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

George Ntaios, MD; Vasileios Papavasileiou, MD; Haralampos Milionis, MD; Konstantinos Makaritsis, MD; Anastasia Vemmou, MD; Eleni Koroboki, MD; Efstathios Manios, MD; Konstantinos Spengos, MD; Patrik Michel, MD; Konstantinos Vemmos, MD

Background and Purpose—Information about outcomes in Embolic Stroke of Undetermined Source (ESUS) patients is unavailable. This study provides a detailed analysis of outcomes of a large ESUS population.

Methods—Data set was derived from the Athens Stroke Registry. ESUS was defined according to the Cryptogenic Stroke/ESUS International Working Group criteria. End points were mortality, stroke recurrence, functional outcome, and a composite cardiovascular end point comprising recurrent stroke, myocardial infarction, aortic aneurysm rupture, systemic embolism, or sudden cardiac death. We performed Kaplan–Meier analyses to estimate cumulative probabilities of outcomes by stroke type and Cox-regression to investigate whether stroke type was outcome predictor.

Results—2731 patients were followed-up for a mean of 30.5±24.1 months. There were 73 (26.5%) deaths, 60 (21.8%) recurrences, and 78 (28.4%) composite cardiovascular end points in the 275 ESUS patients. The cumulative probability of survival in ESUS was 65.6% (95% confidence intervals [CI], 58.9%–72.2%), significantly higher compared with cardioembolic stroke (38.8%, 95% CI, 34.9%–42.7%). The cumulative probability of stroke recurrence in ESUS was 29.0% (95% CI, 22.3%–35.7%), similar to cardioembolic strokes (26.8%, 95% CI, 22.1%–31.5%), but significantly higher compared with all types of noncardioembolic stroke. One hundred seventy-two (62.5%) ESUS patients had favorable functional outcome compared with 280 (32.2%) in cardioembolic and 303 (60.9%) in large-artery atherosclerotic. ESUS patients had similar risk of composite cardiovascular end point as all other stroke types, with the exception of lacunar strokes, which had significantly lower risk (adjusted hazard ratio, 0.70 [95% CI, 0.52–0.94]).

Conclusions—Long-term mortality risk in ESUS is lower compared with cardioembolic strokes, despite similar rates of recurrence and composite cardiovascular end point. Recurrent stroke risk is higher in ESUS than in noncardioembolic strokes. (Stroke. 2015;46:2087-2093. DOI: 10.1161/STROKEAHA.115.009334.)

Key Words: embolic stroke of undetermined source ■ ESUS ■ mortality ■ outcome ■ stroke recurrence
ESUS patients, this antithrombotic strategy might be suboptimal, which in turn could have important consequences on their outcome. Therefore, information about outcomes in this patient group would be valuable; unfortunately, no such data are currently available for patients with ESUS because this is defined by the Cryptogenic Stroke/ESUS International Working Group.1

The aim of the present study is to provide a detailed analysis of outcomes of a large ESUS population derived from a large prospective stroke registry during a long follow-up period.

Methods

Study Population and Definitions

The study population was derived from the Athens Stroke Registry, which includes all consecutive patients with an acute first-ever ischemic stroke admitted in Alexandra University Hospital, Athens, Greece, between June 1992 and December 2011.7 Patients with recurrent stroke have not been included in the registry. The scientific use of the data collected in the Athens Stroke Registry was approved by the local Ethics Committee.

The methodology followed to register data in the Athens Stroke Registry was described elsewhere.4 With regard to AF detection, all patients had a 12-lead ECG at admission. In patients on sinus rhythm, AF paroxysms were sought by (1) repeated ECGs during hospital stay, (2) continuous ECG monitoring for 1 week or until discharge for patients treated in the acute stroke unit; ECG was observed by trained nurse personnel and intermittently analyzed by the treating physician, and (3) 24-hour Holter ambulatory ECG monitoring in cases that AF was strongly suspected from the clinical presentation and brain imaging findings (eg, multilobar infarcts, strokes presenting with maximum severity at onset, largely dilated left atrium), and a and b were negative.

ESUS was defined according to the criteria proposed by the Cryptogenic Stroke/ESUS International Working Group as a visualized nonlacunar brain infarct in the absence of (1) extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischemia, (2) major-risk cardioembolic source, and (3) any other specific cause of stroke (eg, arteritis, dissection, intracranial anatomic site or vascular territory different from that of the index event, was mandatory to support the diagnosis of recurrent stroke during the first 3 weeks after stroke onset to ensure that systemic causes of clinical deterioration after an initial stroke (eg, hypoxia, hypotension, hyperglycemia, infection) and worsening of symptoms because of progression of the initial stroke were not misclassified as a recurrent cerebrovascular event. To determine the occurrence of recurrent ischemic stroke or intracerebral hemorrhage, we evaluated all the available information obtained from death certificates, hospital records, physicians’ notes in private practice, necropsy findings, and the patients’ clinical presentation at the regular follow-up assessments.

