>
</tr>
<tr>
<td><strong>Stroke of undetermined etiology</strong></td>
</tr>
<tr>
<td>a. Two or more causes identified</td>
</tr>
<tr>
<td>b. Negative evaluation</td>
</tr>
<tr>
<td>c. Incomplete evaluation</td>
</tr>
</tbody>
</table>

TOAST, Trial of Org 10172 in Acute Stroke Treatment.  
*Possible or probable depending on results of ancillary studies.

2. **Causative Classification System for Ischemic Stroke (CCS)**

Developed by the A. A. Martinos Center for Biomedical Imaging and the Stroke Service at the Massachusetts General Hospital, Harvard Medical School, Boston MA

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Continue to Login Page Introduction Training Module Certification Module CCS Form without Login

- Brain imaging: CT or MR
- Vessel imaging: CTA, MRA, ultrasound
- Clinical symptoms: lacunar syndrome, systemic embolism
- Heart evaluation: clinical + ECG

Undetermined unknown - other cryptogenic

Undetermined unknown - cryptogenic embolism

https://ccs.mgh.harvard.edu/ccs_title.php
2. **CAUSATIVE CLASSIFICATION SYSTEM FOR ISCHEMIC STROKE (CCS)**

Developed by the A. A. Martinos Center for Biomedical Imaging and the Stroke Service at the Massachusetts General Hospital, Harvard Medical School, Boston MA

- Brain imaging: CT or MR
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- Clinical symptoms: lacunar syndrome, systemic embolism
- Heart evaluation: clinical + ECG

Undetermined unknown - other cryptogenic

**Undetermined unknown - cryptogenic embolism**

https://ccs.mgh.harvard.edu/ccs_title.php
3. A-S-C-O

- Atherothrombosis: aortic arch, cervical, intracranial vessels
- Small vessel: clinical symptoms
- Cardioembolism: Minimum is negative ECG + auscultation by a cardiologist
- Other

In cases where all A-S-C-O are 0, the cause is completely unknown.

4. ESUS

Cryptogenic stroke

ESUS

Intermediate findings
- Minor cardiac sources
- Carotid artery stenosis <50%
- Migraine
- Hypertension, other risk factors
- Genetic disorders

True ESUS*

ESUS = embolic stroke of undetermined source
*presuming that cryptogenic clots cannot evolve "in situ" in cerebral vessels

Lindgren A. Nordic Stroke, Århus 25 Aug 2017
4. ESUS

![Diagram showing the classification of stroke of unknown cause and embolic stroke of undetermined source.]

**Figure 1** Stroke of unknown cause and embolic stroke of undetermined source. pAF, paroxysmal atrial fibrillation; ESUS, embolic stroke of undetermined source.

4. ESUS

Figure 1 Stroke of unknown cause and embolic stroke of undetermined source. pAF, paroxysmal atrial fibrillation; ESUS, embolic stroke of undetermined source.

<table>
<thead>
<tr>
<th>Table 1. Criteria for Diagnosis of Embolic Stroke of Undetermined Source (ESUS)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ischemic stroke detected by CT or MRI that is not lacunar†</td>
</tr>
<tr>
<td>2. Absence of extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischemia</td>
</tr>
<tr>
<td>3. No major risk cardioembolic source of embolism‡</td>
</tr>
<tr>
<td>4. No other specific cause of stroke identified (e.g., arteritis, dissection, migraine/vasospasm, and drug abuse)</td>
</tr>
</tbody>
</table>

CT indicates computed tomography; and MRI, indicates magnetic resonance imaging.

*Requires minimum diagnostic evaluation that includes cardiac rhythm monitoring for >24 hours with automated rhythm detection.†

†Lacunar defined as a subcortical infarct ≤1.5 cm (≤2.0 cm on MRI diffusion images) in largest dimension, including on MRI diffusion-weighted images, and in the distribution of the small, penetrating cerebral arteries of the cerebral hemispheres and pons.
Panel 1: Causes of embolic strokes of undetermined source

**Minor-risk potential cardioembolic sources***

*Mitral valve*
- Myxomatous valvulopathy with prolapse
- Mitral annular calcification

*Aortic valve*
- Aortic valve stenosis
- Calcific aortic valve

*Non-atrial fibrillation 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
- Chiari network

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

**Covert paroxysmal atrial fibrillation**

**Cancer-associated**
- Covert non-bacterial thrombotic endocarditis
- Tumour emboli from occult cancer

**Arterioigenic 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 sources are more often incidentally present than is the stroke cause when identified in an individual stroke patient, are associated with a low or uncertain rate of initial stroke, and consequently cause-effect relation and management implications are usually unclear.

