

Embolitic stroke of undetermined source: a retrospective analysis from an Italian Stroke Unit

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ABSTRACT

The new clinical construct of embolic stroke of undetermined source (ESUS) suggests that many cryptogenic strokes are related to minor-risk covert embolic cardiac sources or to embolus from non-occlusive plaques in the aortic arch or in the cerebral arteries. The authors analyzed the prevalence of ESUS in a real-life condition in Italy and compared the recurrence rates in cryptogenic strokes, cardioembolic strokes, and ESUS. The authors retrospectively reassessed according to ESUS criteria 391 consecutive admissions in a stroke unit where extensive diagnostic search was routinely performed. Recurrences in each stroke type within a 3-year follow-up period (mean time: 25.44 months - standard deviation: 9.42) were also compared. The prevalence of ESUS in the aforementioned cohort was 10.5%. All ESUS patients received antiplatelet agents. Warfarin was prescribed in 56.9% of cardioembolic strokes. The recurrence rate in ESUS patients was 4.4% per year, slightly higher than in cardioembolic strokes (3.5%) and significantly higher than in cryptogenic non-ESUS (1.2%) ($P < 0.0001$). This is the first description of a cohort of ESUS patients in an Italian stroke unit. Patients with ESUS have a significantly higher risk of recurrence than in those with non-ESUS cryptogenic strokes, and slightly higher than in those with cardioembolic strokes. Results support the hypothesis of a more extensive diagnostic evaluation in cryptogenic strokes and the feasibility of such approach.

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Introduction

Despite more than 25-30% of all ischemic strokes are cryptogenic (of unknown cause), to date no effective secondary prevention strategy in this group has been defined. Recently the idea that most cryptogenic strokes can be thromboembolic has led a group of experts to propose the new clinical construct of embolic stroke of undetermined source (ESUS).¹ According to those authors, ESUS represents a group of cryptogenic strokes in which an adequate diagnostic assessment has excluded major-risk cardioembolic sources of embolism, lacunar strokes at computed tomography (CT) or magnetic resonance imaging (MRI), extra cranial or intra cranial atherosclerosis causing $\geq 50\%$ luminal stenosis in arteries supplying the area of ischemia and/or other specific causes of stroke (*e.g.*, arteritis, dissection, migraine/vasospasm, drug misuse). The proposed diagnostic assessment for ESUS consists in brain CT or MRI, 12-lead electrocardiogram (EKG), cardiac monitoring for ≥ 24 h with automated rhythm detection, precordial echocardiography, and imaging of both the extra cranial and intracranial arteries supplying the area of brain ischemia (catheter, MRI, or CT angiography, or cervical duplex plus trans cranial Doppler ultrasonography).

In patients with ESUS, embolism may be related to minor-risk covert embolic cardiac sources or to embolus from non-occlusive plaques in the aortic arch or in the cerebral arteries.

In order to find out the prevalence of ESUS in real-life condition in Italy, all patients admitted to our stroke unit who underwent extensive diagnostic search were reassessed to identify those who could match the criteria of ESUS. Recurrences in patients with ESUS, cryptogenic stroke, and cardioembolic stroke in a mean follow-up time of 2 years were also compared.

Materials and Methods

According to our protocol since 2010 all patients routinely perform an hyperacute brain CT followed by a 48-72 h delayed brain CT, a 12-lead EKG plus a 72 h continuous cardiac monitoring, a precordial echocardiography, and a cervical duplex ultrasonography. Transcranial Doppler ultrasonography and/or CT angiography follow when indicated.

All data is prospectively stored in a stroke registry.

In this study we retrospectively reassessed the diagnosis of 391 patients admitted in a 30-month period from May 2010 to December 2012 (Figure 1).² Of these, 87 had hemorrhagic stroke, ischemic strokes of rare causes, transient ischemic attack (TIA), or were

admitted to palliative care and/or died as inpatients. Subtypes of the remaining 304 strokes according to modified TOAST criteria were atherothrombotic in 53, lacunar in 52 and cardioembolic in 85. A potential dual etiology was supposed in 23. A final group of 91 patients had cryptogenic strokes. In this group precordial echocardiography was performed in 84 (92.3%). Conditions compatible with minor-risk cardiac sources according to the criteria of ESUS were found in 41 patients (48.8%) as shown in Figure 2.¹ The characteristics of patients with potential ESUS are reported in Table 1. All patients with cryptogenic stroke were discharged with antiplatelet therapy.

