Research article
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Prevalence and overlap of potential embolic sources in embolic stroke of undetermined source: a retrospective cohort

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Introduction. Embolic strokes of an undetermined source may be caused by various potential embolic sources, which can be better managed by anticoagulant or antiplatelet therapy. Identifying these sources may have diagnostic and therapeutic implications. Our objectives were to assess the prevalence and overlap of different potential embolic sources identified in a population of patients with embolic strokes of undetermined sources, and to evaluate the stroke recurrence rate according to the type and number of potential embolic sources.

Methods. We used data from consecutive patients with ischemic stroke admitted to the department of neurology in Fattouma Bourguiba hospital (Monastir, Tunisia), between January 2017 and December 2020. Patients who met the embolic strokes of undetermined source diagnostic criteria according to the criteria of the Cryptogenic Stroke "embolic strokes of undetermined source" International Working Group were selected. The presence of each potential embolic source was assessed, and patients were categorised according to the identified potential embolic sources. The main outcome was ischemic stroke recurrence, and it was collected prospectively during follow-up after the index stroke.

Results. Among 330 patients admitted between 2017 and 2020, 66 (20.6%) were classified as embolic strokes of undetermined source (68.2% were men, mean age 57 ±11 years). The three most prevalent potential embolic sources were atrial cardiopathy (N = 47/66; 71.2%), arterial atherosclerosis (N = 46/66; 69.7%) and left ventricular disease (N = 26/66; 39.4%). Most patients (N = 56/66; 84.8%) had ≥2 potential embolic sources. After 6-month of follow up, ischemic stroke recurrence occurred in 18 (27.3%) patients. In survival analysis, the type and the number of potential embolic sources were not statistically associated with stroke recurrence.

Conclusion. Most patients with embolic strokes of undetermined source had multiple potential embolic sources, which overlap considerably. The type and number of potential sources were not associated with stroke recurrence. This finding may explain the negative results of large trials of secondary prevention in the Embolic strokes of undetermined source population.

Keywords: embolic stroke of undetermined source, ischemic stroke, potential embolic sources, overlap, stroke recurrence

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Prévalence et chevauchement des sources emboliques potentielles dans l'AVC embolique de source indéterminée : une cohorte rétrospective

Introduction. Les AVC emboliques d'origine indéterminée peuvent être causés par diverses sources emboliques potentielles, qui peuvent être mieux gérées par un traitement anticoagulant ou antiplaquettaire. L'identification de ces sources peut avoir des implications diagnostiques et thérapeutiques. Nos objectifs étaient d'évaluer la prévalence et le chevauchement des différentes sources emboliques potentielles identifiées dans une population de patients présentant des AVC emboliques de source indéterminée, et d'évaluer le taux de récidive des AVC en fonction du type et du nombre de sources emboliques potentielles.

Méthodes. Nous avons utilisé les données des patients consécutifs présentant un AVC ischémique admis au service de neurologie de l'hôpital Fattouma Bourguiba (Monastir, Tunisie), entre janvier 2017 et décembre 2020. Les patients qui répondaient aux critères de diagnostic des accidents vasculaires cérébraux emboliques de source indéterminée selon les critères du groupe de travail international sur les accidents vasculaires cérébraux cryptogéniques "embolic strokes of undetermined source" ont été sélectionnés. La présence de chaque source embolique potentielle a été évaluée, et les patients ont été classés en fonction des sources emboliques potentielles identifiées. Le principal critère de jugement était la récidive de l'AVC ischémique, et il a été recueilli de manière prospective pendant le suivi après l'AVC.

Résultats. Parmi 330 patients admis entre 2017 et 2020, 66 (20,6 %) ont été classés comme des AVC emboliques de source indéterminée (68,2 % étaient des hommes, âge moyen 57 ±11 ans). Les trois sources emboliques potentielles les plus répandues étaient la cardiopathie auriculaire (N = 47/66 ; 71,2 %), l'athérosclérose artérielle (N = 46/66 ; 69,7 %) et la maladie ventriculaire gauche (N = 26/66 ; 39,4 %). La plupart des patients (N = 56/66 ; 84,8%) avaient ≥2 sources emboliques potentielles. Après 6 mois de suivi, une récidive d'AVC ischémique est survenue chez 18 (27,3 %) patients. Dans l'analyse de survie, le type et le nombre de sources emboliques potentielles n'étaient pas statistiquement associés à la récurrence de l'AVC.

Conclusion. La plupart des patients présentant des AVC emboliques de source indéterminée avaient plusieurs sources emboliques potentielles, qui se chevauchent considérablement. Le type et le nombre de sources potentielles n'étaient pas associés à la récidive de l'AVC. Cette constatation peut expliquer les résultats négatifs des grands essais de prévention secondaire dans la population des AVC emboliques de source indéterminée.