The time of initial stroke was the inception of follow-up. Patients were prospectively followed-up at 1, 3, and 6 months after discharge and yearly thereafter. Follow-up was routinely performed in the outpatient clinic. In case of patients with severe handicap, clinical follow-up was assessed at patient’s residence or by telephone interview. Lost-to-follow-up was defined as inability to reach the patient or the patient’s proxies at a scheduled time point.

Statistical Analysis

Continuous data are summarized as mean value and standard deviation and categorical data as absolute numbers and proportion. For patients lost during follow-up, survival data were censored at the last time known to be alive. Patients who experienced >1 composite vascular event during the follow-up period were censored at the time of the first event. The Kaplan–Meier product limit method was used to estimate the cumulative probability of each outcome by stroke type (ie, ESUS, cardioembolic, large-artery atherosclerotic, lacunar, undetermined other than ESUS, and miscellaneous). Differences in Kaplan–Meier curves were evaluated with the log-rank test. Univariate and multivariate Cox regression analyses were performed to investigate whether stroke type was a predictor of outcomes. The covariates entered in the analyses included age, sex, stroke severity (evaluated by the national Institute of Health Stroke Scale [NIHSS] score), stroke type (as described earlier), cardiovascular risk factors and comorbidities (history of hypertension, diabetes mellitus, smoking, dyslipidemia, heart failure, coronary artery disease, atrial fibrillation, admission blood pressure, and glucose), and in-hospital treatment (thrombolysis, antiplatelet therapy). Factors that were significant in the univariate analyses were included in the multivariate Cox model. For the univariate analysis, the level of significance was set at 10% to reduce the risk of a type II error. In the final multivariate analyses, the level of significance was set at 5%. Associations are presented as hazard ratios with their corresponding 95% confidence intervals (95% CI) using the ESUS type as the comparator. Statistical analyses were performed with the Statistical Package for Social Science (SPSS Inc, version 17.0 for Windows, Chicago, IL).

Results

Among 2731 patients admitted between June 1992 and December 2011 and included in this analysis, 275 patients (10.0%) were classified as ESUS. The baseline characteristics of these patients, as well as their diagnostic investigation, pattern of symptomatology, arterial territory of the ischemic lesion, and the potential underlying causes have been described in detail elsewhere and are provided as supplemental files (Table I and Figure I in the online-only Data Supplement).
All patients had a CT at admission; 1401 (51.3%) patients had a second CT at 7 to 10 days, 729 (26.7%) had an MRI, and 208 (7.6%) had both a second CT and an MRI. From the 264 ESUS patients alive at discharge, the majority (n=194, 73.5%) were treated with an antipla telet, 44 (16.7%) were treated with anticoagulant, 14 (5.3%) were treated with a combination of antipla telet and anticoagulant, and 12 (4.5%) were not treated with an antithrombotic.

Fifty-nine (2.16%) patients were lost-to-follow-up immediately after hospital discharge. 248 (9.1%) were lost-to-follow-up at some point during their follow-up (ie, between 3 and 57 months). The mean follow-up of the overall and the ESUS populations were 30.5±24.1 and 38.7±22.1 months corresponding to 83295 and 10642 patient-years, respectively.

There were 890 (32.6%) deaths in the overall population during the follow-up corresponding to 12.8 deaths per 100 patient-years. In particular, there were 73 (26.5%) deaths in the ESUS group (8.2 deaths per 100 patient-years), 449 (51.6%) in cardioembolic (27 deaths per 100 patient-years), 106 (21.3%) in large-artery atherosclerotic (7.0 deaths per 100 patient-years), 78 (12.5%) in lacunar (4.1 deaths per 100 patient-years), 159 (43.4%) in undetermined stroke other than ESUS (22.0 deaths per 100 patient-years), and 25 (25%) in patients with miscellaneous causes of stroke (8.7 deaths per 100 patient-years). The cumulative probability of survival in the ESUS group was 65.6% (95% CI, 58.9%–72.2%) which was significantly higher compared with the cumulative probability in patients with cardioembolic stroke (38.8%, 95% CI, 34.9%–42.7%) and undetermined stroke other than ESUS (46.4%, 95% CI, 40.1%–52.7%), similar to the large-artery atherosclerotic group (72.8%, 95% CI, 68.3%–77.3%) and significantly lower compared with the lacunar group (81.0%, 95% CI, 77.1%–84.9%; Table, Figure 1A). In the Cox-regression analysis, there was significantly higher mortality risk in patients with cardioembolic stroke (adjusted hazard ratios, 1.67 [95% CI, 1.29–2.15], P<0.01) and in patients with undetermined stroke other than ESUS (adjusted hazard ratios, 1.87 [95% CI, 1.41–2.48], P<0.01) compared with ESUS (Figure 2).

