Embolic Stroke of Undetermined Source and Detection of Atrial Fibrillation on Follow-Up: How Much Causality Is There?

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Background: There is increasing debate whether atrial fibrillation (AF) episodes during follow-up in patients with embolic stroke of undetermined source (ESUS) are causally associated with the event. AF-related strokes are more severe than strokes of other etiologies. In this context, we aimed to compare stroke severity between ESUS patients diagnosed with AF during follow-up and those who were not. We hypothesized that, if AF episodes detected during follow-up are indeed causally associated with the index event, stroke severity in the AF group should be higher than the non-AF group. *Methods:* Dataset was derived from the Athens Stroke Registry. ESUS was defined by the Cryptogenic Stroke/ESUS International-Working-Group criteria. Stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS) score. Cumulative probabilities of recurrent stroke or peripheral embolism in the AF and non-AF ESUS groups were estimated by

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Kaplan–Meier analyses. *Results:* Among 275 ESUS patients, AF was detected during follow-up in 80 (29.1%), either during repeated electrocardiogram monitoring (18.2%) or during hospitalization for stroke recurrence (10.9%). NIHSS score was similar between the two groups (5 [2-13] versus 5 [2-14], $P = .998$). More recurrent strokes or peripheral embolisms occurred in the AF group compared with the non-AF group (42.5% versus 13.3%, $P = .001$). *Conclusions:* Stroke severity is similar between ESUS patients who were diagnosed with AF during follow-up and those who were not. Given that AF-related strokes are more severe than strokes of other etiologies, this finding challenges the assumption that the association between ESUS and AF detected during follow-up is as frequently causal as regarded. **Key Words:** Stroke—atrial fibrillation—embolism—stroke severity.

Introduction

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 standard investigation. Potential embolic sources include covert atrial fibrillation (AF), mitral and aortic valves, the left cardiac chambers, the proximal cerebral arteries of the aortic arch, the venous system via paradoxical embolism, artery-to-artery embolism (even without stenosis), in situ thrombosis, prothrombotic disorders, and others.[1]

In a recent analysis of the Athens Stroke Registry, episodes of AF were detected during follow-up in approximately one third of ESUS patients, either at repeated electrocardiogram (ECG) monitoring or during hospitalization for a recurrent stroke.[2] Although covert AF could potentially be the causative mechanism in these patients, there is increasing debate whether episodes of AF during follow-up of an ischemic stroke patient are causally associated with the event—especially for AF episodes detected remotely after the index event—or represent only a (still) innocent bystander.[3]

Numerous studies have shown that AF-related strokes have more severe clinical presentation compared with other etiologies.[4-6] In this context, we aimed to compare stroke severity between ESUS patients who were diagnosed with AF during follow-up and those who were not. We hypothesized that if AF episodes detected during follow-up are indeed causally associated with the index event, stroke severity in the AF group should be higher than in the non-AF group. Second, we compared the long-term risk of stroke recurrence and peripheral embolism between these two groups.

Methods

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] The methodology followed to register data in the Athens Stroke Registry was described elsewhere.[2] The scientific use of the data collected in the Athens Stroke Registry was approved by the local Ethics Committee.

Patients were classified as ESUS when the related diagnostic work-up (as described by the Cryptogenic Stroke/ESUS International-Working-Group criteria) was completed. In particular, ESUS was defined as a visualized nonlacunar brain infarct in the absence of the following: (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 (e.g. arteritis, dissection, migraine/vasospasm, drug misuse).[1]

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 a 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/or brain imaging findings (e.g. multiterritorial infarcts, strokes presenting with maximum severity at onset, largely dilated left atrium) and (1) and (2) were negative.

Stroke severity was evaluated with the National Institutes of Health Stroke Scale (NIHSS) score.[8] For the study period between 1992 and 1998, NIHSS was calculated from the Scandinavian Stroke Scale using the following formula: NIHSS score = 25.68 – (.43*Scandinavian Stroke Scale score).[9] Functional outcome was assessed by the modified Rankin scale score.

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.

Recurrent stroke was defined as a cerebrovascular event of sudden onset, lasting >24 hours, subsequent to the initial

stroke, which clearly resulted in a new neurologic deficit or an increase in an existing deficit.[10] Visualization of a new lesion on brain imaging, involving an anatomical 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 (e.g. 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. AF during follow-up was diagnosed either during hospitalization for a stroke recurrence or after repeated ECG monitoring.

