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ORIGINAL ARTICLE

Embolic Stroke of Undetermined Source (ESUS) and Stroke in Atrial Fibrillation Patients: not so Different after all?

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Abstract

Background: Stroke related to atrial fibrillation (AF) is associated with high recurrence and mortality rates. Embolic Stroke of Undetermined Source (ESUS) is associated with fewer vascular risk factors, less disability, and a high recurrence rate.

Objective: To compare risk factors, functional outcomes and the occurrence of primary endpoint (a composite of recurrent stroke, cardiovascular death, and myocardial infarction) between AF stroke and ESUS patients.

Method: A retrospective analysis was conducted including all consecutive patients with first-ever ischemic stroke admitted to the *Hospital de Clinicas* (Clinical Hospital) of the Federal University of Paraná from October 2012 to January 2017 (n=554). There were 61 patients with stroke due to AF and 43 due to ESUS. Both groups were compared for demographic characteristics and vascular risk factors. Logistic regression models were performed to assess the impact of each variable on the primary endpoint in a 12-month follow-up. Statistical significance was considered for p-values < 0.05.

Results: ESUS patients, as compared to AF patients, were younger and more likely to be smokers. ESUS patients presented a mean CHADS2VASc score of 4, while the AF group presented a score of 5 (p <0.001). The primary endpoint was observed in 9 (20.9%) ESUS and 11 (18.0%) AF patients over a 12-month period (p=0.802). Higher glucose levels upon hospital admission (p=0.020) and a higher modified Rankin Scale upon hospital discharge (p=0.020) were predictors of the primary endpoint occurrence.

Conclusion: AF and ESUS stroke patients presented very similar independence rates upon hospital discharge and outcomes after 12 months, despite some baseline differences, including stroke recurrence, vascular death, and myocardial infarction.

Keywords: Cerebrovascular Disorders; Stroke; Brain Infarction; Atrial Fibrillation; Embolism, Intracranial; Brain, Infarction.

Introduction

Embolic Stroke of Undetermined Source (ESUS) is a non-lacunar infarct without proximal occlusive atherosclerosis or major-risk cardioembolic sources. Recent studies have demonstrated a high variability (ranging from 10-39%) in the proportion of ESUS patients, who are subsequently diagnosed with atrial fibrillation (AF) in a long-term follow-up. This result suggests that some groups of ESUS patients can present AF as underlying cause of stroke.[2-5] Approximately one-third of the patients who met the inclusion criteria for ESUS trials presented AF in continuous heart rhythm monitoring for up to three years. A higher AF prevalence was also observed with an increasing number of $CHADS_2$ risk factors. [6]

This definition is important, since AF is the most common embolic source in the cardioembolic stroke

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mechanism. AF presents the worse functional outcome, higher recurrence rates, and greater mortality when compared to strokes resulting from other causes, including a subgroup of ESUS in this profile.[2,7]

The aim of the present study is to compare the occurrence of recurrent stroke, cardiovascular death, and myocardial infarction in a composite endpoint between ESUS and AF stroke patients one year after the first-ever ischemic stroke (IS).

Methods

This study was a retrospective analysis of a prospective data bank including all the consecutive patients with first-ever IS admitted to the *Hospital de Clinicas* (Clinical Hospital) of the Federal University of Paraná from October 2012 to January 2017. This study was approved by the local Ethics Committee.

All the patients with first-ever IS secondary to AF and ESUS were included, based on the TOAST[8] and according to Cryptogenic Stroke/ESUS International-Working-Group criteria,[1] respectively. For the stroke diagnosis, all patients needed to have at least one confirmatory brain image (CT or MR) confirming a brain lesion consistent with the clinical syndrome presented during hospital admission. Patients with AF were submitted to a minimal investigation, including electrocardiography, extracranial and intracranial Doppler ultrasound, and transthoracic echocardiography. For a ESUS diagnosis, besides the screening reported for AF, patients were submitted to 24-hour Holter monitoring and CT angiography, MR angiography, or digital angiography in order to exclude other stroke mechanisms. Although it was not required by the International Criteria, all ESUS patients were also submitted to transesophageal echocardiography (TEE). No patients were submitted to cardiac monitoring for more than 24 hours, as this resource is not available in the Brazilian public healthcare system.

