Embolic Stroke of Undetermined Source
A Systematic Review and Clinical Update

Robert G. Hart, MD; Luciana Catanese, MD; Kanjana S. Perera, MBBS; George Ntaios, MD, PhD; Stuart J. Connolly, MD

Background and Purpose—Embolic stroke of undetermined source (ESUS) designates patients with nonlacunar cryptogenic ischemic strokes in whom embolism is the likely stroke mechanism. It has been hypothesized that anticoagulation is more efficacious than antiplatelet therapy for secondary stroke prevention in ESUS patients. We review available information about ESUS.

Methods—Systematic literature review to assess the frequency of ESUS, patient features, and prognosis using PubMed from 2014 to present, unrestricted by language.

Results—On the basis of 9 studies, the reported frequency of ESUS ranged from 9% to 25% of ischemic strokes, averaging 17%. From 8 studies involving 2045 ESUS patients, the mean age was 65 years and 42% were women; the mean NIH stroke score was 5 at stroke onset (4 studies, 1772 ESUS patients). Most (86%) ESUS patients were treated with antiplatelet therapy during follow-up, with the annualized recurrent stroke rate averaging 4.5% per year during a mean follow-up of 2.7 years (5 studies, 1605 ESUS patients).

Conclusions—ESUS comprises about 1 ischemic stroke in 6. Patients with ischemic stroke meeting criteria for ESUS were relatively young compared with other ischemic stroke subtypes and had, on average, minor strokes, consistent with small emboli. Retrospective methods of available studies limit confidence in stroke recurrence rates but support a substantial (>4% per year) rate of stroke recurrence during (mostly) antiplatelet therapy. There is an important need to define better antithrombotic prophylaxis for this frequently occurring subtype of ischemic stroke. (Stroke. 2017;48:867-872. DOI: 10.1161/STROKEAHA.116.016414.)

Key Words: diagnosis ■ embolism ■ prognosis ■ secondary prevention ■ stroke

In 2014, the clinical construct of “embolic stroke of undetermined source” (ESUS) was introduced to identify patients with nonlacunar cryptogenic ischemic strokes in whom embolism was the likely stroke mechanism.1 It was hypothesized that anticoagulants might be more efficacious than antiplatelet agents for secondary stroke prevention in ESUS patients. At the time of the original publication, little information was available to estimate the frequency of ESUS, patient features, or prognosis. Interest in ESUS has been fueled, in part, by 3 ongoing randomized trials comparing nonvitamin K antagonist direct-acting oral anticoagulants with aspirin for secondary stroke prevention.2-4

Here, we report the results of a systematic review of published studies about ESUS and summarize additional recent information relevant to the ESUS construct.

Methods

A PRISMA-guided systematic PubMed search strategy was initiated to identify the studies of interest (the last searched on December 6, 2016; Figure).5 We also performed a hand searching of bibliographies and citations of included studies. For the online search strategy, the terms (embolic stroke of unknown source OR ESUS) were combined with (embolic stroke OR cryptogenic stroke OR embolism), and results were restricted to those published since 2014. Two coauthors (R.G.H. and L.C.) independently reviewed articles that emerged from the searches for potential inclusion in review. Studies published in abstract only were not included. Discrepancies between the reviewers were resolved by consensus. Publications in any language were included if reporting new information based on the ESUS criteria proposed by the Cryptogenic Stroke/ESUS International Working Group (Table 1). One study reporting a highly selected ESUS cohort was not included,6 nor were 5 published case reports.7-11 Investigators of included studies were selectively contacted seeking additional data.12

Because ascertainment bias between different studies could potentially be more misleading than random error related to sample sizes, the pooled results are presented both as weighted (by numbers of patients) and unweighted (averaging values for each study) means.
of ESUS diagnosis, completeness of the diagnostic evaluation of patients with cryptogenic stroke required for ESUS diagnosis, treatment cross-overs, or numbers lost-to-follow-up.

Frequency of ESUS

We identified 12 studies that reported the frequency of ESUS as a fraction of all ischemic strokes, with prevalences ranging from 7% to 42% (Table 2).

In the 2 studies15,16 reporting the lowest frequencies, most patients with ischemic stroke did not undergo cardiac rhythm monitoring required for the diagnosis of ESUS; the study reporting the highest ESUS frequency17 was restricted to young patients with stroke (18–55 years). In the remaining 9 studies, the reported frequency of ESUS ranged from 9% to 25%,12–14,18–23 with both weighted and unweighted average frequencies of 17%. In 1 study involving 19 different countries, there was no observed difference in the frequency of ESUS across global regions.19

Patient Features of ESUS

Eight studies reported patient features of 2045 ESUS patients (Table 3). Pooling these studies, the mean age of ESUS patients was 65 years and 42% were women. ESUS patients were younger and with lower frequencies of conventional vascular risk factors than non-ESUS patients with ischemic stroke13,15,16; in 1 study, ESUS patients were significantly younger than other patients with ischemic stroke even after patients with atrial fibrillation were excluded.19 Three studies reported that patent foramen ovale was present in 25%,19 28%,25 and 58%22 of ESUS patients who underwent transesophageal echocardiography. The NIH Stroke Scale score near ESUS onset averaged 5 based on 4 studies involving 1772 ESUS patients (Table 3).