Statistical Analysis

Continuous data are summarized as median value and interquartile range, 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 recurrent strokes 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 recurrent stroke and peripheral embolism in the AF and non-AF groups. Differences in Kaplan–Meier curves were evaluated with the log-rank test. Cox-regression analysis was performed to investigate which of the following factors were independent predictors of recurrent stroke and peripheral embolism: detection of AF during follow-up, age, sex, stroke severity (evaluated by the NIHSS score), cardiovascular risk factors and comorbidities (history of hypertension, diabetes, smoking, previous transient ischemic attack, dyslipidemia, coronary artery disease, admission blood pressure and glucose), in-hospital treatment (thrombolysis, antithrombotics), length of hospitalization, and antithrombotic treatment on discharge. All variables reaching a 10% level of statistical significance in the univariate analysis were included into the multivariate model where the level of statistical significance was 5%. Associations are presented as hazard ratios (HRs) with their corresponding 95% confidence intervals (95% CIs). Sensitivity analyses (Kaplan-Meier and Cox regression) were also performed including only patients discharged with antiplatelets.

Statistical analyses were performed with the Statistical Package for Social Science (SPSS Inc., version 17.0 for Windows, Chicago, IL).

Results

Among 2731 patients with acute first-ever ischemic stroke who were admitted between June 1992 and December 2011 and included in this analysis, 275 (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, potential etiologies, and outcomes have been described previously in detail.[2,11]

AF was detected during follow-up in 80 (29.1%) ESUS patients, either during repeated ECG monitoring (n = 50, 18.2%) or during hospitalization for a recurrent stroke (n = 30, 10.9%). The baseline characteristics of the AF and non-AF groups are summarized in Table 1. The NIHSS score was similar between the two groups (5[2-13] versus 5,[2-14] $P = .998$). Only age (69 [65-76) versus 66 (57-75), $P = .01$) and history of coronary artery disease (15.2% versus 27.2%, $P = .03$) were statistically different between the two groups. Functional outcome at 3 months was similar between the two groups (50 [62.5%] patients in the AF ESUS group and 137 ([70.3%] in the non-AF ESUS group had modified Rankin scale: 0-2, $P = .210$).

The mean follow-up of the AF and non-AF groups were 43.8 ± 21.2 and 40.8 ± 22.0 months, respectively, corresponding to 3504 and 7956 patient-years. There were significantly more events (recurrent strokes or peripheral embolisms in the AF group compared with the non-AF group [34 (42.5%) versus 26 (13.3%), $P = .001$]) corresponding to .970 and .327 events per 100 patient-years. The cumulative probability of stroke recurrence or peripheral embolism in the AF group was significantly higher compared with the non-AF group (50.9% versus 17.6%, $P < .001$) (Fig 1).

In the multivariate Cox-regression analysis, the detection of AF during follow-up was associated with an increased risk for recurrent stroke or peripheral embolism (HR: 3.64, 95% CI: 2.09-6.32, $P < .001$). Age (HR: 1.02, 95% CI: .99-1.04, $P > .05$) and days of hospitalization (HR: 1.04, 95% CI: 1.01-1.06, $P = .001$) were also included in this model. In a sensitivity analysis including only patients discharged on antiplatelets, the Kaplan–Meier analysis (Fig 2) and the Cox-regression analysis (HR: 3.37, 95% CI: 1.77-6.43) gave similar results.

Discussion

The present study shows that stroke severity is similar between ESUS patients who were diagnosed with AF during follow-up and those who were not. Second, the risk of recurrent stroke or peripheral embolism during the long-term follow-up was significantly higher in the former group.

AF-related strokes generally present with greater severity compared with strokes of other etiologies due to the larger size of the occluding material.[4,5] In this context, it could be hypothesized that stroke severity would be higher in ESUS patients who are detected with AF during follow-up than in those who are not detected with AF, assuming that the AF detected during follow-up is causally associated with the index stroke. However, this hypothesis

Table 1. *Baseline characteristics of ESUS patients who were diagnosed with AF during follow-up (AF group) and those who were not (non-AF group)*

	AF ESUS (n = 80)	Non-AF ESUS (n = 195)	*P* value
Demographics			
Female gender	34 (42.5%)	65 (33.3%)	.15
Age (years)	69.0 (65.0-76.0)	66.0 (57.0-75.0)	.01
Comorbidities—risk factors			
Hypertension	58 (72.5%)	120 (61.5%)	.08
Diabetes mellitus	23 (28.7%)	42 (21.5%)	.20
Smoking	23 (28.7%)	60 (30.8%)	.74
Previous TIA	5 (6.2%)	22 (11.3%)	.20
Heart failure	3 (3.8%)	19 (9.7%)	.09
Dyslipidemia	35 (43.8%)	105 (53.8%)	.12
Coronary artery disease	12 (15.2%)	53 (27.2%)	.03
Clinical and laboratory values			
Systolic blood pressure (mmHg)	148 (136-170)	150 (130-160)	.42
Diastolic blood pressure (mmHg)	85 (80-92)	84 (80-90)	.44
Glucose (mg/dL)	117 (93-147)	106 (92-138)	.23
NIHSS score	5 (2-13)	5 (2-14)	.99
Days of hospitalization	10 (8-13)	10 (7-15)	.92
Treatment on discharge			
Anticoagulation and antiplatelet(s)	7 (8.8%)	7 (3.6%)	.02
Antiplatelet(s) (monotherapy)	52 (67.5%)	142 (75.9%)	.16
Anticoagulation (monotherapy)	17 (22.1%)	27 (14.4%)	.13