The following variables were analyzed: age, sex, $CHADS_2$, and $CHADS_2VaS_2C$. The last two variables included some of the most significant modifiable risk factors for embolic stroke, such as hypertension and diabetes, and prevalent non-modifiable risk factors, like congestive heart failure and coronary artery disease. The National Institutes of Health Stroke Scale (NIHSS), systolic blood pressure, and diastolic blood pressure upon hospital admission were some of the analyses performed in the hospital. The modified Rankin score (mRS) was analyzed upon hospital discharge, after which patients were evaluated to identify the occurrence of: 1) stroke recurrence (a focal neurological impairment of sudden onset lasting more than 24 hours and confirmed by a brain image during the follow-up period); 2) myocardial infarction (defined as a rise in blood concentrations of cardiac troponins and/or creatine kinase in the context of spontaneous ischemic symptoms or coronary intervention); and 3) cardiovascular death (resulting from an acute myocardial infarction, sudden cardiac death, heart failure, stroke, cardiovascular procedures, hemorrhage, or other cardiovascular causes).

Statistical Analysis

Analyses were performed using the IBM SPSS Statistics v 2.0.0 software. Categorical variables were presented as frequencies and percentage. Quantitative variables with normal distribution were described by mean value and standard deviation (SD). Quantitative variables without normal distribution were described by median and interquartile range.

When comparing etiological groups, Fisher's exact test was used for categorical variables. For quantitative variables, an unpaired Student's t-test was used for those with normal distribution, while a Mann-Whitney test was applied for variables without normal distribution and severity scores. The normality condition of the variables was assessed by the Kolmogorov-Smirnov test. The impact of each variable was analyzed by adjusting the variables for each subgroup (ESUS and AF), using the logistic regression models and the Wald test. Statistical significance was accepted for p-values < 0.05.

Results

During the study, from 544 patients with first-ever IS, 61 (11.2%) presented AF as a stroke mechanism and 43 (7.90%) fulfilled all ESUS criteria. Compared to AF patients (70.9±11.2 years old), ESUS patients (52.5±15.7 years old) were younger ($p<0.001$) and presented a higher frequency of smoking (34.9% for ESUS and 14.8% for AF patients, $p=0.020$). When analyzing risk factors through $CHADS_2$ and $CHADS_2VASc$ scores, ESUS patients exhibited a lower score than did the AF patients, as presented in Table 1. Upon hospital discharge, only 7% of ESUS patients were submitted to anticoagulation therapy, as compared to 75.4% of AF patients, $p=0.001$. All other hospital admission characteristics were presented in Table 1.

In ESUS patients, transesophageal echocardiography demonstrated abnormalities in 22 patients (52.1%), with

Table 1 – Baseline Characteristics

Variable	ESUS (n=43)	Atrial Fibrillation (n=61)	p value
Age (years) mean ±sd	52.5 ± 15.7	70.9 ± 11.2	<0.001
Female sex n(%)	13 (59.1)	30 (49.2)	0.661
Hypertension n(%)	28 (65.1)	43 (70.5)	0.670
Diabetes n(%)	8 (18.6)	13 (21.3)	0.808
Hypercholesterolemia n(%)	10 (23.3)	12 (19.7)	0.808
Current smoking n(%)	15 (34.9)	9 (14.8)	0.020
Alcohol abuse n(%)	5 (11.6)	6 (9.8)	0.759
Previously known AF n(%)	0 (0)	24 (39.3)	<0.001
CHADS2 Score median (Q1 - Q3)	3 (2-5)	4 (2-6)	<0.001
CHA2DS-VASc Score median (Q1 - Q3)	4 (2-7)	5 (2-7)	0.001
NIHSS at admission median (Q1 - Q3)	9 (0-23)	10 (0-26)	0.632
Blood gluose levels (mean) ±sd	115 ± 68,7	122 ±59,2	0.310
IV thrombolysis n(%)	17 (39.5)	30 (49.2)	0.424
Hemorrhagic transformation n(%)	0 (0)	2 (3.3)	1
Anticoagulation at discharge n(%)	3 (7)	46 (75.4)	<0.001
mRS median (Q1 - Q3)	2 (0-5)	2 (0-6)	0.420