There were 364 (13.3%) stroke recurrences in the overall population during the follow-up corresponding to 5.2 per 100 patient-years, of which there were 164 (45%) confirmed ischemic strokes and 9 (2.5%) confirmed hemorrhagic strokes, whereas for the rest 191 (52.5%), the stroke type was unknown. In particular, there were 60 (21.8%) recurrences in the ESUS group (6.8 per 100 patient-years), 117 (13.5%) in cardioembolic (7.0 per 100 patient-years), 83 (13.3%) in lacunar (4.4 per 100 patient-years), 65 (13.1%) in large-artery atherosclerotic (4.3 per 100 patient-years), 38 (10.4%) in undetermined stroke other than ESUS (5.3 per 100 patient-years), and 1 (1.0%) in patients with miscellaneous causes of stroke (0.3 per 100 patient-years). The cumulative probability of stroke recurrence in ESUS patients was 29.0% (95% CI, 22.3%–35.7%), which was similar to patients with cardioembolic stroke (26.8%, 95% CI, 22.1%–31.5%; Table, Figure 1B). In the Cox-regression analysis, ESUS patients had significantly higher risk of recurrence compared with all other stroke types, with the exception of cardioembolic strokes where a strong but statistically not significant trend was identified (Figure 2).

At the end of follow-up, 172 (62.5%) ESUS patients had favorable functional outcome compared with 280 (32.2%) in cardioembolic, 303 (60.9%) in large-artery atherosclerotic, 516 (82.2%) in lacunar, 151 (41.2%) in undetermined other than ESUS, and 71 (69.6%) in miscellaneous strokes. The distribution of functional outcome across the modified Rankin Scale in the different stroke types is presented in Figure 3.

There were 597 (21.9%) composite cardiovascular events in the overall population during the follow-up corresponding to 8.6 events per 100 patient-years. In particular, there were 80 (29.1%) events in the ESUS group (9.0 per 100 patient-years), 192 (22.1%) in cardioembolic (11.6 per 100 patient-years), 123 (19.8%) in lacunar (6.5 per 100 patient-years), 111 (22.3%) in atherosclerotic (7.3 per 100 patient-years), 73 (19.9%) in undetermined other than ESUS (10.1 per 100 patient-years), and 18 (17.6%) in patients with miscellaneous causes of stroke (6.3 per 100 patient-years). The cumulative probability of the composite cardiovascular event was similar across different stroke types (Table, Figure 1C). In the Cox-regression analysis, ESUS patients had similar risk of the composite cardiovascular event with all other stroke types, with the exception of patients with lacunar strokes who had significantly lower risk (adjusted hazard ratios 0.70 [95% CI, 0.52–0.94], P<0.05; Figure 2).

Discussion
This is the first description of long-term outcomes of a large ESUS population defined according to the criteria proposed.

Table. Cumulative 5-Year Probabilities of Survival, Stroke Recurrence, and Composite Cardiovascular Event

<table>
<thead>
<tr>
<th>Event</th>
<th>ESUS (n=275)</th>
<th>Cardioembolic (n=869)</th>
<th>Large-Artery Atherosclerotic (n=497)</th>
<th>Lacunar (n=622)</th>
<th>Undetermined Other Than ESUS (n=366)</th>
<th>Miscellaneous (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Survival</strong></td>
<td></td>
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</tr>
<tr>
<td>Cumulative probability</td>
<td>65.6%</td>
<td>38.8%</td>
<td>72.8%</td>
<td>81.0%</td>
<td>46.4%</td>
<td>66.9%</td>
</tr>
<tr>
<td>95% confidence intervals</td>
<td>58.9%–72.2%</td>
<td>34.9%–42.7%</td>
<td>68.3%–77.3%</td>
<td>77.1%–84.9%</td>
<td>40.1%–52.7%</td>
<td>55.7%–78.1%</td>
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<tr>
<td><strong>Stroke recurrence</strong></td>
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<tr>
<td>Cumulative probability</td>
<td>29.0%</td>
<td>26.8%</td>
<td>17.1%</td>
<td>18.9%</td>
<td>15.9%</td>
<td>1.3%</td>
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<tr>
<td>95% confidence intervals</td>
<td>22.3%–35.7%</td>
<td>22.1%–31.5%</td>
<td>13.2%–21.0%</td>
<td>14.2%–23.6%</td>
<td>10.8%–21.0%</td>
<td>0%–3.9%</td>
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<tr>
<td><strong>Composite cardiovascular event</strong></td>
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<tr>
<td>Cumulative probability</td>
<td>38.1%</td>
<td>38.2%</td>
<td>29.8%</td>
<td>28.2%</td>
<td>29.0%</td>
<td>24.3%</td>
</tr>
<tr>
<td>95% confidence intervals</td>
<td>31.1%–45.2%</td>
<td>33.3%–43.1%</td>
<td>24.9%–34.7%</td>
<td>23.7%–32.7%</td>
<td>22.7%–35.3%</td>
<td>13.3%–35.1%</td>
</tr>
</tbody>
</table>
recently by the Cryptogenic Stroke/ESUS International Working Group.\(^1\) Mortality in ESUS patients was lower compared with patients with cardioembolic stroke and patients with undetermined stroke other than ESUS, but similar to patients with lacunar or large-artery atherosclerotic stroke. Functional outcome in ESUS patients was similar to large-artery atherosclerotic and better than in patients with cardioembolic. Stroke recurrence in ESUS was higher compared with all other stroke types, with the exception of cardioembolic strokes where a strong but statistically not significant trend was identified. The risk of composite cardiovascular event was similar to all other stroke types, with the exception of patients with lacunar strokes who had significantly lower risk.