Oral anticoagulant (OAC) was prescribed as warfarin (VKA) in 56.9% of patients with cardioembolic stroke. None received new oral anticoagulants (NOAC) as they were not available in Italy until 2014.

Continuous data is summarized as mean value and standard deviation and categorical data as absolute numbers and proportion. Incidence rates were compared using chi-squared test and analysis of variance. Statistical analysis was performed with Microsoft Excel 2011 for Mac.

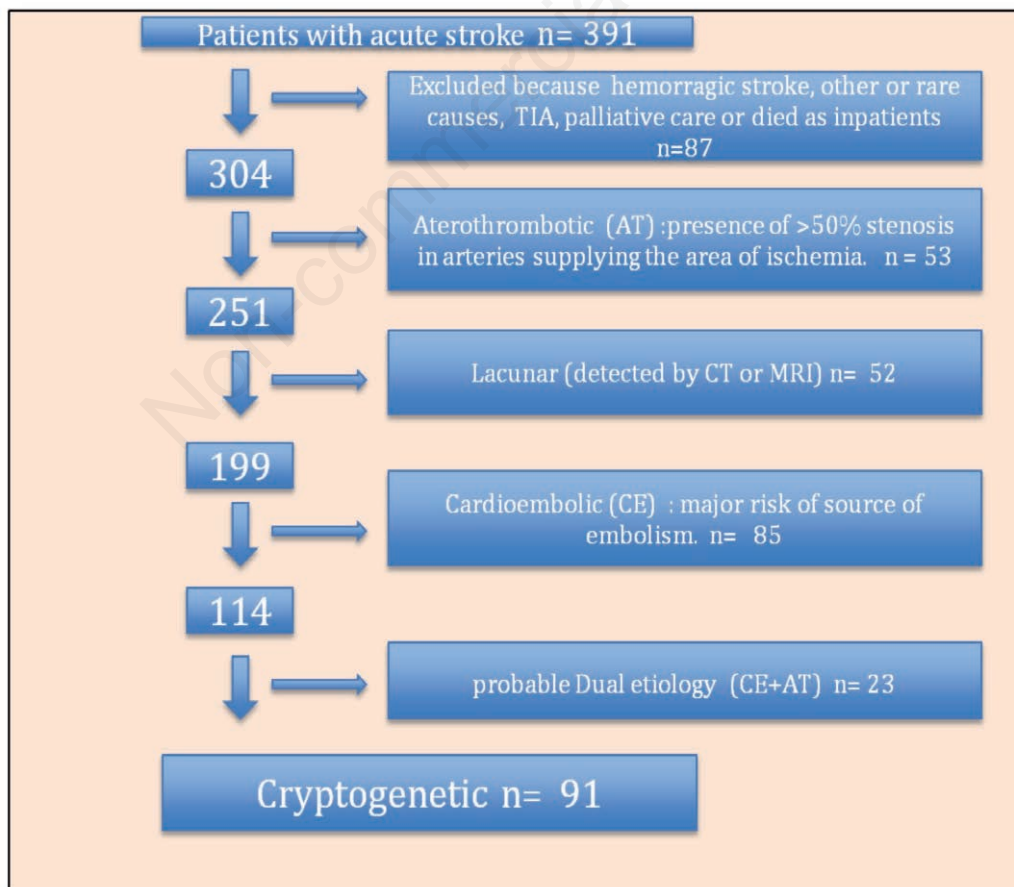


Figure 1. Flow diagram of cryptogenic stroke diagnosis (according to ESUS criteria). TIA, transient ischemic attack; CT, computed tomography; MRI, magnetic resonance imaging.

Results

Within a 2-year follow-up (mean time: 25.44 months - standard deviation: 9.42), 5 new ischemic cerebrovascular events occurred in the group of cardioembolic strokes (incidence 3.5% per year) and 5 in the group of cryptogenic strokes (incidence 2.6% per year). Four out of five recurrences in cryptogenic strokes

Table 1. Characteristics of patients with potential embolic stroke of undetermined source.

