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

A new clinical entity termed Embolic Stroke of Undetermined Source (ESUS) was recently introduced by the Cryptogenic Stroke/ESUS International Working Group, which describes stroke patients for whom the source of embolism remains undetected despite recommended investigation; potential embolic sources include the mitral and aortic valves, the left cardiac chambers, the proximal cerebral arteries of the aortic arch, and the venous system via paradoxical embolism.1 ESUS has been proposed as a potential therapeutic entity with a hypothesis which is currently tested in randomized controlled trials.2,3

Recently, we presented a descriptive analysis of an ESUS population originating from the Athens Stroke Registry.4 Among the overall stroke population, 10% of patients were classified as ESUS.4 These strokes were of mild–moderate severity, and covert atrial fibrillation (AF) was identified as the underlying etiopathogenetic mechanism in ≈40% of ESUS patients.4

In routine clinical practice, and based on randomized studies,5,6 the vast majority of ESUS patients are treated with antiplatelets for secondary stroke prevention. However, given that covert AF is the underlying pathogenesis in ≈40% of
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 to Alexandra University Hospital, Athens, Greece, between June 1992 and December 2011.3 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, multifocal 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, malingering/vasospasm, drug misuse).1 ESUS patients were classified without knowledge of follow-up outcomes. Large-artery atherosclerotic stroke was defined as a stroke with clinical and brain imaging findings of either significant (>50%) stenosis or occlusion of a major brain artery or branch cortical artery, presumably because of atherosclerosis.1 Cardioembolic stroke was defined as a stroke as a result of embolus arising in the heart.1 Lacunar stroke was defined as a subcortical brain infarct ≤1.5 cm in largest dimension in the distribution of the small, penetrating cerebral arteries.1 A stroke was characterized as miscellaneous when a specific cause other than large-artery atherosclerotic, cardioembolic, or lacunar stroke was identified. Patients without identification of the underlying etiopathogenic mechanism because of incomplete evaluation were classified as undetermined other than ESUS. According to the imaging protocol, patients had a computed tomography (CT) during admission and a second CT or magnetic resonance imaging (MRI) at 7 to 10 days. The choice of CT or MRI for the 7 to 10 days imaging depended on available resources and clinical presentation (eg, in patients with symptoms suggestive of posterior circulation infarct, MRI was preferred). Patients who had an early recurrent strokes in hospital before the investigations were finished and were included in the ESUS group if the pathogenesis of stroke was not identified after the completion of all necessary investigations.

Outcomes and Follow-Up

The primary end-point of the study was mortality. The secondary outcomes were stroke recurrence, functional outcome (favorable functional outcome was defined as modified Rankin Scale Score ≤2), and a composite cardiovascular end point comprising of recurrent stroke, myocardial infarction, aortic aneurysm rupture, systemic embolism, or sudden cardiac death. Death was assessed from death certificates, patients’ hospital records, and information from general practitioners or family physicians.

Outcome was defined as a cerebrovascular event of sudden onset, lasting ≥24 hours, subsequent to the initial stroke, which clearly resulted in a new neurological deficit or an increase in an existing deficit.5 Visualization of a new lesion on brain imaging, involving an 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, antithrombotics). 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 elsewhere6 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 antiplatelet, 44 (16.7%) were treated with anticoagulant, 14 (5.3%) were treated with a combination of antiplatelet 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.
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. 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 outcome10,11 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.4 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.13 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

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 antithrombotic, antihypertensive, and lipid-lowering drugs, and efficiency of anticoagulation 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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**Supplemental Table I: Baseline characteristics of patients with ESUS and other types of ischaemic stroke.**

<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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
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</tr>
<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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</tr>
<tr>
<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>
</tr>
<tr>
<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>
</tr>
<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>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<td><strong>Pattern of presentation</strong></td>
<td></td>
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<tr>
<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>
</tr>
<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>
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</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>
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<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>
<tr>
<td>Clinical and laboratory values</td>
<td>3 (1.1%)</td>
<td>4 (0.8%)</td>
<td>20 (2.3%)</td>
<td>1 (0.2%)</td>
<td>9 (2.5%)</td>
<td>9 (8.8%)</td>
</tr>
<tr>
<td>-------------------------------</td>
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</tr>
<tr>
<td><strong>Clinical and laboratory values</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mmHg)</strong></td>
<td>150 (130-160)</td>
<td>150 (140-170)</td>
<td>150 (130-170)</td>
<td>160 (140-180)</td>
<td>150 (135-170)</td>
<td>140 (120-150)</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure (mmHg)</strong></td>
<td>85 (80-90)</td>
<td>90 (80-90)</td>
<td>85 (80-90)</td>
<td>90 (80-100)</td>
<td>84 (80-90)</td>
<td>80 (70-90)</td>
</tr>
<tr>
<td><strong>Glucose (mg/dL)</strong></td>
<td>109 (93-141)</td>
<td>111 (95-154)</td>
<td>118 (98-153)</td>
<td>105 (92-139)</td>
<td>116 (98-163)</td>
<td>100 (90-125)</td>
</tr>
<tr>
<td><strong>NIHSS score</strong></td>
<td>5 (2-14)</td>
<td>5 (2-15)</td>
<td>13 (4-22)</td>
<td>2 (1-4)</td>
<td>8 (3-18)</td>
<td>4 (1-12)</td>
</tr>
<tr>
<td><strong>Continuous ECG monitoring in the stroke unit</strong></td>
<td>195 (70.9%)</td>
<td>276 (55.5%)</td>
<td>564 (64.9%)</td>
<td>289 (46.5%)</td>
<td>187 (51.1%)</td>
<td>55 (53.9%)</td>
</tr>
<tr>
<td><strong>24-hours Ambulatory Holter Monitoring</strong></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><strong>No rhythm monitoring modality other than admission ECG</strong></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><strong>Transthoracic echocardiography</strong></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><strong>Transesophageal echocardiography</strong></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><strong>Any angiography (CT or MR or digital)</strong></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><strong>Cervical artery ultrasound</strong></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><strong>No cervical artery imaging</strong></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.
表 5年間の累積生存確率、脳卒中再発、複合心血管系イベント