Mortality was significantly higher in patients with cardioembolic stroke compared with ESUS patients. The fact that the risks of stroke recurrence and composite cardiovascular event were similar in these 2 groups shows that the difference in mortality was not driven by the rate of vascular events which occurred during follow-up. A more plausible explanation is that the difference in mortality was the result of different characteristics of the recurrent strokes between the 2 groups, that is, recurrent strokes may have been more severe or may have occurred in older age in patients with cardioembolic index stroke compared with patients with ESUS index stroke. This may be hypothesized based on the similar finding when comparing the severity of the index strokes: as we showed previously, the index stroke in patients with cardioembolic stroke was of higher severity (NIHSS, 13 versus 5) and occurred in older patients (76 versus 68 years) compared with ESUS.\(^4\) NIHSS and age are 2 important predictors of functional outcome\(^10,11\) and mortality,\(^12\) and if our

Figure 1. Cumulative probability of survival (A), stroke recurrence (B), and composite cardiovascular event (C) by stroke type. ESUS indicates embolic stroke of undetermined source.
hypothesis is correct, they could possibly explain the difference in mortality and functional outcome between ESUS and cardioembolic strokes. A similar explanation could perhaps explain also the difference in functional outcome between ESUS and cardioembolic strokes. Unfortunately, we do not have data about the severity of the recurrent strokes to confirm this hypothesis.

Covert AF was the potential etiopathogenetic mechanism in ≈44% of our ESUS patients. The vast majority of these patients was treated with an antiplatelet rather than an anticoagulant for secondary stroke prevention, that is, was inadequately treated given that anticoagulants are more efficacious than antiplatelets in patients with AF-related stroke. This seems to be the most plausible explanation for the finding of the present study that the risk of stroke recurrence was higher in ESUS patients compared with noncardioembolic stroke types. In addition, these results emphasize further the need for prolonged monitoring of heart rhythm in patients with cryptogenic stroke (as shown recently in the 30-Day
Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event study [EMBRACE] and in the Study of Continuous Cardiac Monitoring to Assess Atrial Fibrillation After Cryptogenic Stroke [CRYSTAL-AF]. Also, our results seem to provide further support to the rationale of the randomized controlled trials of anticoagulants in ESUS patients (like the recently announced Randomized Evaluation in Secondary Stroke Prevention Comparing the Thrombin Inhibitor Dabigatran Etxeilate Versus Aspirin in Embolic Stroke of Undetermined Source [RE-SPECT ESUS]3 and Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source [NA VIGATE ESUS]2 trials). The main strengths of this first description of vascular outcomes of an ESUS population are the large size of the study population involving consecutive patients, the long follow-up, the assessment of hard clinical end points, including mortality and stroke recurrence, and the definition of ESUS according to the criteria proposed by the Cryptogenic Stroke/ESUS International Working Group.1

Nonetheless, this study is characterized by the inherent limitations of any retrospective analysis of prospectively collected data, such as collection and registration bias. Also, it is a single-center study which may have introduced selection bias. In addition, other potential confounders were not systematically assessed, such as crossover treatment allocations, adherence to antiplatelet, antihypertensive, and lipid-lowering drugs, and efficiency of antiagulation in patients treated with vitamin K antagonists. In addition, continuous ECG monitoring was not automated, and it is possible that some AFs may have been missed. Also, the proportion of ESUS might have been larger if further work-up were performed in patients with cryptogenic strokes because of incomplete investigations. Finally, in approximately half of stroke recurrences, we were not able to classify whether the event was ischemic or hemorrhagic.