Demographics	ESUS No. 40
Age, years \pm SD (range)	76.9 \pm 12.2 (59-93)
Female sex	56.1%
Comorbidities - Risk factors	
Hypertension	31 (75.6%)
Diabetes	9 (21.9%)
Dyslipidemia	11 (26.8%)
Coronary heart disease	7 (17.9%)
Heart failure	1 (9.4%)
Prior stroke/TIA	5 (12.2%)
AF	0 (0%)
Minor-risk embolic sources in ESUS patients	
Mitral valve prolapse	4 (10%)
Mitral annular calcification	10 (25%)
Aortic valve stenosis	4 (10%)
Aortic valve calcification	6 (15%)
Atrial septal aneurism	1 (2.5%)
Moderate systolic/diastolic dysfunction	29 (77%)

ESUS, embolic stroke of undetermined source; SD, standard deviation; TIA, transient ischemic attack; AF, atrial fibrillation.

occurred in patients matching the criteria of ESUS.

Cryptogenic stroke non-ESUS had 1 recurrence (incidence=1.2% per year): the patient had cardioembolic recurrent stroke following paroxysmal atrial fibrillation (AF) and myocardial infarction (MI). She had moderate diastolic dysfunction at first event and was in antiplatelet therapy.

ESUS patients had 4 recurrences (incidence=4.2% per year): i) 1 patient had embolic recurrent stroke following paroxysmal AF and auricular thrombus. She had moderate systolic dysfunction at first event and was in antiplatelet therapy; ii) 2 patients had cryptogenic recurrent strokes. They both were in antiplatelet therapy and had moderate systolic or diastolic dysfunction associated with slight-to-moderate atrial enlargement (1) or mitral prolapse (1) at first event; iii) 1 patient had a vertebral-basilar TIA. She had mitral-annular-calcification plus moderate atrial enlargement and took double antiplatelet therapy.

Cardioembolic strokes had 5 recurrences (incidence=3.5% per year). All recurrences were cardioembolic: i) 2 patients were in VKA therapy for AF and their international normalized ratio was in therapeutic range (recurrence rate 3.9% per year); ii) 3 patients were in antiplatelet therapy despite paroxysmal AF or MI at first event (recurrence rate 3.2% per year).

Discussion and Conclusions

We performed retrospective analysis of real-life data from a single stroke unit registry in which an extensive diagnostic protocol (including precordial echocardiography and a 72-h long continuous EKG monitoring) has been routinely performed. Cardioembolic etiology was found in 28% of all strokes. The extensive search may explain the high rate of cardioembolic strokes that is around the top end of the range reported in literature (14%-30%).³⁻⁶

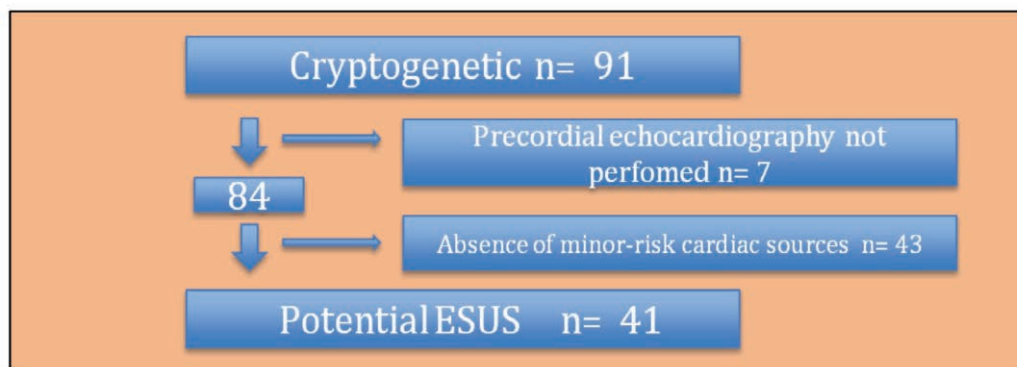


Figure 2. Flow chart of selection of potential embolic stroke of undetermined source (ESUS) patients (according to Hart et al.¹).