Note: ESUS: Embolic Stroke of Undetermined Source, AF: atrial fibrillation, NIHSS: National Institute of Health Stroke Scale; IV: intravenous, mRS: modified Rankin Score.

left atrial enlargement in 14 (32.5%), patent foramen ovale in 12 (27.9%), septal atrium aneurysm in seven (16.2%), and ascending aortic ectasia in three (6.9%). Other minor-risk sources of emboli are listed in Table 2.

At 12 months of follow-up, the primary endpoint occurred at the same rate in both groups: nine patients in the ESUS group (20.9%) and 11 patients in the AF group (18.0%), p=0.408. In the ESUS group, there were seven stroke recurrences (16%), two cardiovascular deaths (4.65%), and no myocardial infarction. Glucose levels upon hospital admission and mRS upon hospital discharge were the only predictors of the outcome in a multivariate analysis model, as presented in Table 3.

Discussion

The current study demonstrated that ESUS patients, despite being younger and with fewer risk factors when compared to AF patients, presented a similar outcome in the first twelve months after the first-ever IS.

In this study, ESUS patients were almost 20 years younger than patients with AF. This difference is consistent with a larger study, in which ESUS patients presented an average age of 68 and cardioembolic stroke patients of 76.[9] When the ESUS group was compared to other cryptogenic stroke patients, they were also significantly younger.[10]

A lower prevalence of vascular risk factors has been previously reported in ESUS patients when compared to AF patients.[11] In our cohort, ESUS and AF patients presented similar risk factors, such as hypertension, diabetesm and hypercholesterolemia. Current smoking was the only isolated risk that proved to be more frequent in ESUS. In a recent study, the authors demonstrated a strong relation between tobacco use and cryptogenic stroke in young adults.[12] A possible explanation for this could be an increased risk of AF for current smokers in a dose dependent manner.[13]

If the isolated vascular risk factors were not so different, except for age and smoking habit, the score values of $CHADS_2$ and CHA_2DS_2VASc revealed a more benign profile of ESUS when compared to AF. Besides being younger, ESUS patients are less likely to present cardiac failure and peripheral vascular disease. There are no current studies comparing these

Table 2 – Possible causes of embolic stroke of undetermined source

Minor-risk embolic sources	N	%
Left atrial enlargement (≥ 40mm)	14	32.55
Patent foramen ovale	12	27.90
Cerebral artery non-stenotic plaques	11	25.58
Non-atrial fibrillation atrial dysrhythmias	8	18.60
Septal atrial aneurysm	7	16.27
Moderate systolic of diastolic dysfunction	6	13.90
Ascending aortic ectasia	3	6.97
Calcific aortic valve disease	2	4.65
Atrial appendage stasis with spontaneous echodensities	2	4.65
Aortic arch atherosclerotic plaques	1	2.32

Table 3 – Predictors of the primary endpoint

Variable	Outcome	Mean (min-max)	p Value	OR (CI 95%)
Glucose levels	No	117.5 (74-319)	0.017	1.11 (1.02-1.22)
	Yes	128 (99-480)		
mRS at discharge	No	2 (0-5)	0.024	1.38 (1.04-1.83)
	Yes	2 (0-6)		