ESUS is a recent clinical entity1 and further research is warranted to implement it in clinical practice; the RE-SPECT-ESUS3 and NAVIGATE ESUS2 trials aim to identify the optimal antithrombotic treatment in this population. Also, it would be clinically useful to identify the predictors of covert AF in the ESUS population because this would obviously influence the choice of antithrombotic treatment. In addition, the prognostic validity of stroke prognostication scores like the ASTRAL score,10 the CHADS2 score,16,17 and the CHA2DS2-VASc score18,19 needs to be confirmed in the ESUS population. Also, it would be interesting to see whether outcomes differ between AF-related and non-AF related ESUS patients.

In conclusion, the mortality risk in ESUS patients is lower compared with patients with cardioembolic stroke despite similar rates of stroke recurrence and composite cardiovascular events. Also, the risk of stroke recurrence is higher in ESUS patients than in patients with noncardioembolic strokes, which could be a sign that the current antithrombotic strategy of treating ESUS patients with antiplatelets is suboptimal. In any case, the current findings suggest that ESUS patients are heterogeneous, requiring ongoing monitoring for stroke causes, risk factors, and preventive strategies.

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Disclosures
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References
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Supplemental Table I: Baseline characteristics of patients with ESUS and other types of ischaemic stroke.

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<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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<td><strong>Demographics</strong></td>
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<tr>
<td>Female gender</td>
<td>99 (36.0%)</td>
<td>114 (22.9%)</td>
<td>461 (53.0%)</td>
<td>173 (27.8%)</td>
<td>166 (45.4%)</td>
<td>49 (48.0%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>68.0 (58.0-76.0)</td>
<td>67.0 (60.0-73.0)</td>
<td>76.0 (70.0-82.0)</td>
<td>69.0 (60.0-75.0)</td>
<td>74.0 (67.0-81.0)</td>
<td>56.0 (43.0-74.0)</td>
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<td><strong>Comorbidities – risk factors</strong></td>
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<td>Hypertension</td>
<td>178 (64.7%)</td>
<td>382 (76.9%)</td>
<td>631 (72.6%)</td>
<td>518 (83.3%)</td>
<td>259 (70.8%)</td>
<td>50 (49.0%)</td>
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<td>Diabetes mellitus</td>
<td>65 (23.6%)</td>
<td>163 (32.8%)</td>
<td>192 (22.1%)</td>
<td>181 (29.1%)</td>
<td>115 (31.4%)</td>
<td>17 (16.7%)</td>
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<tr>
<td>Smoking</td>
<td>83 (30.2%)</td>
<td>251 (50.5%)</td>
<td>157 (18.1%)</td>
<td>235 (37.8%)</td>
<td>111 (30.3%)</td>
<td>39 (38.2%)</td>
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<tr>
<td>Previous TIA</td>
<td>27 (9.8%)</td>
<td>102 (20.5%)</td>
<td>53 (6.1%)</td>
<td>59 (9.5%)</td>
<td>39 (10.7%)</td>
<td>17 (16.7%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>22 (8.0%)</td>
<td>23 (4.6%)</td>
<td>139 (16.0%)</td>
<td>15 (2.4%)</td>
<td>31 (8.5%)</td>
<td>10 (9.8%)</td>
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<tr>
<td>Dyslipidemia</td>
<td>140 (50.9%)</td>
<td>273 (55.3%)</td>
<td>266 (30.7%)</td>
<td>306 (49.4%)</td>
<td>159 (43.6%)</td>
<td>40 (39.2%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>65 (23.7%)</td>
<td>132 (26.8%)</td>
<td>169 (19.5%)</td>
<td>84 (13.6%)</td>
<td>86 (23.7%)</td>
<td>16 (15.7%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0 (0.0%)</td>
<td>21 (4.2%)</td>
<td>774 (89.1%)</td>
<td>36 (5.8%)</td>
<td>41 (11.2%)</td>
<td>0 (0.0%)</td>
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<tr>
<td><strong>Pattern of presentation</strong></td>
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<td><strong>Mode of onset</strong></td>
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<tr>
<td>Maximal at onset</td>
<td>204 (74.2%)</td>
<td>255 (51.3%)</td>
<td>713 (82.1%)</td>
<td>290 (46.6%)</td>
<td>219 (59.8%)</td>
<td>58 (56.9%)</td>
</tr>
<tr>
<td>Gradual worsening</td>
<td>37 (13.5%)</td>
<td>112 (22.5%)</td>
<td>82 (9.4%)</td>
<td>99 (16.0%)</td>
<td>62 (16.9%)</td>
<td>15 (14.7%)</td>
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<tr>
<td>Shuttering/Stepwise</td>
<td>15 (5.5%)</td>
<td>66 (13.3%)</td>
<td>24 (2.8%)</td>
<td>132 (21.3%)</td>
<td>25 (6.8%)</td>
<td>9 (8.8%)</td>
</tr>
<tr>
<td>Fluctuating</td>
<td>4 (1.5%)</td>
<td>23 (4.6%)</td>
<td>10 (1.2%)</td>
<td>40 (6.5%)</td>
<td>11 (3.0%)</td>
<td>8 (7.8%)</td>
</tr>
<tr>
<td>Unknown or missing data</td>
<td>15 (5.5%)</td>
<td>41 (8.2%)</td>
<td>39 (4.5%)</td>
<td>59 (9.5%)</td>
<td>49 (13.4%)</td>
<td>12 (11.8%)</td>
</tr>
<tr>
<td><strong>Time of onset</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During sleep</td>
<td>48 (17.5%)</td>
<td>108 (21.7%)</td>
<td>155 (17.8%)</td>
<td>209 (33.6%)</td>
<td>77 (21.0%)</td>
<td>17 (16.7%)</td>
</tr>
<tr>
<td>1-2h after awakening</td>
<td>57 (20.7%)</td>
<td>86 (17.3%)</td>
<td>187 (21.5%)</td>
<td>70 (11.3%)</td>
<td>69 (18.9%)</td>
<td>10 (9.8%)</td>
</tr>
<tr>
<td>During usual activity</td>
<td>141 (51.3%)</td>
<td>249 (50.1%)</td>
<td>420 (48.3%)</td>
<td>281 (45.2%)</td>
<td>167 (45.6%)</td>
<td>48 (47.1%)</td>
</tr>
<tr>
<td>During stress</td>
<td>12 (4.4%)</td>
<td>21 (4.2%)</td>
<td>30 (3.5%)</td>
<td>23 (3.7%)</td>
<td>6 (1.6%)</td>
<td>10 (9.8%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>14 (5.1%)</td>
<td>29 (5.8%)</td>
<td>57 (6.6%)</td>
<td>38 (6.1%)</td>
<td>38 (10.4%)</td>
<td>8 (7.8%)</td>
</tr>
</tbody>
</table>
During hospitalization for other reason | 3 (1.1%) | 4 (0.8%) | 20 (2.3%) | 1 (0.2%) | 9 (2.5%) | 9 (8.8%)