Excluding strokes with plausible dual etiology (8%), cryptogenic (no lacunar) strokes represented about 30% of the total. Patients who matched the criteria of ESUS represented 10.5% of all strokes, the same as reported by Ntaios in the Athens Stroke Registry.⁷ Features of the cohort of patients meeting the ESUS criteria are reported in Table 1. Our patients are old and female. Hypertension is the most frequent risk factor followed by dyslipidemia, diabetes, coronary heart disease, and prior stroke/TIA. The Athens Registry and the few studies analyzed by Hart widely differed and a typical pattern of demographic or risk factors in patients with ESUS is still unknown. Among minor-risk embolic sources, systolic or diastolic dysfunctions are the most common (77%) followed by mitral valve calcification (25%). That can be related to the advanced age of our patients (about 77 years).

In literature recurrence in cryptogenic strokes ranges from 3% to 6% per year depending on the different diagnostic criteria adopted.¹ ESUS recurrence rate is reported to be similar to that of cardioembolic strokes and higher than that of non-cardioembolic strokes.⁸ In our experience cryptogenic stroke as a whole had a recurrence rate of 2.6% per year, the same as reported in the German Stroke Registry (2.2%-2.8%).^{9,10} Our patients with ESUS had a recurrence rate of 4.4% per year (Figure 3), slightly higher than that of cardioembolic stroke (3.5%) and significantly higher than that of cryptogenic not-ESUS 1.2% ($P < 0.0001$).

This is the first description of a cohort of ESUS

patients in an Italian stroke unit. Our experience has limitations. This is a single-center analysis and the small number of patients reduces the value of statistical analysis. The diagnostic assessment of aortic arch and of intracranial artery was performed on clinical basis and some patients could have been excluded from the diagnosis of ESUS. The OAC therapy was prescribed in 56.9% of patients with cardioembolic strokes (the same rate reported in literature),⁶ but only VKA was administered because NOACs were not yet available in our country at that time.

However, our results confirm that patients with ESUS have a significantly higher risk of recurrence than those with non-ESUS cryptogenic strokes, and a slightly higher risk than those with cardioembolic strokes. Remarkably ESUS recurrences showed a typical cardioembolic source only in one out of four patients. That is interesting and needs further investigation.

Our results support the hypothesis that a more extensive diagnostic evaluation should be carried out in cryptogenic strokes. Presently, main stroke guidelines [American Heart Association/American Stroke Association (AHA/ASA) and European Stroke Organisation (ESO)] do not recommend echocardiography in diagnostic assessment of stroke. However, to diagnose an ESUS, echocardiography and prolonged rhythm monitoring are mandatory.

Aspirin or other antiplatelet agents are recommended in non-cardioembolic stroke but no specific therapy is suggested for cryptogenic stroke.^{11,12} As a subgroup of cryptogenic strokes, ESUS includes a