Mots-clés : AVC embolique de source indéterminée, AVC ischémique, sources emboliques potentielles, chevauchement, récidive d'AVC

Abbreviations

ARCADIA: atrial cardiopathy and antithrombotic drugs in prevention after cryptogenic stroke
CI: confidence interval
COMPASS: cardiovascular outcomes for people using anti-coagulation strategies
CT scan: computed tomography scan
ECG: electrocardiogram
EF: ejection fraction
ESUS: embolic stroke of undetermined source
HR: hazard ratios
LV: left ventricle
MRI: magnetic resonance imaging
mRS: modified Rankin scale
NAVIGATE ESUS: rivaroxaban versus aspirin in secondary prevention of stroke and prevention of systemic embolism in patients with recent embolic stroke of undetermined source
NIHSS: National Institute of Health Stroke score
NT Pro-BNP: N-terminal pro-B-type natriuretic peptide
PES: potential embolic source
PFO: patent foramen ovale
RE-SPECT ESUS: dabigatran etexilate for secondary stroke prevention in patients with ESUS
SD: standard deviation
TEE: trans-oesophageal echography
TOAST: trial of ORG 10172 in acute stroke treatment
TTE: transthoracic echography

1. Introduction

About 10–30% of ischemic strokes have no identifiable cause despite a thorough diagnostic evaluation (cryptogenic stroke) [1,2]. In 2014, researchers proposed the concept of “embolic stroke of undetermined source” (ESUS) [2], which is defined as a non-lacunar brain infarct without a significant (≥50%) stenosis of extracranial or intracranial arteries, major cardio-embolic sources or any other specific cause of stroke such as arteritis, dissection, and vasospasm [3].
As its diagnosis is based on an exclusive process, ESUS represents an etiologically heterogeneous group and may be caused by various potential sources of thromboembolism, which may respond better to anticoagulation or antiplatelet therapy [4,5]. Despite the increased number of published studies focusing on the aetiologies of the ESUS, little is known about the prevalence and overlap of potential embolic sources (PES) in north African patients with ESUS [6].
In this study, we, therefore, aimed to assess the prevalence and degree of overlap of different PES, and to evaluate the stroke recurrence rate by identifying PES among Tunisian patients with ESUS.

2. Methods

We assessed all consecutive ischemic stroke patients admitted to our department of neurology in Fattouma Bourguiba hospital (Monastir, Tunisia), between January 2017 and December 2020.

The scientific use of the data collected was approved by the local Ethics Committee. Data were prospectively obtained from digital hospital records including demographics, medical history and associated vascular risk factors, prior medications, time of stroke onset and hospital admission, duration of hospitalisation, stroke severity assessed by the National Institute of Health Stroke scale score (NIHSS), results of routine laboratory and imaging investigations, and initial and discharge treatments.

Stroke was defined according to the World Health Organisation criteria as an episode of acute neurological dysfunction based on a new infarct visualised in brain imaging or symptoms persisting over 24 hours [7]. For ischemic stroke diagnosis, work up included cerebral CT and/or MRI if available. In search of potential cardio-embolic aetiologies, in addition to the electrocardiogram, we performed a first 24-hour rhythmic holter, in the acute phase of the ischemic stroke, then we performed a second holter, during follow-up, to identify heart rhythm disorders such as atrial fibrillation, atrial flutter, atrial hyperexcitability. We also performed a transthoracic echocardiography supplemented by a trans-oesophageal echocardiography in search of major or minor cardio-embolic causes (valvular heart disease, atrial cardiopathy, etc.). The assay of the NT- pro-BNP was carried out.

In search of stenotic or non-stenotic (<50%) carotid, vertebrobasilar and aortic arch atheromatous plaques, all patients initially had an ultrasound of the supra-aortic trunks, supplemented by angio-CT scan and/or angio-MRI if available.

The aetiologies of ischemic strokes were classified using the modified trial of ORG 10172 in acute stroke treatment (TOAST) and ESUS criteria [3,8].

2.1. Definition of ESUS and PES

ESUS was defined according to the criteria proposed by the Cryptogenic Stroke/ESUS International Working Group [3] as a visualised non-lacunar brain infarct with an embolic infarct pattern on a brain computed tomography or MRI, in the absence of: (1) extracranial or intracranial ipsilateral atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischemia; (2) major-risk cardio-embolic source, and (3) any other specific cause of stroke (e.g. arteritis, dissection, migraine/vasospasm, drug misuse).

Major risk sources of cardiac embolism included permanent or paroxysmal AF, sustained atrial flutter, left ventricular ejection fraction <30%, intracardiac thrombus, prosthetic cardiac valve, mitral stenosis, atrial myxoma or other cardiac tumours.

Patients known to have AF, mechanical valves, and intracardiac thrombus were excluded from the ESUS group.