Abbreviations: AF, atrial fibrillation; ESUS, embolic strokes of undetermined source; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

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).

was not confirmed in the present study, raising doubts whether the association between ESUS and AF detected during follow-up is as frequently causal as it is generally regarded. It may be possible that in a significant proportion of these patients, another embolic source may actually be the causative mechanism of the index stroke (e.g., aortic atherosclerotic plaque, <50% stenosis of the internal carotids, and others on the post index event imaging), whereas AF is only an incidental finding.[12,13] This could perhaps explain why stroke severity is similar between the AF and the non-AF ESUS patients, given that the size of the occluding material is not usually as large in these cases as in AF.

Another explanation why stroke severity is similar between the AF and the non-AF ESUS groups in this study is that perhaps a substantial proportion of patients with AF were also included in the non-AF group, but the arrhythmia was not detected. This explanation seems unlikely for two reasons. First, stroke severity in both AF and non-AF groups was much lower (median NIHSS = 5) than in patients with cardioembolic stroke at the same stroke population (median NIHSS = 12) as was previously shown.[5] One would expect that stroke severity of ESUS patients would be closer to the severity of patients with cardioembolic stroke if AF was indeed the causative agent. Second, long-term outcome was poorer in the AF ESUS group than in the non-AF ESUS group, which is in line with cardioembolic strokes being associated with poorer outcome compared with strokes of other etiologies. Indeed, had the non-AF group included a substantial proportion of patients with undetected AF, outcomes would be expected to be similarly poor in both groups.

The present study raises doubts whether AF detected during follow-up in ESUS patients is the etiologic mechanism of the index stroke as frequently as regarded. This may have diagnostic and therapeutic implications not only for ESUS but also for cardioembolic strokes: some of the embolic strokes which are (mis?) classified as cardioembolic because of the detection of AF during the follow-up of the patient may actually be caused by another embolic source; that is, atrial fibrillation may be overestimated as a stroke mechanism. This may have clinical implications at the diagnostic level: typically, an embolic stroke in a patient with AF is easily attributed to AF, and no other diagnostic workup is usually performed. As this study suggests, this approach may actually be suboptimal, given that some of the embolic strokes in patients with AF detected during follow-up may actually be caused by other embolic sources, for example, a <50% stenotic carotid plaque.

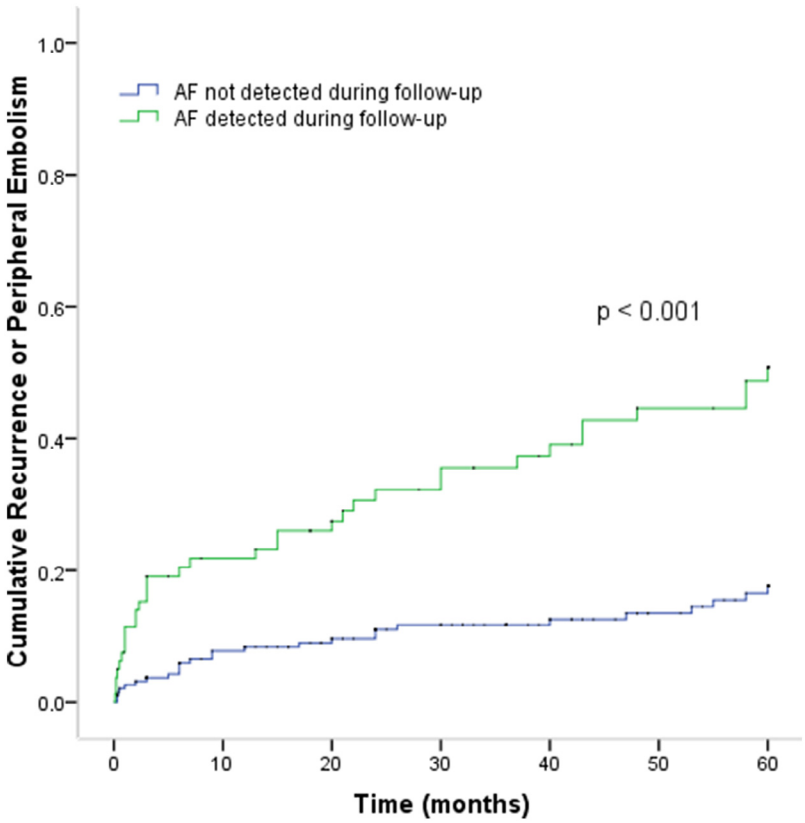

Figure 1. *Cumulative probability of recurrent stroke or peripheral embolism in the AF and non-AF ESUS patients.*