Prognosis of ESUS Patients

Five studies that included1605 ESUS patients provided data on the rate of recurrent stroke during follow-up of ESUS patients (Table 4). Most (86%) ESUS patients were treated with antiplatelet therapy during follow-up, and 13% were given oral anticoagulants. Incomplete reporting of lost-to-follow-up and unspecified selection for oral anticoagulant therapy confound available data; annualized recurrent stroke rates averaged 4.5% per year during a mean follow-up of 2.7 years (Table 4). ESUS patients had higher rates of stroke recurrence compared with non-ESUS patients in 2 studies.16,26 One study reported that atrial fibrillation was subsequently diagnosed in 29% of ESUS patients during 3.2 years of follow-up;13 in this study, for the diagnosis of ESUS, Holter ECG monitoring was used in 52% of ESUS patients and cardiac telemetry in most of the remainder.26,27

Additional Recent Information Relevant to the ESUS Construct or to Cryptogenic Stroke

On the basis of histopathologic analysis of specimens extracted by the endovascular treatment of acute stroke in ESUS patients, most thrombi were erythrocyte-rich (13%) or of mixed composition (80%), with platelet-rich thrombi in only 8%.28 In another study, thrombi extracted from ESUS patients more closely resembled cardioembolic clots versus noncardioembolic thrombi.29

In mid-2014, 2 high-quality studies reported that episodes (usually brief, lasting several minutes) of previously unrecognized atrial fibrillation could be detected in 10% to 20% of patients with cryptogenic ischemic stroke if the duration of cardiac monitoring was prolonged beyond 24 hours of Holter ECG monitoring.30,31 This has been confirmed by others,14,32,33 with the frequency of detection of atrial fibrillation directly related to the duration of cardiac rhythm monitoring. Stroke severity of ESUS patients who are later diagnosed with atrial fibrillation is similar to strokes in ESUS patients without atrial fibrillation.34

Left atrial myopathy/dysfunction unassociated with atrial fibrillation may be a cause of ESUS.35,36 Other studies have emphasized a relationship of nonstenotic cervical carotid artery
plagues with cryptogenic stroke and with ESUS. Wider availability of computed tomography imaging of the aortic arch allows assessment of aortic plaque without transesophageal echocardiography. There has been additional emphasis on occult cancer in patients with cryptogenic stroke.

**Discussion**

Methodological limitations in existing studies likely contributed to relatively wide ranges in the estimated frequencies of ESUS patients, their features, and prognosis. About 17% of patients with ischemic stroke met criteria for ESUS based on studies published to date, but this may be an underestimate because several diagnostic tests are required to make a diagnosis of ESUS, and there has been incomplete diagnostic evaluation in all studies reported to date. The different types and duration of cardiac rhythm monitoring undertaken in the available studies influenced the frequency of detection of covert paroxysmal atrial fibrillation (that excludes ESUS) and

<table>
<thead>
<tr>
<th>Table 2. Frequency of ESUS*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
</tr>
<tr>
<td><strong>Design</strong></td>
</tr>
<tr>
<td>Ntaios et al</td>
</tr>
<tr>
<td>Mahagne et al</td>
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<td>Li et al</td>
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<td>Putala et al</td>
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<td>Ladeira et al</td>
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<td>Takasugi et al</td>
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<td>Perera et al</td>
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<td>Montero et al</td>
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<td>Coutinho et al</td>
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<tr>
<td>Ueno et al</td>
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<tr>
<td>Masina et al</td>
</tr>
<tr>
<td>Arauz et al</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; ESUS, embolic stroke of undetermined source; f/up, follow-up; inpt, inpatient (ie, during hospitalization); NAVIGATE, New Approach Rivaroxaban Inhibition of Factor Xa in a Global trial vs ASA to Prevent Embolism in ESUS; NR, not reported; pts, patients; and TIA, transient ischemic attacks.

*ESUS criteria per Cryptogenic Stroke/ESUS International Working Group (Table 1) unless otherwise noted in the comments column.
†Additional unpublished information from Prof. M. Masina (personal communication).
likely contributed further to the range of reported prevalences of ESUS14 (Table 2).