For patients included in the ESUS group, we defined the potential embolic sources (PES) as previously reported in the literature (Table 1): atrial cardiopathy, atrial fibrillation diagnosed during follow-up, left ventricular (LV) disease, cardiac valvular disease, patent foramen ovale (PFO), arterial atherosclerotic disease and cancer [4,5].

We did not include contralateral carotid atherosclerosis in these PES. For each patient, the presence/absence of each PES was determined, and patients were categorised in ≥1 groups according to the identified PES. The prevalence and degree of overlap of PES were determined.

Table 1. Definition of PES: definition is based on a secondary analysis of NAVIGATE-ESUS [9] and on the ARCADIA [10] trial inclusion criteria.

Cardioembolic sources
(1) Atrial cardiopathy (AD), any of:
- Left atrial diameter > 38 mm female, > 40 mm male
- Left atrial volume/body surface area > 34 mL/m^2
- Intra-atrial spontaneous contrast detected on echocardiography
- Supraventricular tachycardia on ambulatory ECG
- Atrial premature beats (>720/24h) on ambulatory ECG (≥ 20h duration)
- Atrial fibrillation (AF) (atrial arrhythmias lasting ≥ 30 seconds) or atrial flutter during follow-up *
- P-wave indices in ECG, any of • PTFV1 ≥ 5000 μV.ms • P-wave dispersion ≥ 40 ms
- Elevated serum NT-pro-BNP > 250 pg/mL
(2) Left ventricular dysfunction, any of:
- Moderately—severely impaired left ventricular global contractility
- Regional wall motion abnormality present
- Diastolic or systolic dysfunction (30 ≤ left ventricular ejection fraction < 49%) **
- Left ventricular non compaction
(3) Cardiac valve disease, any of:
- Bioprosthetic heart valve
- Mitral valve abnormalities: moderate-severe mitral annular calcification, valve prolapsus
- Aortic valve abnormalities: moderate-severe aortic stenosis, valve thickening, bileaflet valve
- Patent foramen ovale detected on TTE or TEE with a high risk of embolism (large shunt, atrial septal aneurysm)
Non-cardioembolic sources
(1) Arterial atherosclerosis disease, any of:
- Non stenotic carotid artery plaque (causing < 50% stenosis) ipsilateral to qualifying infarct in any of internal carotid, middle cerebral, or anterior cerebral territory detected by CT or MR angiogram or sonography
- Non stenotic vertebral artery plaque (causing < 50% stenosis) ipsilateral to qualifying infarct in either vertebral or posterior cerebral artery territory detected by CT scan or MR angiogram
- Aortic arch plaque on TEE or CT angiogram
(2) Cancer
- History of cancer at baseline whether the cancer is active or in remission, excluding skin cancer

* Atrial fibrillation not initially present and identified during follow-up is considered the cause of ESUS.

** Patients with left ventricular ejection fraction <30% were excluded.

PTFV1= P-wave terminal force in lead V1; NT pro-BNP = N-terminal pro-B-type natriuretic peptide; TTE = trans-thoracic echocardiography; TEE = trans-esophageal echocardiography; CT= computed tomography; mR= Magnetic resonance; Cancer: active or in remission

2.2. Assessment of outcome

Patients with ESUS underwent a follow-up of at least 6 months after index stroke. Outcome of interest was ischemic stroke recurrence during follow-up. The assessment of stroke recurrence was performed by onsite patient visits or by contact with the patient and/or his primary physician.
Ischemic stroke recurrence was defined as a sudden focal neurological deficit that was due to presumed arterial occlusion lasting over 24 hours and with evidence of ischemic stroke on brain imaging. For ESUS group patients, recurrent ischemic strokes by number of PES and by the degree of overlap of PES were also determined.
The outcome was evaluated in the modified Rankin scale (mRS) score at discharge from the hospital, at 3 months and 12 months post stroke, respectively. Unfavourable outcome was defined as death or dependency (modified Rankin score (mRS) score 3–6).

2.3. Statistical analysis

Continuous data were expressed as means ± standard deviation, median and interquartile range (IQR), and nominal variables as counts and percentages.
The association between time to stroke recurrence and PES, was assessed with a Cox proportional-hazards model. Adjustments were realized on demographics (age and sex), medical history (hypertension, dyslipidaemia, diabetes mellitus, smoking status, and coronary artery disease) and NIHSS score at admission.
For patients lost during follow-up, survival data were censored at the last time known to be alive. For patients who experienced >1 recurrence during the follow-up period, the time of the first event was used in the analysis.
Associations are presented as hazard ratios (HRs) with their corresponding 95% CIs, and the level of significance was set at 5% ($p < 0.05$). Statistical analyses were performed by a certified statistician with the Statistical Package for Social Science (SPSS Inc., version 25.0.0 for Windows, Armonk, NY).