Prevalence of cryptogenic stroke of possible cardiac origin

• Gene expression profile in blood – RNA - suggests that cardioembolic embolism accounts for 58% of cryptogenic strokes

Jickling GC et al. Stroke 2012;43:2036-41
Cardiac embolic sources
Cardiac changes related to thromboembolism, modified from Hart RG. Lancet, 1992;339:589-94

<table>
<thead>
<tr>
<th>Major potential sources</th>
<th>Minor potential sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation (not an Echo diagnosis)</td>
<td>Patent foramen ovale</td>
</tr>
<tr>
<td>New (&lt;3 months) AMI</td>
<td>Atrial septal aneurysm</td>
</tr>
<tr>
<td>Thrombus left atrium/ventricle</td>
<td>Mitral valve prolapse</td>
</tr>
<tr>
<td>Dilated cardiomyopathy (EF ≤35 %)</td>
<td>Mitral annular calcification</td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>Calcific aortic stenosis</td>
</tr>
<tr>
<td>Myxoma</td>
<td>Spontaneous echo contrast</td>
</tr>
<tr>
<td>Mechanical valve prosthesis</td>
<td>Other (AVII, pre-excitation etc)</td>
</tr>
<tr>
<td>Infektious endocarditis</td>
<td></td>
</tr>
<tr>
<td>Non-infectious endocarditis</td>
<td></td>
</tr>
</tbody>
</table>

**Protruding aortic plaque**

Major: Causal relationship
Minor: Over represented in stroke studies but no certain causal relationship
Prevalence of TEE-identified Low-risk embolic sources. n (% of 287) excluding those with concomitant high-risk source (n=41)

<table>
<thead>
<tr>
<th>Category</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>176 (61.3%)</td>
</tr>
<tr>
<td>Aortic plaque &lt; 4mm</td>
<td>117 (40.8%)</td>
</tr>
<tr>
<td>PFO alone</td>
<td>51 (17.8%)</td>
</tr>
<tr>
<td>PFO + ASA</td>
<td>16 (5.6%)</td>
</tr>
<tr>
<td>Mitral/aortic valve involvement</td>
<td>16 (5.6%)</td>
</tr>
<tr>
<td>Spontaneous echo contrast (in left atrium)</td>
<td>12 (4.2%)</td>
</tr>
<tr>
<td>ASA alone</td>
<td>7 (2.4%)</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>Other (dilated cardiomyopathy (n = 3), intrapulmonary shunt (n = 3), fibrin excrescence, lipomatous hypertrophy of the intraatrial septum (n = 3), aortic aneurysm, pulmonary vein mass, aortic thrombus, and left ventricular aneurysm)</td>
<td>14 (4.9%)</td>
</tr>
</tbody>
</table>

Young J Stroke Cerebrovasc Dis 2011;20:503-09
## TEE findings after major sources excluded

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patients (n=67)</th>
<th>Controls (n=58)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>37 (55%)</td>
<td>25 (43%)</td>
<td>ns</td>
</tr>
<tr>
<td>Atrial septal aneurysm (ASA)</td>
<td>17 (25%)</td>
<td>9 (16%)</td>
<td>ns</td>
</tr>
<tr>
<td>Patent foramen ovale (PFO)</td>
<td>17 (25%)</td>
<td>15 (26%)</td>
<td>ns</td>
</tr>
<tr>
<td>Protruding plaque ascending aorta</td>
<td>4 (6%)</td>
<td>1 (25%)</td>
<td>ns</td>
</tr>
<tr>
<td>Calcific aortic stenosis</td>
<td>3 (4%)</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>1 (1.5%)</td>
<td>1 (2%)</td>
<td>ns</td>
</tr>
<tr>
<td>Annular calcification</td>
<td>14 (20%)</td>
<td>10 (17%)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Recurrence rate

Cryptogenic stroke <56 yrs: 1.9% recurrence first year, then 0.8%

ESUS - recurrent stroke rate 4.5% per year
N=1605 patients
Large differences between ESUS studies
How to handle patients with ESUS?

- Ensure that no major cause is present
- PFO?
Panel 3: Proposed diagnostic assessment for embolic stroke of undetermined source*

- Brain CT or MRI
- 12-lead ECG
- Precordial echocardiography
- Cardiac monitoring for ≥24 h with automated rhythm detection†
- Imaging of both the extracranial and intracranial arteries supplying the area of brain ischaemia (catheter, MR, or CT angiography, or cervical duplex plus transcranial doppler ultrasonography)

*Imaging of the proximal aortic arch is not needed; special blood tests for prothrombotic states only if the patient has a personal or family history of unusual thrombosis or associated systematic signs or disorder. †Cardiac telemetry is not sufficient.
Ischemic stroke or TIA

History
Physical examination

Stroke topography
MRI of the brain
CT of the brain

Vessels
MRA of the head and neck
CTA of the head and neck
Carotid duplex ultrasonography and transcranial Doppler ultrasonography

Cardiac — structure
TTE
TEE

Cardiac — rhythm
12-Lead ECG
Inpatient cardiac telemetry
24-Hr Holter monitor

Hematologic testing
Complete blood count
Platelet count
INR
Partial-thromboplastin time

