International Journal of Stroke WSO

International Journal of Stroke
2017, Vol. 0(0) 1–5
© 2017 World Stroke Organization
Reprints and permissions:
sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/1747493017724624
journals.sagepub.com/home/wso
SAGE

Differential characteristics, stroke recurrence, and predictors of covert atrial fibrillation of embolic strokes of undetermined source

Maximiliano A Hawkes[1], Mauricio F Farez[2], Lucia Pertierra[2], Maia M Gomez-Schneider[2], José M Pastor-Rueda[2] and Sebastián F Ameriso[2]

Abstract

Background and purpose: Identifying embolic strokes of undetermined source (ESUS) patients likely to harbor atrial fibrillation may have diagnostic and therapeutic implications. Our aim was to examine differences between ESUS and cardioembolic strokes, to evaluate stroke recurrence rate among ESUS and to identify baseline characteristics of ESUS patients who were later diagnosed with atrial fibrillation.

Materials and methods: We assessed all ischemic stroke patients admitted between June 2012 and November 2013. ESUS were compared to cardioembolic strokes at discharge. After at least 12-month follow-up, ESUS patients diagnosed with atrial fibrillation were compared to those who remained as ESUS.

Results: There were 236 ischemic strokes, 32.6% were ESUS. Compared to cardioembolic strokes, ESUS were younger ($p < 0.0001$), had milder strokes ($p < 0.05$), less prevalence of hypertension ($p < 0.05$), peripheral vascular disease ($p < 0.05$), and previous ischemic stroke ($p < 0.05$). After follow-up, 15% of ESUS patients had stroke recurrences and 12% evidenced paroxysmal atrial fibrillation. ESUS patients diagnosed with atrial fibrillation in the follow-up were older ($p < 0.0001$), had higher erythrocyte sedimentation rate ($p < 0.05$), and were more likely to have ≥ 2 infarcts in the same arterial territory in the initial magnetic resonance imaging ($p < 0.05$).

Conclusions: Older age, small-scattered infarcts on initial magnetic resonance imaging and high erythrocyte sedimentation rate levels appear to identify ESUS patients more likely to be diagnosed of atrial fibrillation during follow-up.

Keywords

ESUS, covert atrial fibrillation, cryptogenic stroke

Received: 6 February 2017; accepted: 9 May 2017

Introduction

A significant percentage of cryptogenic strokes harbor covert atrial fibrillation (AF) and may benefit from anticoagulation.[1,2] The Warfarin-Aspirin Recurrent Stroke Study failed to demonstrate a benefit of warfarin for stroke recurrence prevention in this population,[3] yet it included a large number subcortical infarcts probably caused by small vessel disease.

Embolic stroke of undetermined source (ESUS) is a clinical concept aimed to identify embolic cryptogenic strokes based on the visualization of embolic infarcts and the exclusion of major embolic sources.[4] Average ESUS frequency worldwide is 17%, ranging from 1% to 36% in different cohorts.[5,6] The stroke recurrence among them is similar to cardioembolic strokes[7] and can be predicted with the CHADS2 and CHA2DS2-VASc scores.[8] Paroxysmal AF can be diagnosed in one third of ESUS patients during follow-up.[9]

Due to a suspected underlying embolic etiology,[4] three clinical trials are testing the efficacy of direct oral anticoagulants in this population.[9–11] Identifying a subset of patients at highest risk of harboring AF may have clinical significance.[12] Our aim was to examine the

[1]Department of Neurology, Division of Critical Care Neurology, Mayo Clinic, Rochester, MN, USA
[2]Department of Neurology, Institute for Neurological Research FLENI, Buenos Aires, Argentina

Corresponding author:
Maximiliano A Hawkes, 200 First Street Southwest, Rochester, MN 55905, USA.
Emails: Hawkes.Maximiliano@mayo.edu/maximilianohawkes@gmail.com

baseline differences between ESUS and cardioembolic strokes, to evaluate the stroke recurrence rate among ESUS, and to identify distinctive characteristics of ESUS patients who had AF during the follow-up.