OR: odds ratio, CI: confidence interval, mRS: modified Rankin Score.

scores between ESUS and cardioembolic or AF stroke patients. However, both $CHADS_2$ and CHA_2DS_2VASc scores have been associated with a higher recurrence risk in ESUS.[14]

There was no difference in the primary endpoint in the groups. In a 5-year follow-up, Ntaios et al.[9] found a cumulative probability of 38.1% of composite cardiovascular events in an ESUS cohort, which is almost identical to cardioembolic stroke patients (38.2%). However, in a Finnish population, cardioembolic stroke patients exhibited nearly 4-fold increased risk for composite vascular events when compared to young-onset ESUS patients. The difference in secondary endpoints was mainly due to myocardial infarction rather than to stroke or TIA; moreover, ESUS patients were younger in this study.[15]

During hospital stay, all the ESUS patients were submitted to a 24-hour cardiac rhythm monitoring to be classified as ESUS.[1] None of our 43 ESUS patients presented any episodes of AF in the 24-hour Holter monitoring. However, large RCTs have demonstrated that long-term monitoring increases the chances of detecting brief paroxysmal AF with an unknown clinical significance.[16-18] In a CRYSTAL-AF trial, only 1.3% of arrhythmia events were detected with a 24-hour Holter, compared to a 22.8% detection rate with a 30-day cardiac monitoring,[17] Prolonged monitoring is not available in the Brazilian public healthcare system, which represents a limitation of our analysis.

Ntaios reported a cumulative probability of stroke recurrence similar to cardioembolic strokes, 29% vs 26.8%, respectively.[9] A systematic review reported an annual rate of stroke recurrence ranging from 5% to 14.5%. [5] In our study, 16% of ESUS patients presented recurrence in 12 months, which is slightly higher than that presented in the literature. This probably reflects the poor risk factor control and low adherence to medical therapy by Brazilian patients.[19]

Although AF continues to be a leading candidate for an occult mechanism of ESUS, findings from recent clinical

trials suggest that about 70% of patients with ESUS have no AF. However, the same study demonstrated that the incidence of AF is higher among patients with higher $CHADS_2$ scores.[6] In our cohort, the median $CHADS_2$ score for the ESUS group was 3, two points higher than previously demonstrated.[14] We can thus hypothesize that, in a Brazilian population, with poor risk factor control, ESUS patients are more likely to present higher $CHADS_2$ scores and, therefore, are more likely to present paroxysmal AF. Nevertheless, an important proportion of these patients may have other mechanisms for embolic stroke, such as patent foramen ovale or large aortic arch plaques.[20]

Even when no AF is detected, ESUS may be associated with atrial cardiomyopathy. A recent study with late-gadolium-enhancement MRI demonstrated that ESUS and AF patients showed similar rates of atrial fibrosis, supporting the hypothesis that both entities may have different presentations, but a similar physiopathology.[21]

For secondary prophylaxis, anticoagulation therapy was prescribed for 75.4% of the patients in the AF group. This proportion is higher than that observed in non-stroke patients with atrial fibrillation in Latin America.[22] In the clinical base, patients with large stroke size, palliative care, and lower independence outcomes are unlikely to receive OAC. Furthermore, there are safety concerns regarding OAC prescriptions for fragile patients and families with cultural and socioeconomic barriers to adherence. Although a higher number of patients with OAC could reduce the recurrence rate, the current study demonstrated similar recurrence rates when compared to previous studies.[9]

By contrast, ESUS patients were left with single antiplatelet therapy, as recommended by 2015 AHA/ASA Guideline.[23] None of them presented closed patent foramen ovale (PFO). Twelve (27.9%) ESUS patients presented right-to-left shunt, of whcih four (36%) recurred. It is possible that percutaneous closure of PFO could have prevented any of these recurrences; however, a recent meta-analysis comparing percutaneous closure versus medical therapy for stroke with PFO showed a number of 39 was needed to properly treat recurrent stroke.[24] Hence, it is unlikely that PFO closure would change our analysis.