3. Results

Between January 2017 and December 2020, 330 patients with acute first-ever ischemic stroke were included in our study. Nine patients were excluded from this analysis because of missing data (cardiac explorations (n = 5) and supra-aortic vascular imaging (n = 4). Of the remaining 321 patients, 66 (20.6%) were classified as ESUS (Figure 1).

3.1. Baseline characteristics, prevalence, and overlap of PES in ESUS patients

The major baseline characteristics of patients with ESUS according to PES are summarised in Table 2. The mean age was 57.1 ±11,1 years, and 45 (68.2%) were men. TTE and TEE were performed in 66 (100%) and 56 (84.8%) ESUS patients, respectively. In addition, 61 (92.4%) patients benefited from two 24-hour holter monitoring. Sonography and CT/MRI angiogram were performed in 66 (100%) and 59 (89.4%) ESUS patients, respectively.
At least one PES was identified in 90.9% of ESUS patients. The 3 most prevalent PES were atrial cardiopathy (N = 47/66; 71.2%), arterial atherosclerotic disease (N = 46/66; 69.7%) and left ventricular disease (N =26/66 39.4%) (Table 3).
Patients with PFO were young (49.8y; SD = 11) and had a low prevalence of current smoking (N = 2/16; 12.5%), dyslipidaemia (N = 0/16; 0%), diabetes mellitus (N = 2/16 12.5%) and coronary artery disease (N = 0/16; 0%). ESUS were of moderate severity (median NIHSS = 6; IQR (4-8)), NIHSS was

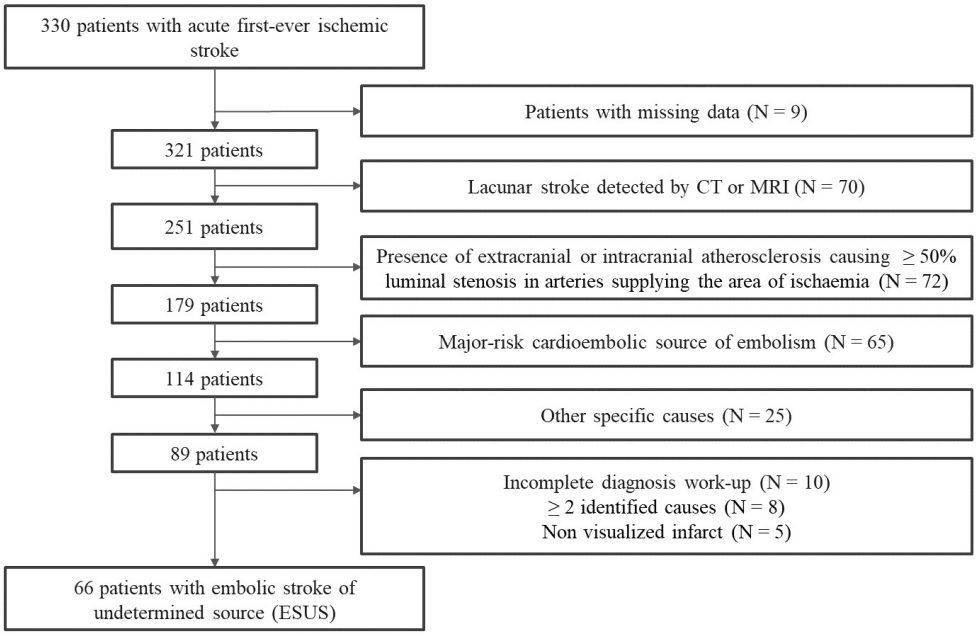

Figure 1. Flow chart.
CT: Computed tomography; MRI: Magnetic resonance imaging; ESUS: embolic strokes of undetermined source.

Table 2. Repartition of each PES in the ESUS population.

	N (%)
Cardioembolic sources	
Atrial cardiopathy	47 (71.2)
Atrial fibrillation *	12 (18.2)
Left ventricular dysfunction	26 (39.4)
Diastolic dysfunction with preserved EF	11 (16.7)
Diastolic or systolic dysfunction with reduced EF (30 ≤ left ventricular ejection fraction < 49%) **	15 (22.7)
Mitral valve	
Mitral annular calcification	6 (9.1)
Valve prolapsus	4 (6.1)
Aortic valve	
Aortic valve stenosis	4 (6.1)
Calcific aortic valve	8 (12.1)
Patent Foramen oval	16 (24.2)
+ Atrial septal aneurysm	4 (6.1)
Non cardioembolic sources	
Arterial atherosclerotic disease	46 (69.7)
Non stenotic carotid artery plaque for anterior circulation stroke	20 (30.3)
Non stenotic vertebral artery plaque for posterior circulation stroke	8 (12.1)
Aortic arch plaque	18 (27.3)
Cancer	5 (7.6)

* Atrial fibrillation not initially present and identified during follow-up is considered the cause of ESUS.