Methods

We assessed all ischemic stroke patients admitted to a referral hospital in Buenos Aires, Argentina, between June 2012 and November 2013. Data were obtained from digital hospital records including demographics, previous disability assessed by the modified Rankin Scale (mRS), vascular risk factors, prior medications, stroke severity assessed by the National Institute of Health Stroke Scale score (NIHSS), laboratory and imaging investigations, and initial and discharge treatments. Stroke was defined as an episode of neurological dysfunction based on a new infarct visualized on brain imaging or symptoms persisting $\geq$24 h.[13] Patients were classified at hospital discharge using Trial of ORG 10172 in Acute Stroke Treatment (TOAST)[14] and ESUS[4] criteria. Stroke patients without a magnetic resonance imaging (MRI) of the brain, in whom the computed tomography (CT) did not show the culprit infarct, were classified as undetermined non-ESUS. Echocardiographic findings were defined according to current guidelines.[15]

We compared the baseline characteristic of ESUS and cardioembolic strokes. ESUS patients were followed for at least 12 months. Stroke recurrence, diagnosis of AF, antithrombotic therapy, and residual disability were evaluated in this group. Patients who did not return for a one-year follow-up were contacted by phone. ESUS patients later diagnosed of AF were compared to those who remained classified as ESUS.

The study was approved by the local ethics committee.

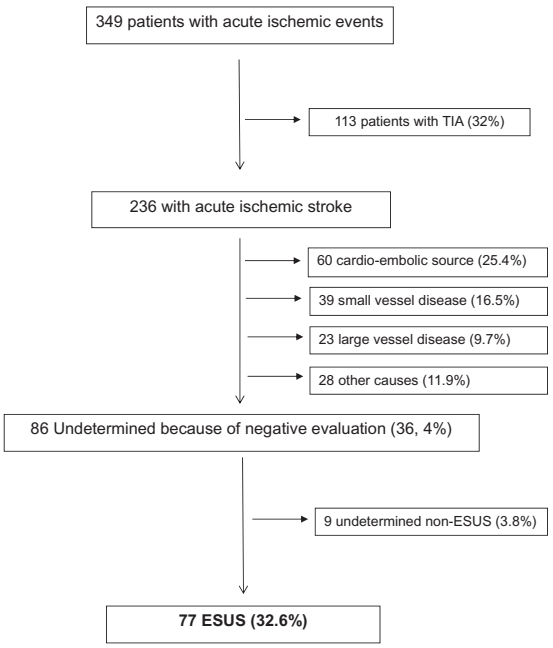
Statistical analysis

Statistical analysis was performed using STATA version 12.1 (Statacorp). The level of two-tailed significance was set at $p < 0.05$ for all statistical procedures. Normal distribution in continuous variables was assessed using a Kurtosis test. If variables were not normally distributed, a non-parametric Mann–Whitney test was applied. Otherwise, an analysis of variance was performed with Bonferroni correction to evaluate differences between groups. Qualitative variables were analyzed with the χ^2 test or Fisher's exact test depending on the number of observations.

Results

Among 236 ischemic strokes, 86 (36.4%) were classified as undetermined because of negative evaluation by TOAST criteria. Most of them (32.6%) met criteria for ESUS (Figure 1).

Figure 1. Patients' flowchart. Etiological classification at hospital discharge according to TOAST and ESUS criteria. ESUS: embolic stroke of undetermined source; TIA: transient ischemic attack; TOAST: Trial of ORG 10172 in Acute Stroke Treatment.



All patients had neck and intracranial vessel imaging, cardiac ultrasound, and 24-h cardiac telemetry with automated AF detection or Holter. Most patients had brain MRI (96%) and the remainder CT.

Compared with patients with cardioembolic strokes, ESUS patients were younger ($p < 0.0001$), had less prevalence of hypertension ($p < 0.05$), peripheral vascular disease ($p < 0.05$), prior ischemic stroke ($p < 0.05$), and lower NIHSS ($p < 0.05$). Echocardiographic studies showed less prevalence of aortic valve calcification ($p < 0.05$), systolic dysfunction ($p < 0.05$), regional hypokinesis ($p < 0.05$), and left atrial dilation ($p < 0.0001$) in the ESUS group. Patent foramen ovale (PFO) was more frequent in ESUS patients ($p < 0.05$). Large cortical infarcts with subcortical extension predominated in patients with cardioembolic strokes ($p < 0.05$) (Table 1, Supplemental Table 1).

Thirteen patients (16%) were contacted by phone. After a median follow-up of 17 $\pm$ 7 months, 11 ESUS patients (15%) had recurrent strokes and 9 (12%) evidenced asymptomatic paroxysmal AF (PAF) in standard 24-h Holter monitoring. All patients were on