The high outcome rates observed in the ESUS patients of the present study could be reduced with a high anticoagulation therapy rate, although the best treatment choice for ESUS is still controversial. Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source (NAVIGATE-ESUS) trial recently proved that rivaroxaban was not superior to aspirin in the prevention of recurrent stroke, with a higher risk of bleeding.[25] In Dabigatran Etexilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source (RE-SPECT ESUS) trial, Dabigatran was no better than aspirin in preventing a second stroke after ESUS, but the rate of major bleeding was similar in both arms.[26] Meanwhile, Apixaban for the Treatment of Embolic Stroke of Undetermined Source (ATTICUS)[27] and Atrial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke (ARCADIA) trials are still ongoing.[28]

The present study presents several limitations. This study was conducted in a single center with a retrospective small sample, which might have underestimated the differences in outcomes between ESUS and AF stroke patients. Nevertheless, ESUS and AF populations were clearly different, considering demographic characteristics and embolic risk factors demonstrated by CHADS and $CHADS_2$VASc scores. Furthermore, in a 12-month follow-up, the outcome was similar. These results could be different if a non-composite outcome was chosen, in which a larger sample size would be necessary to access stroke recurrence, MI, and cardiovascular death in an isolated analysis.

Conclusion

ESUS and AF stroke patients presented different profiles of embolic risk factors, but similar independence rates and outcomes were observed. Occult paroxysmal AF and atrial cardiomyopathy are the possible links to explain the high recurrence rate in ESUS patients.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the *Universidade Federal do Paraná* under the protocol number 19474013.0.3001.5225. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Author Contributions

Conception and design of the research: Zetola VHF, Lange MC. Acquisition of data: Scavasine VC, Ribasa GC, Costa TR, Ceccato GHW. Analysis and interpretation of the data: Scavasine VC, Lange MC. Statistical analysis: Marcia Olandoski. Writing of the manuscript: Scavasine VC, Lange MC. Critical revision of the manuscript for intellectual content: Zetola VHF, Lange MC.