### Clinical and laboratory values

**Systolic blood pressure (mmHg)**
- 150 (130-160)
- 150 (140-170)
- 150 (130-170)
- 160 (140-180)
- 150 (135-170)
- 140 (120-150)

**Diastolic blood pressure (mmHg)**
- 85 (80-90)
- 90 (80-90)
- 85 (80-90)
- 90 (80-100)
- 84 (80-90)
- 80 (70-90)

**Glucose (mg/dL)**
- 109 (93-141)
- 111 (95-154)
- 118 (98-153)
- 105 (92-139)
- 116 (98-163)
- 100 (90-125)

**NIHSS score**
- 5 (2-14)
- 5 (2-15)
- 13 (4-22)
- 2 (1-4)
- 8 (3-18)
- 4 (1-12)

### Etiologic work-up

<table>
<thead>
<tr>
<th>Etiologic work-up</th>
<th>195 (70.9%)</th>
<th>276 (55.5%)</th>
<th>564 (64.9%)</th>
<th>289 (46.5%)</th>
<th>187 (51.1%)</th>
<th>55 (53.9%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous ECG monitoring in the stroke unit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hours Ambulatory Holter Monitoring</td>
<td>142 (51.6%)</td>
<td>26 (5.2%)</td>
<td>56 (6.4%)</td>
<td>17 (2.7%)</td>
<td>40 (10.9%)</td>
<td>24 (23.5%)</td>
</tr>
<tr>
<td>No rhythm monitoring modality other than admission ECG</td>
<td>0 (0.0%)</td>
<td>206 (41.4%)</td>
<td>296 (34.1%)</td>
<td>322 (51.8%)</td>
<td>156 (42.6%)</td>
<td>30 (29.4%)</td>
</tr>
<tr>
<td>Transthoracic echocardiography</td>
<td>247 (89.8%)</td>
<td>221 (44.5%)</td>
<td>365 (42.0%)</td>
<td>277 (44.5%)</td>
<td>123 (33.6%)</td>
<td>67 (65.7%)</td>
</tr>
<tr>
<td>Transesophageal echocardiography</td>
<td>83 (30.2%)</td>
<td>22 (4.4%)</td>
<td>83 (9.6%)</td>
<td>20 (3.2%)</td>
<td>16 (4.4%)</td>
<td>12 (11.8%)</td>
</tr>
<tr>
<td>Any angiography (CT or MR or digital)**</td>
<td>239 (86.9%)</td>
<td>323 (65.0%)</td>
<td>53 (6.1%)</td>
<td>150 (24.1%)</td>
<td>33 (9.0%)</td>
<td>50 (49.0%)</td>
</tr>
<tr>
<td>Cervical artery ultrasound</td>
<td>252 (91.6%)</td>
<td>465 (93.6%)</td>
<td>376 (43.3%)</td>
<td>516 (83.0%)</td>
<td>177 (48.4%)</td>
<td>80 (78.4%)</td>
</tr>
<tr>
<td>No cervical artery imaging</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>481 (55.4%)</td>
<td>92 (14.8%)</td>
<td>186 (50.8%)</td>
<td>15 (14.7%)</td>
</tr>
</tbody>
</table>