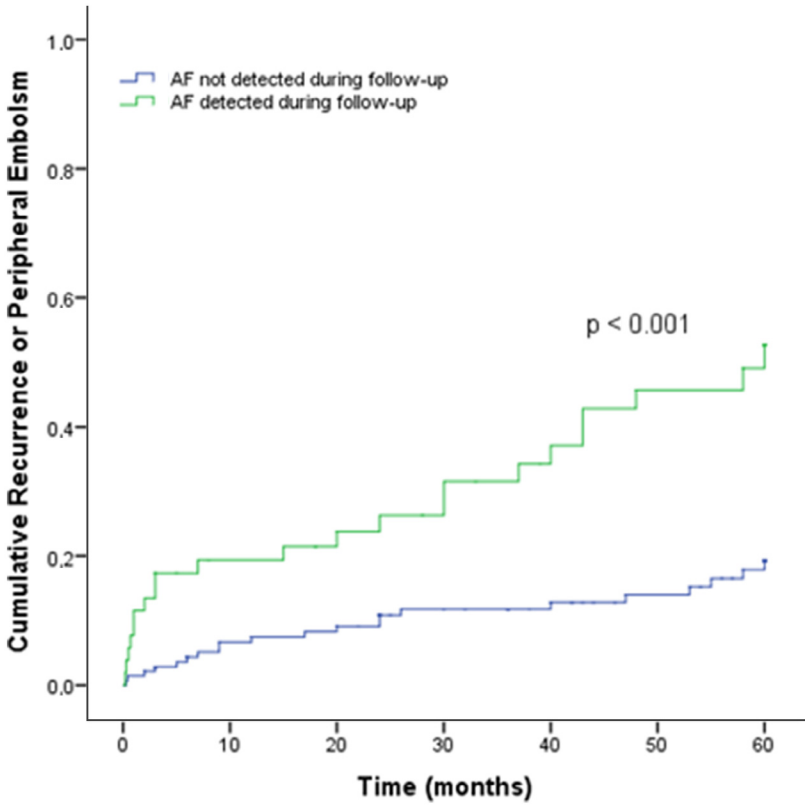

Figure 2. *Cumulative probability of recurrent stroke or peripheral embolism in the AF and non-AF ESUS patients on antiplatelets.*

Thus, further diagnostic workup may be warranted in patients with embolic stroke and AF, at least for some selected cases such as in patients that AF was detected remotely after the index stroke. In addition, the findings of the present study may have implications also at the therapeutic level, given that AF is associated with significantly higher embolic risk than any other etiology and, therefore, any patient with AF and ≥1 stroke risk factors should be anticoagulated. Nevertheless, misclassification of a stroke as AF-related could perhaps disorientate the treating physician from ordering other therapeutic interventions which would have been necessary if the real cause of stroke was actually identified, for example, the aggressive treatment with statin in an ESUS patient with AF detected during follow-up and a <50% stenotic carotid plaque. This may also explain why patients with cardioembolic stroke who are discharged with a statin have lower risk of recurrent stroke compared with those who are not treated with a statin.[14]

The main strengths of this analysis are the large size of the study population involving consecutive patients, the long follow-up, and the standardized definition of ESUS based on the criteria proposed by the Cryptogenic Stroke/ESUS International Working Group.[1] On the other hand, it is characterized by the inherent limitations of any retrospective analysis of prospectively collected data such as collection and registration bias, as well as unregistered confounding factors. Also, it is a single-center study which may have introduced selection bias. Finally, the assessments of AF detection, stroke recurrence, and stroke severity were not performed blinded nor was there formal adjudication because this was a registry that aimed at assessing many exposures and outcomes.

In conclusion, stroke severity is similar between ESUS patients who were diagnosed with AF during follow-up and those who were not. Given that AF-related strokes are more severe than strokes of other etiologies, our study questions whether the association between ESUS and AF detected during the follow-up is as frequently causal as it is regarded. Thus, AF may be overestimated as a cause of stroke, at least in ESUS patients.[15] In selected patients with embolic stroke and AF, further diagnostic workup may still be warranted to identify coexisting potential embolic sources.

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