** Patients with left ventricular ejection fraction <30% were excluded.

N = number of patients; EF = ejection fraction

low in the PFO group (median NIHSS = 3; IQR (2-6)) (Table 2). Most patients with ESUS had a single ischemic stroke confirmed with brain imaging, and only 6 (9,1%) patients had a multi-territory qualifying stroke (AF = 4; atrial cardiopathy without AF = 2). Most patients classified as ESUS had favourable outcomes (mRS = 0, 1 or 2; IQR (1-2)) at discharge from hospital (N = 48/66; 72.7%), at 3 months (N = 51/66; 77.3%) and 12 months (N = 54/66; 81.8%), respectively.

Most patients (N = 56/66; 84.8%) had ≥2 PES, whereas only 6.1% and 9.1% of patients had a single or no PES, respectively. There were 20 (30.3%) patients who had 3 or more identified PES.

3.2. Recurrent ischemic stroke by individual PES and degree of PES overlap

All patients had a 6-month follow-up after the index ESUS stroke, the median duration was 16 months (IQR (8-30)). A recurrent ischemic stroke during follow-up occurred in 18 (27.3%) patients with ESUS (Table 4). The prevalence of stroke recurrence was high for patients with cancer (N = 1/5; 20%), and AF (N = 2/16; 16.7%). Whereas the lowest prevalence was reported in patients with heart valvular disease (N = 1/12; 4.5%) and PFO (N = 1/16; 6.2%). In the survival analysis, the different types of PES and the absence of PES were not significantly associated with recurrence of stroke (Table 5). The rates of ischemic stroke recurrence were similar between patients with ≤1, 2 and ≥3 PES (Table 6). In the survival analysis, the number of PES was not significantly associated with recurrence of stroke (Table 6).

4. Discussion

This is the first description of a Tunisian ESUS cohort using the criteria proposed by the Cryptogenic Stroke/ESUS International Working Group in 2014. In our study, we found that approximately 20% of all included ischemic strokes (n = 330) were classified as ESUS type and they were more prevalent among young adults. Our data are consistent with a systematic review of published studies and trials evaluating ESUS patients, where frequency of ESUS ranged from 7% to 42% of all ischemic strokes with an average of 17% and the mean age ranged from 53 to 69 years [9,11,12]. Some discrepancies between studies may result from differences in methods and frequency in providing diagnostic workup in various countries, as well as the heterogeneity of the characteristics of the patients included in these studies [5,13].

The present study of 66 consecutive patients with ESUS shows that the most common potential causes of ESUS were atrial cardiopathy (71.2%), arterial atherosclerosis (69.7%) and left ventricular disease (39.4%). Added to that, there was a major overlap of PES in patients with ESUS: most patients (84.8%) had ≥ 2 PES, whereas one third of patients had at least 3 PES. The identification of many PES in our study likely relies on the practice of a panel of investigations that are not routinely used in most of our patients with ESUS. Added to basic explorations proposed by the Cryptogenic Stroke/ESUS International Working Group [3] (standard 12-lead ECG, transthoracic echocardiogram, extracranial vascular imaging, and automated cardiac rhythm monitoring), most patients with ESUS were investigated with contrast trans-oesophageal echocardiogram for PFO detection, serum NT-pro-BNP [10,14] and P-wave indices in ECG for the assessment of atrial cardiopathy [15,16], intracranial and aortic imaging for the assessment of arterial atherosclerosis disease [17-19].

Investigated with such an exhaustive diagnostic work-up, which is unrealistic in terms of availability of resources, patients with ESUS would have much identified PES and most included patients would rarely have a single PES [5,20].

In our ESUS cohort, increasing numbers of PES was not statistically associated with increased risk of recurrent stroke. Similar to our results, The NAVIGATE ESUS (rivaroxaban

Table 3. Baseline characteristics and outcomes of patients per PES.

			Age						
	N	Male N (%)	Mean	SD	Hypertension N (%)	Smoking N (%)	Dyslipidemia N (%)	Diabetes mellitus N (%)	Coronary disease N (%)
Total	66	45 (68.2)	57.1	11	35 (53)	32 (48.5)	21 (31.8)	26 (39.4)	21 (31.8)
Cardioembolic sources									
Atrial cardiopathy	47	32 (68.1)	57	11	23 (48.9)	24 (51.5)	8 (17)	18 (38.3)	7 (14.9)
Atrial fibrillation *	12	5 (41.6)	57.8	11	9 (75)	6 (50)	4 (33.3)	4 (33.3)	3 (25)
Left ventricular dysfunction **	26	18 (69.2)	57.1	12	15 (57.7)	15 (57.7)	8 (30.7)	15 (57.7)	8 (30.7)
Cardiac valvular disease	2 2	16 (72.7)	58.6	11	11 (50)	13 (59.1)	9 (13.6)	10 (45.4)	2 (9.1)
Patent Foramen ovale	16	11 (68.7)	49.8	11	(18.7)	2 (12.5)	0 (0)	2 (12.5)	0 (0)
Non cardioembolic sources									
Arterial disease	46	40 (86.9)	59.9	7	22 (47.8)	26 (56.5)	20 (43.4)	22 (47.8)	18 (39.1)
Cancer	5	3 (60)	59.8	12	1 (20)	4 (80)	1 (20)	1 (20)	1 (20)
Absence of PES	6	3 (50)	58	11	2 (33.3)	2 (33.3)	2 (33.3)	3 (50)	0 (0)

* Atrial fibrillation not initially present and identified during follow-up is considered the cause of ESUS.