Continuous variables are presented as median ± interquartile range.

Nominal variables are presented as absolute number and percent (percent refers to recorded values only; missing values have been excluded).

*(i.e ≥2 causes or incomplete evaluation)*

**: refers to both intracranial and extracranial imaging
Patients with acute first-ever ischaemic stroke, n=2735

- Patients with missing data, n=4

n=2731

- Patients with lacunar stroke detected by CT or MRI, n=622

n=2109

- Presence of extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischaemia, n=497

n=1612

- Major-risk cardioembolic source of embolism, n=869

n=743

- Other/rare specific causes, n=102

n=641

- Incomplete diagnostic work-up (or ≥2 causes identified) or non-visualized infarct, 366

Patients with embolic stroke of undetermined source (ESUS), n=275

Supplemental figure I: Flow diagram of the study.
背景および目的：脳卒中の原因が不明の脳卒中（Embolic Stroke of Undetermined Source：ESUS）患者の転帰に関する情報はまだ得られていない。本研究では、大規模なESUS集団の転帰について詳細な分類分析を行った。

方法：データセットは、Athens Stroke Registryから得た。ESUSの定義は、Cryptogenic Stroke／ESUS International Working Groupの基準に基づいた。評価項目は、死亡率、脳卒中再発、機能転帰、および複合心血管系評価項目（脳卒中再発、筋肉発症、大動脈硬化症、全身性塩基症。もしくは心臓突然死を含む）。Kaplan-Meier解析で脳卒中のタイプ別の転帰の累積確率を推測し、Cox回帰分析で脳卒中のタイプが転帰の予測因子となるか否かを調べた。

結果：2,731例の患者24.1カ月間の追跡調査した。ESUS患者275例のうち、死亡数は73例（26.5%）、脳卒中再発60例（21.8%）、複合心血管系評価項目のイベントの発現数は78例（28.4%）であった。ESUS患者の生存累積確率は65.6%（95%信頼区間[CI]：58.9%～72.2%）で、心原性脳卒中患者（38.8%、95% CI：34.9%～42.7%）と比較して有意に高かった。ESUS患者の脳卒中再発の累積確率は29.0%（95% CI：22.3%～35.7%）で心原性脳卒中患者（26.8%、95% CI：22.1%～31.5%）と同様であったが、そのタイプの非心原性脳卒中よりも有意に高かった。機能転帰が良好であったのは、ESUS患者は127例（62.5%）、心原性脳卒中患者280例（32.2%）、大動脈のアテローム性動脈硬化症患者は303例（60.9%）であった。ESUS患者の複合心血管評価項目のリスクを有意なリスク低下[調整ハザード比：0.70（95% CI：0.52～0.94）]を示したラクナ梗塞以外のタイプの脳卒中患者と類似していた。

結論：ESUS患者と心原性脳卒中患者では再発率や複合心血管系評価項目は類似していたが、長期的な死亡リスクはESUS患者の方が低かった。脳卒中再発リスクは非心原性脳卒中患者よりESUS患者の方が高かった。
Abstract 7

아테네 뇌졸중 등록체계에서 원인불명 색전뇌졸중
결과 분석

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

George Ntaios, MD; Vasileios Papavasileiou, MD; Haralampos Milionis, MD; Konstantinos Makaritsis, MD; Anastasia Vemmou, MD; Eleni Koroboki, MD; Efstathios Manios, MD; Konstantinos Spengos, MD; Patrik Michel, MD; Konstantinos Vemmos, MD

(Stroke. 2015;46:2087-2093.)

Key Words: embolic stroke of undetermined source ■ ESUS ■ mortality ■ outcome ■ stroke recurrence

배경과 목적
원인불명 색전뇌졸중(embolic stroke of undetermined source, ESUS) 환자의 임상적 결과에 대한 자료는 충분하지 않다. 이 연구는 대규모의 ESUS 환자를 대상으로 하여, 임상적 결과에 대한 자세한 분석을 시행하였다.