Table 1. Comparison of between ESUS and cardioembolic strokes on admission

	ESUS (n = 77)	Cardioembolic (n = 60)	p value (ESUS vs. cardioembolic)
Age, years (median, range)	68 (20–88)	76 (52–100)	<0.0001
Hypertension (%)	61	83.33	0.004
Peripheral vascular disease (%)	3.7	30.77	0.011
Ischemic stroke (%)	9.21	25.00	0.013
NIHSS on admission (median, range)	2 (0–21)	4 (0–36)	0.0025
Aortic valve calcification (%)	24.68	48.33	0.004
Systolic LV dysfunction (%)	2.6	11.67	0.042
Regional hypokinesis (%)	5.19	23.33	0.002
Patent foramen ovale (%)	16.88	1.67	0.003
Left atrial enlargement (%)	36.36	75.00	<0.0001
Cortico-subcortical infarction (%)	28.57	53.57	0.018
Creatinine level, mg/dl (mean, range)	1 (0.4–1.4)	0.8 (0.3–1.3)	0.0498

NIHSS: National Institute of Health Stroke Scale; LV: left ventricle; ESUS: embolic stroke of undetermined source.

Table 2. Comparison of baseline characteristics of ESUS who had atrial fibrillation in the follow-up and those who remained as ESUS

	ESUS (n = 67)	Cardioembolic (n = 9)	p value (ESUS vs. cardioembolic)
Age, years (median, range)	67 (20–92)	79 (58–88)	0.0096
≥2 Infarcts in the same arterial territory (%)	19	58	0.027
Erythrocyte sedimentation rate, mm/h (median, range)	13 (2–113)	34 (5–92)	0.01

ESUS: embolic stroke of undetermined source.

antiplatelet drugs at the time of recurrence. Older age ($p < 0.0001$), the presence of two or more small cortical infarcts in the same arterial territory ($p < 0.05$) and higher erythrocyte sedimentation rates ($p < 0.05$) were more frequent in the ESUS-AF group (Table 2, Supplemental Table 2).

Discussion

In this single-center study, ESUS patients were younger, had less prevalence of vascular risk factors, prior strokes, minor-risk cardiac emboli sources, and higher prevalence of PFO compared to cardioembolic strokes. During the follow-up, 12% of ESUS patients were diagnosed of asymptomatic paroxismal atrial fibrillation (PAF). The ESUS group later found to have AF was older, had higher erythrocyte sedimentation rate and small scattered cortical infarcts on the initial MRI.

Whether these episodes of PAF are the cause of the index stroke is a matter of debate in the literature. Brief episodes of asymptomatic PAF have been frequently detected by prolonged ambulatory cardiac rhythm monitoring after stroke, regardless of the etiology, raising questions about their pathogenic role in patients with cryptogenic strokes.[16] However, as PAF predominated in younger patients with embolic infarct patterns, likely ESUS, a causative role in this group has been suggested.[16] AF-related strokes are characteristically more severe than strokes of other etiologies. Thus, the

severity of the index stroke in ESUS patients with and without diagnosis of AF during follow-up are similar, the pathogenic role of AF in this setting has also been questioned.[17]

Even though the causes of ESUS are heterogeneous and may include many different etiologies (e.g. non-stenotic atherosclerotic lesions, PFO, etc.), two facts suggest that PAF could have a pathogenic role at least in a selected subgroup of ESUS. First, ESUS have shown to have maximal intensity of stroke symptoms at onset, similar to what is found in AF-related strokes.[7] Second, strokes caused by PAF have lower severity compared to those caused by persistent or permanent forms.[18] Furthermore, small scattered cortical infarcts, characteristically found in the initial MRI of the ESUS later found to have AF in our study, can be seen in 30% of AF-related strokes. This pattern is associated with lower NIHSS, and it has been linked to microembolia.[19] Also, the frequency of hypertension, left atrial dilation and stroke recurrence, known predictors of AF, had trend in those ESUS later diagnosed with AF.[20]

Similarly to other ESUS cohorts,[5,6] the recurrence rate of stroke of ESUS in our study was noticeably higher than what is reported in cryptogenic strokes (15% vs. 3–6%).[4] All the recurrences occurred while patients were on single antiplatelet treatment. Likewise, 90% of patients in the ESUS Global Stroke Registry were on antiplatelet drugs at the moment of their index event.[6] This was recently confirmed in a recent systematic review,[5] raising questions about the best preventive strategy in this group.

Our study differs from other series in that all patients had a standardized and complete workup during the initial hospitalization. In addition to differences in the characteristics of the population, this could explain the high frequency of ESUS in our study. Supporting this, up to 50% of undetermined strokes in previous reports could not be classified as ESUS because of incomplete diagnostic testing.[6] In this context, the usefulness of the MRI to detect the culprit "embolic infarct" is remarkable, since small scattered cortical brain infarcts, found in a significant proportion of ESUS in our study, can be particularly difficult to identify in a CT scan.