** Patients with left ventricular ejection fraction <30% were excluded.

N = number of patients; SD= standard deviation

Table 4. Index stroke characteristic and stroke recurrence during follow-up per PES.

				NIHSS		mRs (0-2)			
	N	Prior stroke N (%)	Multi territory stroke N (%)	Med	Q1-Q3	at discharge N (%)	at 3 months N (%)	at 12 months N (%)	Stroke recurrence during follow-up N (%)
Total	66	12 (18.2)	6 (9.1)	7	4-13	48 (72.7)	51 (77.3)	54 (81.8)	18 (27.3)
Cardioembolic sources									
Atrial cardiopathy	47	4 (8.5)	6 (12.7)	6	4-11	30 (36.8)	31 (65.9)	33 (70.2)	5 (10.6)
Atrial fibrillation *	12	3 (25)	4 (33.3)	8	4-14	6 (50)	6 (50)	7 (58.3)	2 (16.7)
Left ventricular dysfunction **	26	3 (11.5)	0 (0)	6	4-10	19 (73)	22 (84.6)	22 (84.6)	2 (7.7)
Cardiac valvular disease	12	0 (0)	0 (0)	5	3-7	18 (81.8)	20 (90.9)	20 (90.9)	1 (4.5)
Patent Foramen ovale	16	0 (0)	0 (0)	3	2-6	13 (81.2)	14 (87.5)	14 (87.5)	1 (6.2)
Non cardioembolic sources									
Arterial disease	46	4 (8.7)	0 (0)	7	3-12	29 (63)	29 (63)	32 (69.5)	5 (10.8)
Cancer	5	0 (0)	0 (0)	6	3-8	2 (40)	2 (40)	2 (40)	1 (20)
Absence of PES	6	0 (0)	0 (0)	6	3-8	2 (33.3)	3 (50)	3 (50)	1 (16.6)

* Atrial fibrillation not initially present and identified during follow-up is considered the cause of ESUS.

** Patients with left ventricular ejection fraction <30% were excluded.

N = number of patients; Med = median; NIHSS = National Institute of Health Stroke Scale; mRs= modified Rankin scale; PES= potential embolic source; SD= standard deviation

Table 5. Comparison of stroke recurrence according to type of PES. Hazard ratios (HR) and 95% confidence intervals (CI) computed using a multivariable Cox proportional hazards model. Models were adjusted for age, sex, hypertension, dyslipidaemia, diabetes mellitus, smoking status, coronary artery disease and NIHSS score at admission.

	HR (95% CI)	*P*-value
Cardioembolic sources		
Atrial cardiopathy	1.16 (0.78 - 1.6)	0.426
Atrial fibrillation *	1.37 (0.82 - 2.34)	0.242
Left ventricular dysfunction **	0.89 (0.61 - 1.24)	0.530
Cardiac valvular disease	0.63 (0.45 - 1.28)	0.083
Patent Foramen ovale	0.81 (0.54 - 1.38)	0.385
Non cardioembolic sources		
Arterial disease	1.23 (0.79 - 1.94)	0.373
Cancer	1.6 (0.8 - 2.27)	0.077
Absence of PES	1.49 (0.8 - 2.27)	0.134

* Atrial fibrillation not initially present and identified during follow-up is considered the cause of ESUS.

** Patients with left ventricular ejection fraction <30% were excluded.

versus aspirin in secondary prevention of stroke and prevention of systemic embolism in patients with recent embolic stroke of undetermined source) [9,21] and the RE-SPECT ESUS (dabigatran etexilate for secondary stroke prevention in patients with ESUS) trials [22] as well as several observational studies [4,11], reported that two-thirds of all patients with ESUS had at least 2 potential embolic sources, and the most common ones were non-stenotic large artery disease, left ventricular disease, and atrial cardiopathy. Moreover, one-third of the patients had at least 3 such sources (each was present in nearly half of the study population) [5,9].