References

1. Hart RG, Diener H-C, Coutts SB, Easton JD, Granger CB, O´Donnell MJO, et al. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol. 2014;13(4):429-38.
2. Ntaios G, Papavasileiou V, Milionis H, Makaritsis K, Lemmou A, Korobo KE, et al.et al. Embolic Strokes of Undetermined Source in the Athens Stroke Registry: a descriptive analysis. Stroke. 2015; 46(1):176-81.
3. Makimoto H, Kurt M, Gliem M, Lee JI, Schmidt J, Muller P, et al. High Incidence of Atrial Fibrillation After Embolic Stroke of Undetermined Source in Posterior Cerebral Artery Territory. J Am Heart Assoc. 2017;6:e007448.
4. Israel C, Kitsiou A, Kalyani M,Detection of atrial fibrillation in patients with embolic stroke of undetermined source by prolonged monitoring with implantable loop recorders. Thromb. Haemost. 2017;117:1962-9.
5. Molina-Seguin J, Vena AB, Colas-Campas L. A systematic review of the characteristics and prognosis of subjects who suffer an embolic stroke of undetermined source. Rev Neurol. 2018;66:325-30.
6. Verma N, Ziegler PD, Liu S, Passman RS. Incidence of atrial fibrillation among patients with an embolic stroke of undetermined source: Insights from insertable cardiac monitors. Int J Stroke. 2019 Feb;14(2):146-53.
7. Henninger N, Goddeau RP Jr, Karmarkar A. Atrial Fibrillation Is Associated With a Worse 90-Day Outcome Than Other Cardioembolic Stroke Subtypes. Stroke. 2016;47:1486-92.
8. Adams HP JR, Bendixen BH, Kappelle LJ. 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.
9. Ntaios G, Papavasileiou V, Milionis H. Embolic Strokes of Undetermined Source in the Athens Stroke Registry: An Outcome Analysis. Stroke. 2015;46:2087-93.
10. Tsivgoulis G, Kargiotis O, Katsanos AH. Incidence, characteristics and outcomes in patients with embolic stroke of undetermined source: A population-based study. J Neurol Sci. 2019;401:5–11.
11. Hart RG, Catanese L, Perera KS. Embolic Stroke of Undetermined Source. Stroke. 2017;48:867-72.
12. Jaffre A, Ruidavets JB, Nasr N. Tobacco Use and Cryptogenic Stroke in Young Adults. J Stroke Cerebrovasc Dis. 2015;24:2694-700.
13. Aune D, Schlesinger S, Norat T. Tobacco smoking and the risk of atrial fibrillation: A systematic review and meta-analysis of prospective studies. Eur J Prev Cardiol. 2018 Jan(1) 2047487318780435.
14. Ntaios G, Vemmos K, Lip GYH. Risk Stratification for Recurrence and Mortality in Embolic Stroke of Undetermined Source. Stroke 2016;47: 2278–85.
15. Martinez-Majander N, Aarnio K, Pirinen J. Embolic strokes of undetermined source in young adults: baseline characteristics and long-term outcome. Eur J Neurol. 2018;25: 535–41.
16. Healey JS, Connolly SJ, Gold MR, et al. Subclinical Atrial Fibrillation and the Risk of Stroke. N. Engl. J. Med. 2012;366:120-129.
17. Sanna T, Diener H-C, Passman RS. Cryptogenic Stroke and Underlying Atrial Fibrillation. N. Engl. J. Med. 2014;370:2478-86.
18. Gladstone DJ, Dorian P, Spring M. Atrial Premature Beats Predict Atrial Fibrillation in Cryptogenic Stroke: Results From the EMBRACE Trial. Stroke. 2015;46:936-41.
19. Tavares NUL, Bertoldi AD, Mengue SS. Factors associated with low adherence to medicine treatment for chronic diseases in Brazil. Rev Saude Publica. 2016;50(suppl 2):10s.
20. Ueno Y, Tateishi Y, Doijiri R. Large aortic arch plaques correlate with CHADS2 and CHA2DS2-VASc scores in cryptogenic stroke. Atherosclerosis 2019;284:181–6.
21. Tandon K, Tirschwell D, Longstreth WT Jr, Smith B, Akoum N. Embolic stroke of undetermined source correlates to atrial fibrosis without atrial fibrillation. Neurology. 2019:10.1212/WNL.0000000000007827.
22. Massaro AR, Lip GYH. Stroke Prevention in Atrial Fibrillation: Focus on Latin America. Arquivos Brasileiros de Cardiologia, 2016;107(6): 576–89.
23. Kernan WN, Ovbiagele B, Black HR. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke. 2014;45(7):2160-236.
24. Zhang XL, Kang LN, Wang L, Biao X. Percutaneous closure versus medical therapy for stroke with patent foramen Ovale: a systematic review and meta-analysis. BMC Cardiovasc Disord. 2018;18(1): 45.
25. Hart RG, Sharma M, Mundl H,Kasner SE, Bangdiwala SI, Berkowitz SD, et al. Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source. N. Engl. J. Med. 2018;378:2191-201.
26. Diener H-C, Easton JD, Granger CB,Honin M, Duffy C, Cotton D, 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(8):1309-12.
27. Geisler T, Poli S, Meisner C, Chreieck J, Zuern CS, Nagele T, et al. Apixaban for treatment of embolic stroke of undetermined source (ATTICUS randomized trial): Rationale and study design. Int J Stroke. 2016;12(8):985-90.
28. Kamel H, Longstreth W Jr, Tirschwell DL,Kronmal RA, Broderick J, Palesch Y, et al. The AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke randomized trial: Rationale and methods. Int J Stroke 2018;14(2):207–14.