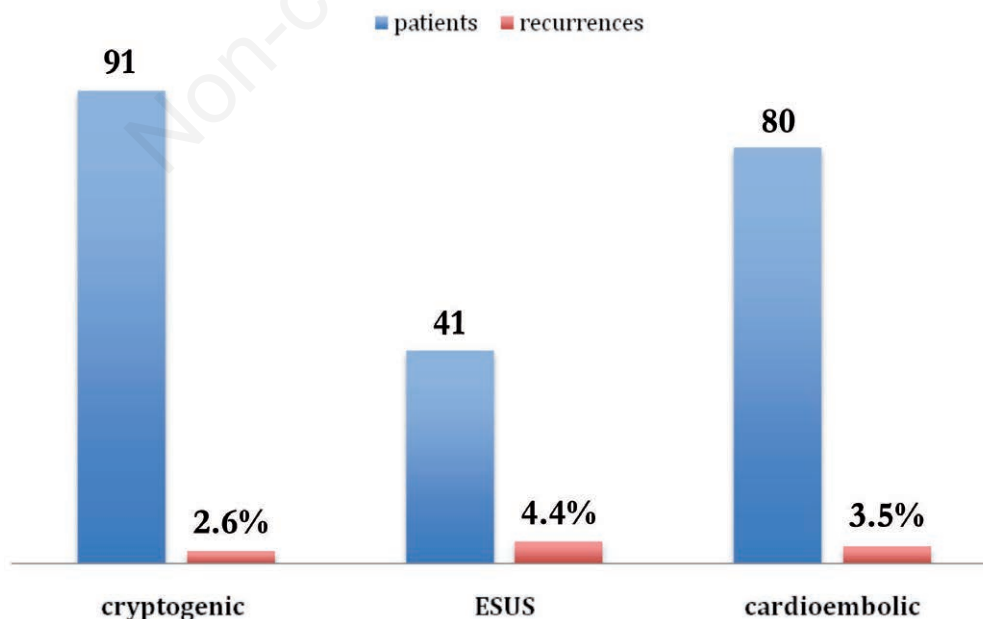


Figure 3. Stroke recurrences per year in cryptogenic strokes, embolic stroke of undetermined source (ESUS) and cardioembolic strokes.

wide range of different etiologies. It is likely that anticoagulant therapy reduces recurrences and/or improve prognosis in some (not necessarily all) conditions labelled as ESUS. The net benefit of new oral anticoagulants in preventing ischemic and/or hemorrhagic events might differ according to different minor embolic causes and needs further investigation. Currently three phase III studies (RE-SPECT ESUS,¹³ Navigate ESUS¹⁴ and The Atticus study¹⁵) are ongoing to test the effectiveness and safety of NOAC in the prevention of recurrent stroke in patients with ESUS. We hope their results will contribute in improving the efficacy of secondary prevention in this subgroup of cryptogenic stroke.

References

- Hart RG, Diener H-C, Coutts SB, et al. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014;13:429-38.
- Goldstein LB, Jones MR, Matchar DB, et al. Improving the reliability of stroke subgroup classification using the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria. *Stroke* 2001;32:1091-8.
- Furie KL, Kasner SE, Adams RJ, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011;42:227-76.
- Arboix A, Alio J. Cardioembolic stroke: clinical features, specific cardiac disorders and prognosis. *Curr Cardiol Rev* 2010;6:150-61.
- Murtagh B, Smalling RW. Cardioembolic stroke. *Curr Atheroscler Rep* 2006;8:310-6.
- Ferro JM. Cardioembolic strokes: an update. *Lancet Neurol* 2003;2:177-88.
- Ntaios G, Papavasileiou V, Milionis H, et al. Embolic strokes of undetermined sources in the Athens Stroke Registry. A descriptive analysis. *Stroke* 2015;46:176-81.
- Ntaios G, Papavasileiou V, Milionis H, et al. Embolic strokes of undetermined source in the Athens Stroke Registry: an outcome analysis. *Stroke* 2015;46:2087-93.
- Weber R, Goerttler M, Benemann J, et al. Prognosis after cryptogenic cerebral ischaemia in patients with coagulopathies. *Cerebrovasc Dis* 2009;28:611-7.
- Weimar C, Holle DN, Benemann J, et al. Current management and risk of recurrent stroke in cerebrovascular patients with right-to-left cardiac shunt. *Cerebrovasc Dis* 2009;28:359-56.
- Kernan WN, Ovbiagele B, Black HR, et al. 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;45:2160-236.
- European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008;25:457-507.
- Boehringer Ingelheim. Dabigatran etexilate for secondary stroke prevention in patients with embolic stroke of undetermined source (RE-SPECT ESUS). *ClinicalTrials.gov* identifier: NCT02239120. Available from: <https://clinicaltrials.gov/ct2/show/NCT02239120> Accessed: 01/01/2016.
- Population Health Research Institute. Stroke and cognition: ESUS Registry, IMPACT, NAVIGATE ESUS. Available from: <http://www.phri.ca/research/stroke-cognition/navigate-esus-111/> Accessed: 01/01/2016.
- Geisler T, Ziemann U. Apixaban for treatment of embolic stroke of undetermined source (ATTICUS). *ClinicalTrials.gov* identifier: NCT02427126. Available from: <https://clinicaltrials.gov/ct2/show/NCT02427126> Accessed: 01/01/2016.