It was also reported that most patients with ESUS have multiple PES, which could explain the neutral results of therapeutic trials: The NAVIGATE ESUS and the RE-SPECT ESUS trials [9,21,22] showed that anticoagulation is not superior to aspirin to prevent stroke recurrence in patients with ESUS, showing that the lumping therapeutic approach of oral anticoagulation for the unselected population with ESUS was not the optimal strategy and indirectly validating the ESUS concept as an etiologically heterogeneous entity [5,12].

The heterogeneity of embolic sources and their remarkable degree of overlap, as reported in the present study, could explain these negative results. Over 40% of patients with ESUS have multiple PES, some of which may be associated with low-blood flow which predisposes to formation of red thrombi that may respond better to anticoagulation, whereas other embolic sources may be associated with atherosclerotic plaque ulceration which triggers the formation of white thrombi that may have responded better to antiplatelet therapy [20].

In this context, treating patients with ESUS with anticoagulants rather than antiplatelets may cause simply exchanging the type of thrombus, with the overall burden of thrombi remaining unchanged and hence, no change in the rate of stroke recurrence.

If this hypothesis is correct, it would be rational to expect that a combination of anticoagulant and antiplatelet in patients with ESUS would be associated with a substantial reduction of stroke recurrences in patients with ESUS. These thoughts are supported by the results of the COMPASS (cardiovascular outcomes for people using anticoagulation strategies) trial which showed that a combination of low-dose rivaroxaban and aspirin was associated with a large reduction of stroke risk compared with aspirin as monotherapy [23,24].

Furthermore, the strategy of combining anticoagulant and antiplatelet therapy may not apply to patients with atrial cardiopathy. Meanwhile, the ARCADIA (atrial cardiopathy and antithrombotic drugs in prevention after cryptogenic stroke) trial [10], which is currently investigating whether oral anticoagulation with apixaban is a better strategy compared with aspirin in patients with atrial cardiopathy, reports positive results.

We found that the risk of stroke recurrence was similar across different PES, which suggest that the thromboembolic risk across these PES is similar. This is in line with the concept of ESUS, which considers all these PES as minor-risk embolic sources [5,9].

Table 6. Comparison of stroke recurrence according to number of PES. Hazard ratios (HR) and 95% confidence intervals (CI) computed using a multivariable Cox proportional hazards model. Models were adjusted for age, sex, hypertension, dyslipidaemia, diabetes mellitus, smoking status, coronary artery disease and NIHSS score at admission.

		Number of patients N	Stroke recurrence during follow-up N (%)	HR (95% CI)	*P*-value
Number of PES	≤1	10	3 (30)	1.13 (0.58-2.1)	0.723
	2	36	9 (25)	1.25 (0.8-2.04)	0.356
	≥3	20	6 (30)	1.22 (0.7-1.96)	0.458

We also found that the risk of stroke recurrence in patients with multiple PES was not further increased. Similar studies with longer follow-up and adequately powered cohort studies are needed to show whether these risk differences would be larger in the long-term.

This is the first description of a Tunisian ESUS population providing detailed data on potential etiologic causes of ESUS and the degree of PES overlap. Another strength of this study is that the definition of ESUS was based on the criteria proposed by the Cryptogenic Stroke/ESUS International Working Group. This may allow future studies to compare other ESUS populations to the current one using standardised criteria. Another strength of the present study is that the estimated degree of PES overlap might be the actual overlap because of the extensive panel of diagnostic work-up investigations that had been performed for most patients, regardless of their ages. Moreover, we used several measurements to define each PES, especially the atrial cardiopathy [9,10]. In this context, our estimates of the prevalence of each PES and of prevalence of multiple PES are likely reasonable. Nevertheless, our study has certain limitations. It is a single-center character rather than a population-based setting, which may have introduced selection bias. In addition, a type II error due to moderate sample size and limited number of events cannot be excluded. Additionally, it is a retrospective analysis of prospectively collected data, which may have introduced collection and registration bias.

In the present study, we conclude that most ESUS patients had multiple PES with a major degree of overlap. Rather, prospective data with advanced diagnostic methods are warranted to identify the true distribution of the underlying stroke aetiology in patients with ESUS. Currently, ESUS may be considered as a developing diagnostic concept that triggers increased diagnostic studies presumably leads to increased detection rates of the underlying stroke cause and subsequently reduces the overall rate of undefined or cryptogenic strokes.

Article information

Ethics statement. The study was approved by the local ethics committee.

Declaration of interest. The authors declare that they have no conflict of interest.