It remains uncertain what fraction of ESUS patients will have atrial fibrillation detected during long-term follow-up, nor is the pathophysiological relationship between late detection of brief episodes of atrial fibrillation and ESUS adequately understood. It is unclear whether brief episodes of atrial fibrillation detected weeks or months after ESUS are

Table 3. Features of ESUS Patients*

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Mean age, y</th>
<th>Women, %</th>
<th>Median NIHSS Score</th>
<th>History of Hypertension, %</th>
<th>Diabetes Mellitus, %</th>
<th>PFO, %†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ntaios et al13</td>
<td>275</td>
<td>68</td>
<td>36</td>
<td>5</td>
<td>65</td>
<td>24</td>
<td>NR</td>
</tr>
<tr>
<td>Li et al15</td>
<td>189</td>
<td>65</td>
<td>47</td>
<td>4</td>
<td>47</td>
<td>12</td>
<td>NR</td>
</tr>
<tr>
<td>Putaala et al16</td>
<td>46</td>
<td>62</td>
<td>43</td>
<td>&lt;6</td>
<td>44</td>
<td>7</td>
<td>NR</td>
</tr>
<tr>
<td>Ntaios et al24‡</td>
<td>1095</td>
<td>68</td>
<td>41</td>
<td>5</td>
<td>60</td>
<td>20</td>
<td>NR</td>
</tr>
<tr>
<td>Perera et al19</td>
<td>351</td>
<td>62</td>
<td>43</td>
<td>4</td>
<td>64</td>
<td>25</td>
<td>25§</td>
</tr>
<tr>
<td>Ueno et al22</td>
<td>177</td>
<td>64</td>
<td>28</td>
<td>3</td>
<td>66</td>
<td>32</td>
<td>58</td>
</tr>
<tr>
<td>Masina et al11‡</td>
<td>84</td>
<td>73</td>
<td>52</td>
<td>NR</td>
<td>74</td>
<td>17</td>
<td>NR</td>
</tr>
<tr>
<td>Arauz et al1#</td>
<td>149</td>
<td>44</td>
<td>49</td>
<td>7</td>
<td>25</td>
<td>9</td>
<td>NR</td>
</tr>
<tr>
<td>Pooled – unweighted average‡</td>
<td>2045</td>
<td>63</td>
<td>43</td>
<td>5</td>
<td>56</td>
<td>19</td>
<td>…</td>
</tr>
<tr>
<td>Pooled – weighted average‡</td>
<td>2045</td>
<td>65</td>
<td>42</td>
<td>5</td>
<td>58</td>
<td>20</td>
<td>…</td>
</tr>
</tbody>
</table>

ESUS indicates embolic stroke of undetermined source; NIHSS, National Institutes of Health Stroke Scale; NR, not reported; and PFO, patent foramen ovale.
*ESUS criteria per Cryptogenic Stroke/ESUS International Working Group (Table 1)1 if not otherwise specified under comments in Table 2. Ladeira et al12 involving young ESUS patients not included.
†Patients from Ntaios et al13 and Putaala et al16 were included in Ntaios et al.24
§Of 123 ESUS patients undergoing transesophageal echocardiography.19
¶Katsanos et al25 reported PFO in 28% of 61 young ESUS patients who underwent transesophageal echocardiography.
‖Subgroup of 292 ESUS patients who underwent transesophageal echocardiography and had follow-up.
¶Additional unpublished information from Prof M. Masina (personal communication).
#Eighty-nine of the 149 ESUS patients included in Ntaios et al24 (A. Arauz, personal communication) and hence are double-counted.