Stroke considered to be cryptogenic after standard evaluation

Stroke considered to be cryptogenic after advanced evaluation

Vessels
- Catheter angioplasty
- Transcranial Doppler monitoring for emboli
- Vasculitis tests

Cardiac — rhythm
- Prolonged (2–4 wk) outpatient cardiac telemetry

Hematologic testing
- Arterial hypercoagulability tests (all patients)
- Venous hypercoagulability tests (if right-to-left shunt)

ESUS

Panel 1: Causes of embolic strokes of undetermined source

Minor-risk potential cardioembolic sources*

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Table 2. Detection of Atrial Fibrillation in the Two Monitoring Groups.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention Group (N = 286)</th>
<th>Control Group (N = 285)</th>
<th>Absolute Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: detection of atrial fibrillation with duration ≥30 sec within 90 days†</td>
<td>45/280 (16.1)</td>
<td>9/277 (3.2)</td>
<td>12.9 (8.0–17.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Intervention – 30 day ECG monitoring

Gladstone DJ et al. EMBRACE trial. NEJM 2014;370:2467-77.
Primary endpoint
A Detection of Atrial Fibrillation by 6 Months

Hazard ratio, $6.4$ (95% CI, 1.9–21.7)  
P<0.001 by log-rank test

Atrial Fibrillation Detected (% of patients)

Months since Randomization

No. at Risk
Control 220 214 200 198 197 197 194
ICM 221 205 198 195 194 193 191

Rate of detection at 6 months 8.9% vs 1.4%

See supplement in:

Supplementary Table S2. Aspects of Tests used to Evaluate Patients with Ischemic Strokes Cryptogenic after Standard Evaluation

<table>
<thead>
<tr>
<th>Advanced Evaluation Components</th>
<th></th>
</tr>
</thead>
</table>
| Blood tests - Hypercoagulable states | Arterial: Blood tests to screen for common arterial hypercoagulable states (antiphospholipid antibodies, hyperhomocysteinemia), which can cause in situ arterial thrombosis or nonbacterial thrombotic endocarditis, are merited in most patients  
  o Anticardiolipin antibodies, DRVVT (lupus anticoagulant), Beta-2 glycoprotein 1 antibodies, Homocysteine (fasting)  
  Venous: screening for common venous hypercoagulable states is worthwhile only in patients with an identified route for paradoxical embolization or with cerebral venous thrombosis  
  o Protein S, Protein C, Activated Protein C Resistance (Factor V Leiden if abnormal), Antithrombin III, Prothrombin gene mutation, Factor VIII level, Fibrinogen. Anticardiolipin antibodies, DRVVT (lupus anticoagulant), Beta-2 glycoprotein 1 antibodies, Homocysteine (fasting) |
| Blood tests – Vasculitis, screening | Screening blood tests include ESR, CRP, ANA, RF, ANCA, though normal values do not rule out the diagnosis |
| Prolonged cardiac monitoring | 2-4 weeks of ambulatory cardiac rhythm monitoring increases the frequency of detecting low burden paroxysmal atrial fibrillation. |
| Transcranial Doppler monitoring for microthrombi | Extended transcranial Doppler monitoring, over 30 to 60 minutes, can detect microthrombi covertly traveling to the brain from proximal aortocardiac or distal arterial sources |
| Catheter angiography | Diagnostic cerebral catheter angiography allows visualization of medium and small arteries not well visualized with any other technique, enabling characterization of a variety of arteriopathies, including vasculitis, reversible cerebral vasoconstriction syndrome, and moyamoya  
  Identifies abnormalities in up to 75% of young stroke patients  
  Highest yield when performed within the first hours after onset, before pathophysiologic findings resolve |
Specialized Evaluation

- Genetic testing
  - Mitochondrial disease
  - CADASIL, Fabry's disease, other genetic causes

- Vessels
  - Detailed autoimmune evaluation
  - CSF examination
  - Brain biopsy

- Cardiac — structure
  - Cardiac CT
  - Cardiac MRI

- Cardiac — rhythm
  - Prolonged (1–3 yr) outpatient loop recording

- Hematologic testing
  - Workup for occult cancer

See supplement in:
Stochastic cause - Random

Having a stroke by chance

• 30% carotid artery stenosis ”causing” a stroke

• Slightly increased blood coagulation tendency having a blood clot

Multifactorial – eg both of the above

”Bad luck” vs ”Good luck”
How to handle patients with ESUS?

• Ensure that no major cause is present

• Antiplatelets

• Enrol in study with NOAC:
  NAVIGATE-ESUS – rivaroxaban vs aspirin
  RE-SPECT-ESUS – dabigatran vs aspirin
Conclusions

• Varying definitions of Cryptogenic stroke
• Cryptogenic stroke is common
• Structured definitions exist
• ESUS – embolic stroke of undetermined source
• ESUS is cardiac in over 50%. AF, PFO
• Algorithms for evaluation have been suggested
• ESUS treatment studies results expected 2018/2019.