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References

[1] Saver JL. Cryptogenic stroke. N Engl J Med. 2016;375:e26. https://doi.org/10.1056/nejmcp1503946

[2] Hart RG, Catanese L, Perera KS, Ntaios G, Connolly SJ. Embolic stroke of undetermined source : a systematic review and clinical update. Stroke. 2017;48:867–72. https://doi.org/10.1161/strokeaha.116.016414

[3] Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, Sacco RL, Connolly SJ, Cryptogenic Stroke/ESUS International Working Group. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol. 2014;13:429–38. https://doi.org/10.1016/s1474-4422(13)70310-7

[4] Ntaios G et al. Embolic strokes of undetermined source in the Athens stroke registry: a descriptive analysis. Stroke. 2015;46:176–81. https://doi.org/10.1161/strokeaha.114.007240

[5] Ntaios G et al. Prevalence and overlap of potential embolic sources in patients with embolic stroke of undetermined source. J Am Heart Assoc. 2019;8:e012858. https://doi.org/10.1161/jaha.119.012858

[6] Al-Rukn S et al. Stroke in the Middle East and North Africa: A 2 -year prospective observational study of stroke characteristics in the region - Results from the Safe Implementation of Treatments in Stroke (SITS) - Middle-East and North Africa (MENA). Int J Stroke. 2019;14:715-22. https://doi.org/10.1177/1747493019874729

[7] Sacco RL et al. An updated definition of stroke for the 21st century. Stroke. 2013;44:2064–89. https://doi.org/10.1161/str.0b013e318296aeca

[8] Chung JW et al. Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification and vascular territory of ischemic stroke lesions diagnosed by diffusion-weighted imaging. JAHA. 2014;3:e001119. https://doi.org/10.1161/jaha.114.001119

[9] Ntaios G et al. Potential embolic sources and outcomes in embolic stroke of undetermined source in the NAVIGATE-ESUS trial. Stroke. 2020;51:1797-04. https://doi.org/10.1161/strokeaha.119.028669

[10] Kamel H et al. The atrial cardiopathy and antithrombotic drugs in prevention after cryptogenic stroke randomized trial: Rationale and methods. Int J Stroke. 2019;14:207-14. https://doi.org/10.1177/1747493018799981

[11] Perera KS et al. Embolic strokes of undetermined source: Prevalence and patient features in the ESUS Global Registry. Int J Stroke. 2016;11:526-33. https://doi.org/10.1177/1747493016641967

[12] Schäbitz WR, Köhrmann M, Schellinger PD, Minnerup J, Fisher M. Embolic Stroke of Undetermined Source : Gateway to a new stroke entity ? Am J Med. 2020;133:795-801. https://doi.org/10.1016/j.amjmed.2020.03.005

[13] Ntaios G. Embolic Stroke of Undetermined Source. J Am Coll Cardiol. 2020;75:333-40. https://doi.org/10.1016/j.jacc.2019.11.024

[14] Verma A, Ha ACT, Kirchhof P, Hindricks G, Healey JS, Hill MD, Sharma M, Wyse DG, Champagne J, Essebag V, Wells G, Gupta D, Heidbuchel H, Sanders P, Birnie DH. The optimal anti-coagulation for enhanced-risk patients postcatheter ablation for atrial fibrillation (OCEAN) trial. Am Heart J. 2018;197:124-32. https://doi.org/10.1016/j.ahj.2017.12.007

[15] Li TYW et al. Association of electrocardiographic P-wave markers and atrial fibrillation in Embolic Stroke of Undetermined Source. Cerebrovasc Dis. 2021;50:46-53. https://doi.org/10.1159/000512179

[16] Lattanzi S et al. The P-wave terminal force in Embolic Stroke of Undetermined Source. J Neurol Sci. 2017;375:175-78. https://doi.org/10.1016/j.jns.2017.01.063

[17] Hirunagi T, Miwa S, Katsuno M. Nonstenotic carotid plaque in patients with anterior circulation embolic stroke of undetermined source. Brain Nerve. 2018;70:1295-99. https://doi.org/10.11477/mf.1416201176

[18] Ntaios G, Wintermark M, Michel P. Supracardiac atherosclerosis in embolic stroke of undetermined source: the underestimated source. Eur Heart J. 2020:32300781. https://doi.org/10.1093/eurheartj/ehaa218

[19] Ntaios G et al. Aortic arch atherosclerosis in patients with Embolic Stroke of Undetermined Source. Stroke. 2019;50:3184-90. https://doi.org/10.1161/strokeaha.119.025813

[20] Ntaios G, Hart RG. Embolic stroke. Circulation. 2017;136:2403-05. https://doi.org/10.1161/circulationaha.117.030509

[21] Hart RG 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;1:146-54. https://doi.org/10.1177/2396987316663049

[22] Diener HC et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. N Engl J Med. 2019;380:1906-17. https://doi.org/10.1056/nejmoa1813959

[23] Perera KS et al. Association between low-dose Rivaroxaban with or without Aspirin and ischemic stroke subtypes: A secondary analysis of the COMPASS Trial. JAMA Neurol. 2020;77:43-48. https://doi.org/10.1001/jamaneurol.2019.2984

[24] Sharma M et al. Stroke outcomes in the COMPASS Trial. Circulation. 2019;139:1134-45. https://doi.org/10.1161/circulationaha.118.035864