Table 4. Prognosis of ESUS Patients*

<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>
</tr>
</thead>
<tbody>
<tr>
<td>Ntaios et al13,26‡</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>
</tr>
<tr>
<td>Li et al15</td>
<td>189 (1)</td>
<td>65</td>
<td>NR</td>
<td>NR</td>
<td>≈5%/y</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Putaala et al16‡</td>
<td>46 (1.8)</td>
<td>62</td>
<td>85% APT, 11% OAC</td>
<td>NR</td>
<td>5.1%/y</td>
<td>NR</td>
<td>1.3%/y</td>
</tr>
<tr>
<td>Ntaios et al24‡</td>
<td>1095 (3.0)</td>
<td>68</td>
<td>87% APT only, 12% OAC</td>
<td>NR</td>
<td>4.8%/y§</td>
<td>NR</td>
<td>4.5%/y</td>
</tr>
<tr>
<td>Masina et al13¶</td>
<td>84 (2.1)</td>
<td>73</td>
<td>99% APT</td>
<td>NR</td>
<td>2.3%/y</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ueno et al22‡</td>
<td>177 (3.5)</td>
<td>64</td>
<td>72% APT, 29% OAC</td>
<td>NR</td>
<td>3.9%/y</td>
<td>5.0%/y**</td>
<td>1.3%/y</td>
</tr>
<tr>
<td>Arauz et al1#</td>
<td>149 (2.3)</td>
<td>66</td>
<td>91% APT, 5% OAC</td>
<td>NR</td>
<td>2.3%/y</td>
<td>NR</td>
<td>0%/y</td>
</tr>
<tr>
<td>Pooled – unweighted average‡,††</td>
<td>1545 (2.4)</td>
<td>68</td>
<td>87% APT, 12% OAC</td>
<td>…</td>
<td>4.0%/y</td>
<td>…</td>
<td>2.9%/y</td>
</tr>
<tr>
<td>Pooled – weighted average‡,††</td>
<td>1605 (2.7)</td>
<td>65</td>
<td>86% APT, 13% OAC</td>
<td>…</td>
<td>4.5%/y</td>
<td>…</td>
<td>3.9%/y</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; APT, antiplatelet; Est, estimated; ESUS, embolic stroke of undetermined source; MI, myocardial infarction; NR, not reported; and OAC, oral anticoagulant.
*ESUS criteria per Cryptogenic Stroke/ESUS International Working Group (Table 1).1 See Table 2 for description of studies.
†Additionally, Mahagne et al14 reported AF identification in 2.1% and ischemia recurrence rate of 1.2% among 243 ESUS patients during a mean follow-up of 2.4 years, but no details about the study have been published.
‡Patients from Ntaios et al13 and Putaala et al16 were included in Ntaios et al.24
§Of recurrent stroke, MI, systemic embolism, ruptured aortic aneurysm, or sudden cardiac death.
¶Additional unpublished information from Prof M. Masina (personal communication).
#Subgroup of 292 ESUS patients who underwent transesophageal echocardiography and had follow-up.
**Included incident peripheral artery disease.
††Eighty-nine (60%) of the 149 ESUS patients included in Ntaios et al24 (A. Arauz, personal communication) and not included in unweighted analysis and adjusted for the weighted analysis.
relevant to stroke cause or identify patients who benefit from anticoagulation.

The mean age of ESUS patients (averaging 65 years) may reflect incomplete diagnostic investigation of older patients with stroke that permit the diagnosis of ESUS.41 This with caveat, the picture of ESUS patients that emerged is of relatively young (compared with atrial fibrillation-associated stroke) patients with mild strokes and with lower frequencies of conventional vascular risk factors compared with non-ESUS patients with ischemic stroke. We speculate that ESUS is usually caused by relatively smaller emboli from valvular and arterial sources rather than larger emboli originating in the cardiac chambers, notably left atrial appendage thrombi in patients with atrial fibrillation that embolize to cause large, devastating strokes.42 Most minor risk emboli sources hypothesized to underlie most ESUS typically produce small emboli.1

Recurrent stroke during follow-up averaged 4.5% per year (Table 4), but this estimate is based on patient cohorts dating back to 199223 and limited by the retrospective design of available studies. Concomitant therapies have evolved, and stroke rates in secondary prevention trials have consistently declined during the past 25 years. Consequently, this estimate of stroke recurrence rate in ESUS patients may be an overestimate. However, ESUS patient features as characterized in this analysis resemble those of participants in 2 clinical trials who had recurrent stroke rates of 7% to 11% within 3 months after an index minor ischemic stroke when treated with aspirin.43,44 It is likely that absolute rates of recurrent stroke will differ among subgroups of ESUS patients according to patient age and comorbidities. Furthermore, it is currently unknown whether the stroke recurrence risk is particularly high in the initial weeks after an ESUS, and this, too, may vary with the presumed ESUS source (ie, PFO-associated ESUS versus aortic arch plaque-associated ESUS).

That most cryptogenic ischemic strokes are embolic is not a new concept.55-56 However, there has been little progress in the secondary prevention for most patients with cryptogenic ischemic stroke in recent decades. The ESUS construct, a repackaging of nonlacunar cryptogenic stroke, was developed to identify patients with cryptogenic stroke in whom the underlying mechanism is likely thromboembolic and to facilitate the design of randomized trials. Available evidence supports that ESUS comprises about 1 ischemic stroke in 6, and that these relatively young patients with stroke have a substantial risk of recurrent stroke during antiplatelet therapy. Doubts have been expressed about the value of the ESUS as a therapeutic target, particularly because of the heterogeneity of the occult embolic sources.25,47,48 Clinical trials comparing oral anticoagulants with aspirin in ESUS patients are ongoing with results anticipated in 2018.

Acknowledgments
We are grateful to Dr M. Masina for kindly providing unpublished data.

Disclosures
All coauthors except Dr Catanese have received financial remuneration from Bayer AG for their participation in the NAVIGATE ESUS trial; In addition, Dr Ntaios has received speaker fees from Boehringer-Ingelheim, Bayer AG, and BMS/Pfizer and a research grant from Pfizer, and he is an advisory board member for Boehringer-Ingelheim. The other authors report no conflicts.

References
Predictors of finding occult atrial fibrillation after cryptogenic stroke.


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