Our study has limitations. The lack of a standardized protocol for AF detection, telephone follow-up in 16% of patients, and the small ESUS sample could be potential explanations for the low percentage of AF detection among ESUS compared to previous studies (12 vs. 30%).[6,12] The small sample size could also explain the lack of statistical significance in the frequency of hypertension, left atrial dilation and stroke recurrence, in the ESUS group later diagnosed with AF.

Conclusions

With complete workup, most undetermined strokes can be classified as ESUS. Compared to cardioembolic strokes, ESUS patients were younger, had less vascular risk factors and minor-risk potential cardiac emboli sources, and smaller and milder strokes. The short-term stroke recurrence of ESUS is high, even while on antiplatelet treatment. Older age, scattered small cortical infarcts on imaging and high ERS levels may help to identify a subgroup of ESUS patients more likely to have covert AF. Whether these findings may help to identify a subgroup of ESUS suitable for loop recorder device implantation or empiric anticoagulation deserves further investigation.

Acknowledgments

This study was performed at the Institute for Neurological Research, FLENI, Buenos Aires, Argentina.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/ or publication of this article: Ameriso and Gomez-Schneider participate in the NAVIGATE-ESUS trial. The other authors have nothing to disclose.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Gladstone DJ, Spring M, Dorian P, et al. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med* 2014; 370: 2467–2477.
2. Sanna T, Diener H-C, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014; 370: 2478–2486.
3. Mohr JP, Thompson JL, Lazar RM, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med* 2001; 345: 1444–1451.
4. Hart RG, Diener H-C, Coutts SB, et al. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014; 13: 429–438.
5. Hart RG, Catanese L, Perera KS, Ntaios G and Connolly SJ. Embolic stroke of undetermined source: a systematic review and clinical update. *Stroke* 2017; 48: 867–872.
6. Perera KS, Vanassche T, Bosch J, et al. Embolic strokes of undetermined source: prevalence and patient features in the ESUS Global Registry. *Int J Stroke* 2016; 11: 526–533.
7. Ntaios G, Papavasileiou V, Milionis H, et al. Embolic strokes of undetermined source in the Athens Stroke Registry: an outcome analysis. *Stroke* 2015; 46: 2087–2093.
8. Ntaios G, Vemmos K, Lip GYH, et al. Risk stratification for recurrence and mortality in embolic stroke of undetermined source. *Stroke* 2016; 47: 2278–2285.

9. Geisler R, Poli S, Meisner C, et al. Apixaban for treatment of embolic stroke of undetermined source (ATTICUS randomized trial): Rationale and study design. *Int J Stroke* 2016; pij 1747493016681079.
10. Diener H-C, Easton JD, Granger CB, et al. Design of randomized, double-blind, Evaluation in secondary stroke prevention comparing the efficacy and safety of the oral Thrombin inhibitor dabigatran etexilate vs. acetylsalicylic acid in patients with Embolic Stroke of Undetermined Source (RE-SPECT ESUS). *Int J Stroke* 2015; 10: 1309–1312.
11. Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for secondary stroke prevention in patients with embolic strokes of undetermined source: design of the NAVIGATE ESUS randomized trial. *Eur Stroke J* 2016; 1: 146–154.
12. Ntaios G, Papavasileiou V, Milionis H, et al. Embolic strokes of undetermined source in the Athens Stroke Registry: a descriptive analysis. *Stroke* 2015; 46: 176–181.
13. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013; 44: 2064–2089.
14. Adams HP, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993; 24: 35–41.
15. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; 28: 1–39.e14.
16. Rabinstein AA, Fugate JE, Mandrekar J, et al. Paroxysmal atrial fibrillation in cryptogenic stroke: a case–control study. *J Stroke Cerebrovasc Dis* 2013; 22: 1405–1411.
17. Ntaios G, Papavasileiou V, Lip GYH, et al. Embolic stroke of undetermined source and detection of atrial fibrillation on follow-up: how much causality is there? *J Stroke Cerebrovasc Dis* 2016; 25: 2975–2980.
18. Ntaios G, Vemmou A, Koroboki E, et al. The type of atrial fibrillation is associated with long-term outcome in patients with acute ischemic stroke. *Int J Cardiol* 2013; 167: 1519–1523.
19. Oh S, Kim SJ, Ryu S-K, et al. The determinants of stroke phenotypes were different from the predictors (CHADS2 and CHA2DS2-VASc) of stroke in patients with atrial fibrillation: a comprehensive approach. *BMC Neurol* 2011; 11: 107.
20. Brunner KJ, Bunch TJ, Mullin CM, et al. Clinical predictors of risk for atrial fibrillation: implications for diagnosis and monitoring. *Mayo Clin Proc* 2014; 89: 1498–1505.