방법
아테네 뇌졸중 등록체계를 통하여 데이터 세트를 도출하였다. ESUS는 Cryptogenic Stroke/ESUS International Working Group 기준에 의거하여 정의되었다. 결과 변수는 사망, 뇌졸중 재발, 기능적 회복 및 전체 심혈관계 질환(뇌졸중 재발, 심근경색, 대동맥류 파열, 전신색전 혹은 갑작스러운 심장사)이었다. 저자들은 카플란-마이어 분석을 통해 뇌졸중의 아형에 따른 결과 변수의 누적 확률을 추정하였으며, 뇌졸중의 아형이 결과 변수의 발생에 영향을 미치는지를 콕스 회귀모델로 분석하였다.

결과
총 2731명의 환자를 평균 30.5±24.1개월 동안 추적관찰하였다. 그 중 275명의 ESUS 환자 가운데 73건(26.5%)의 사망, 60건 (21.8%)의 뇌졸중 재발 및 78건 (28.4%)의 전체 심혈관계 질환이 발생하였다. ESUS 환자에서 생존의 누적 확률은 65.6% (95% 신뢰 구간[confidence interval, CI], 58.9%-72.2%)이었으며, 이는 심장색전증 환자(38.8%, 95% CI 22.3%-35.7%)에 비하여 월등히 높았다. ESUS 환자에서 뇌졸중 재발의 누적 확률은 29.0% (95% CI, 22.3%-35.7%)였으며, 이는 심장색전증 환자(26.8%, 95% CI 22.1%-31.5%)와 유사하였으나 여전히 비-심장색전증 환자에 비해서는 유의하게 높았다. ESUS 환자 중 172명(62.5%)에서 비교적 양호한 기능적 회복을 보였으며, 이는 심장색전증 환자(280명, 32.2%) 및 대동맥 죽상경화증 환자(303명, 60.9%)에 비하여 높은 편이었다. ESUS 환자는 전체 심혈관계 질환의 위험 주변에서 다른 뇌졸중의 아형과 유사한 편이었으나, 유의하 여 낮은 위험성을 가진 일공성 뇌졸중 환자(보정 위험비, 0.70 [95% CI, 0.52-0.94])에 비해는 높았다.

결론
ESUS의 장기적인 사망 위험은 심장색전증에 비하여 낮았으나, 재발 및 전체 심혈관계 질환 발생에 있어서는 큰 차이가 없었다. ESUS 환자에서 뇌졸중의 재발 위험은 비-심장색전증 환자에 비하여 높았다.

Figure 1. Cumulative probability of survival (A), stroke recurrence (B), and composite cardiovascular event (C) by stroke type. ESUS indicates embolic stroke of undetermined source.
Abstract 8

Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation

Effect of Anticoagulation and Its Timing: The RAF Study

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(Stroke. 2015;46:2175-2182.)

Key Words: anticoagulant therapy ■ atrial fibrillation ■ hemorrhagic stroke ■ ischemic stroke ■ secondary prevention

배경과 목적
급성심장색전뇌졸중에서 항응고제 투여의 가장 적절한 시기는 명확하지 않다. 저자들은 급성뇌졸중과 심방세동을 가진 환자들에 대한 전향적인 코호트 연구에서 (1) 재발성 허혈 사건 및 중증 출혈에 대한 위험도, (2) 재발 및 출혈에 대한 위험인자 및 (3) 급성뇌졸중 이후의 항응고 치료 및 시작 시점과 연관된 재발 및 출

Figure 2. Adjusted hazard ratios of 5-year mortality adjusted to age, sex, National Institute of Health Stroke Scale (NIHSS) score on admission, history of smoking, atrial fibrillation, dyslipidemia, coronary artery disease, heart failure and in-hospital use of aspirin (A), stroke recurrence adjusted to age, history of hypertension, smoking, transient ischemic attack, atrial fibrillation, and dyslipidemia (B), and composite cardiovascular event adjusted to age, NIHSS score on admission, history of diabetes mellitus, atrial fibrillation, and coronary artery disease (C) of stroke types compared with ESUS. ESUS indicates embolic stroke of undetermined source.

배경과 목적
급성심장색전뇌졸중에서 항응고제 투여의 가장 적절한 시기는 명확하지 않다. 저자들은 급성뇌졸중과 심방세동을 가진 환자들에 대한 전향적인 코호트 연구에서 (1) 재발성 허혈 사건 및 중증 출혈에 대한 위험도, (2) 재발 및 출혈에 대한 위험인자 및 (3) 급성뇌졸중 이후의 항응고 치료 및 시작 시점과 연관된 재발 및 출

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