<table>
<thead>
<tr>
<th></th>
<th>ESUS (n=275)</th>
<th>心原性脳卒中 (n=869)</th>
<th>大血管のアテローム性動脈硬化 (n=497)</th>
<th>ラクナ梗塞 (n=622)</th>
<th>ESUS以外の塞栓源を特定できない脳卒中 (n=366)</th>
<th>その他 (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>生存</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>累積率</td>
<td>66.6%</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% CI</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>
</tr>
<tr>
<td>脳卒中再発</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>累積率</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>
</tr>
<tr>
<td>95% CI</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>
</tr>
<tr>
<td>複合心血管系イベント</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>累積率</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% CI</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>13.5% ~ 35.1%</td>
</tr>
</tbody>
</table>
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 미치는지 콕스 회귀분석으로 분석하였다.

결과
총 2731명의 환자를 평균 30.5±24.1개월 동안 추적관찰하였다. 그 동안 275명의 ESUS 환자 가운데 73건(27.2%)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 대동맥류 주행성 질환(303명, 60.9%)에 비하여 높은 편이었다. ESUS 환자는 전체 심혈관계 질환의 위험 측면에서 다른 뇌졸중의 아형과 유사한 편이었으나, 유의하 여 낮은 위험성을 가진 입공성 뇌졸중 환자(보정 위험비, 0.70 [95% CI, 0.52~0.94])에 비해서는 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.
급성허혈뇌졸중과 심방세동을 가진 환자들의 조기 재발 및 뇌출혈 항응고치료의 효과와 시기: RAF 연구

 EARLY RECURRENCE AND CEREBRAL BLEEDING IN PATIENTS WITH ACUTE ISCHEMIC STROKE AND ATRIAL FIBRILLATION

Effect of Anticoagulation and Its Timing: The RAF Study

Maurizio Paciaroni, MD; Giancarlo Agnelli, MD; Nicola Falocci, PhD; Valeria Caso, MD, PhD; Simona Marcheselli, MD; Christina Rueckert, MD; Alessandro Pezzini, MD; Loris Poli, MD; Alessandro Padovani, MD, PhD; Laszlo Csiba, MD; Lilla Szabo, MD; Sung-II Sohn, MD, PhD; Tiziana Tassinari, MD; Azmil H. Abdul-Rahim, MD; Patrik Michel, PD-MER; Maria Cordier, MD; Peter Vanacker, MD; Suzette Remillard, MD; Andrea Alberti, MD; Michele Venti, MD, PhD; Umberto Scoditti, MD; Licia Denti, MD; Giovanni Orlandi, MD; Alberto Chiti, MD; Gino Gialdini, MD; Paolo Bovi, MD; Monica Carletti, MD; Alberto Rigatelli, MD; Jukka Putaala, MD; Turgut Tatlisumak, MD; Luca Masotti, MD; Gianni Lorenzini, MD; Rossana Tassi, MD; Francesca Guidieri, MD; Giuseppe Martini, MD; Georgios Tsigougalis, MD; Konstantinos Vadikolias, MD; Chrissoula Lianti, MD; Francesco Corea, MD, PhD; Massimo Del Sette, MD; Walter Ageno, MD; Maria Luisa De Lodovici, MD; Giorgio Bono, MD; Antonio Baldi, MD; Sebastiano D’Anna, MD; Simona Sacco, MD; Antonio Carolei, MD; Cindy Tiseo, MD; Monica Acciarresi, MD; Cataldo D’Amore, MD; Davide Imeriti, MD; Dorjan Zafrani, MD; Boris Dononin, MD; Vera Volodina, MD; Domenico Consoli, MD; Franco Galati, MD; Alessio Pieroni, MD; Danilo Toni, MD, PhD; Serena Monaco, MD; Mario Maimone Baranello, MD; Kristian Barlinn, MD; Lars-Peder Jønslen, MD; Jessica Kepplinger, MD; Ulf Boedeclot, MD; Johannes Gerber, MD; Dirk Deleu, MD, PhD, FRCP; Gayane Melikyan, MD; Faisal Akhtar, MD; Maria Giulia Mosconi, MD; Valentina Bubba, MD; Ilenia Silvestri, MD; Kennedy R. Lees, MD

(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 혈혈 사건 및 중증 출혈에 대한 위험도, (2) 재발 및 출혈에 대한 위험인자 및 (3) 급성뇌졸중 이후의 항응고 치료 및 시작 시점과 연관된 재발 및 출혈 항응고치료의 효과와 시기: RAF 연구

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