

## Embolic Stroke of Undetermined Source: An Updated Review of Potential Mechanisms and their Management

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### Abstract

Embolic strokes of undetermined source (ESUS) are defined as non lacunar ischemic strokes that occur in the absence of extracranial or intracranial atherosclerosis causing > 50% luminal stenosis, have had major cardioembolic sources of embolism excluded by echocardiogram and holter monitoring, and have had other known causes of stroke excluded. ESUS accounts for 15% to 30% of all ischemic strokes. Because the source of embolism remains unclear, secondary prevention in these patients has remained a challenge. Our aim is to summarize the postulated etiologies of ESUS and to review the most up-to-date evidence in this field. We searched PubMed using the keywords 'ESUS' and 'cryptogenic stroke'. Search was also extended based on known etiologies in association with ESUS such as 'atherosclerotic plaque and ESUS', 'aortic arch atherosclerosis and ESUS', 'non stenosing carotid plaques and ESUS', and 'atrial cardiopathy, left ventricular dysfunction, paradoxical embolism in ESUS'. Preference was given to original articles that were published from April 2014 onwards. Majority of the recent studies focused on atrial cardiopathy, aortic arch atherosclerosis, and carotid artery atherosclerotic plaques as the most likely underlying etiologies. There is a limited evidence to support management decision-making in ESUS beyond antiplatelet therapy and optimization of cardiovascular risk factors.

**Keywords:** ESUS; Cryptogenic Stroke; Aortic Arch Atherosclerosis; Carotid Atherosclerotic Plaques; Atrial Cardiopathy

### Introduction

Stroke, the most common cause of disability and one of the leading causes of death, has deleterious socio-economic impacts on patients, their families and healthcare systems worldwide [1]. Among all ischemic stroke subtypes, embolic stroke of undetermined source (ESUS) has generated a great deal of interest in recent years. The term "ESUS" was introduced in 2014 by the Cryptogenic Stroke/ESUS International Working Group to identify patients with non-lacunar strokes who may benefit from anticoagulation [2]. ESUS patients are distinguished from the cryptogenic stroke population by the TOAST criteria, whereby the latter also includes patients with incomplete investigations or those with more than one plausible cause of stroke [3]. The original landmark publication described multiple potential causes of thromboembolism underlying ESUS, including cardiogenic causes, as well as others such as paradoxical and arteriogenic embolism. Since then, three clinical trials have begun, comparing novel anticoagulants to aspirin for secondary stroke prevention in the originally defined ESUS population [4-6]. The first of these trials to be published, the NAVIGATE-ESUS, showed that treatment with rivaroxaban did not reduce stroke recurrence when compared to aspirin in ESUS patients. Therefore, prospective studies to better define ESUS patients and to appropriately select those that would benefit from anticoagulation are warranted. In this review, we present an update on potential sources of embolism in the ESUS population with reflection on novel trials that are currently underway or have been published.

## Methods

We searched PubMed using the keywords: 'ESUS' and 'cryptogenic stroke'. Search was also made for etiologies in association with ESUS such as 'atherosclerotic plaque and ESUS', 'aortic arch atherosclerosis and ESUS', 'non stenosing carotid plaques and ESUS', 'atrial cardiopathy, left ventricular dysfunction, paradoxical embolism in ESUS'. Only articles in English were included (N = 55), with preference given to original articles published from 2014 onwards (N = 30). Last search was conducted on April 29<sup>th</sup>, 2018.

## Results

### Arteriogenic Emboli

**Aortic arch atherosclerosis (AAA):** A mechanistically plausible source of embolism, has been found to be more prevalent in stroke patients without an alternate cause on pathological and radiological studies [7,8]. Trans-esophageal echocardiography (TEE) and CT angiogram (CTA) are both well-established methods of detecting and characterizing AAA [8-11]. Imaging features associated with higher stroke risk include plaque thickness > 4 mm, mobile plaques, and ulceration [6,12-14]. Smaller infarcts scattered across multiple territories may be helpful in differentiating ESUS due to AAA from those with paroxysmal atrial fibrillation [15].

A recent study showed that in ESUS patients with aortic plaques > 4 mm, the risk of recurrent stroke is up to 7.5% per person-year [16]. However, aortic plaques did not independently predict stroke recurrence. AAA may therefore be merely a marker of overall atherosclerotic burden rather than the underlying embolic source in the ESUS population.

Few prospective studies have examined the optimal management of AAA in ESUS. The Aortic Arch-Related Cerebral Hazard (ARCH) trial [17] compared dual antiplatelet therapy to warfarin in TIA and minor stroke patients with aortic arch plaque as the only source of embolism. Due to slow recruitment and low event rate, this trial was underpowered and did not detect a significant difference in the recurrence of primary vascular events. However, death related to vascular events was significantly higher in the warfarin group. Additionally, a small open-label study found that rosuvastatin increased the echogenicity of aortic plaques compared to control, suggesting a potential stabilizing effect on cholesterol-laden aortic atheromas [18]. Collectively, these studies suggest that antiplatelet and lipid lowering therapy remain the preferred treatment in this patient population.

**Non-stenotic carotid artery atherosclerotic plaque:** Carotid artery plaques causing less than 50% narrowing of the lumen has generally been overlooked as a potential source of embolism [3]. However, evidence suggests that degree of stenosis alone is inadequate for determining the vulnerability of a plaque [19]. Advances in imaging modalities have made it possible to risk-stratify patients based on plaque characteristics (i.e. plaque size, composition, and metabolic activity) rather than degree of carotid artery stenosis alone [20].

One study using MRI and <sup>18</sup>F-fluoro-deoxyglucose positron emission tomography (<sup>18</sup>F-FDG PET) imaging to investigate the morphological and biological aspects of non-stenotic carotid atherosclerotic plaques in 18 patients with cryptogenic strokes found complicated atherosclerotic plaque (AHA type VI) in 39% of the ipsilateral carotid arteries compared to 0% in the contralateral side [21]. In patients presenting with at least one complicated plaque on MRI, <sup>18</sup>F-FDG uptake in both carotid arteries was significantly higher compared to those with no complicated lesions, suggesting a diffuse inflammatory process associated with complicated plaques. Another observational study using CTA to measure plaque thickness in ESUS patients found that large ( $\geq 3$  mm thick), non-stenotic (< 50%) carotid artery plaques occurred more commonly in the ipsilateral side when compared to the contralateral side [22]. Most recently, a pilot study comprising 35 consecutive ESUS patients with carotid artery stenosis of less than 50% found that 1 in 5 had carotid artery intraplaque hemorrhage identified by MRI of the vessel wall ipsilateral to the side of the index stroke event [23]. These studies highlight the importance of plaque characteristics, rather than simply the degree of luminal stenosis, in the evaluation of patients with ESUS.

**Atrial Cardiopathy:** Given therapeutic implications, the hypothesis that covert paroxysmal atrial fibrillation (AF) is a leading cause of stroke in ESUS is widely accepted and has led to the current practice of performing prolonged cardiac monitoring in these patients. However, 70% of patients do not manifest AF, even after 3 years of monitoring [24]. This suggests that AF may not be the only necessary substrate for cardio-embolism.

Recent evidence suggest that left atrial thromboembolism can occur without AF through atrial derangements such as chamber dilation [25], endothelial cell dysfunction [26] and impaired myocyte dysfunction [27]. These features together were defined as “atrial cardiopathy” (AC), a term used to describe atrial structural and pathophysiological changes that can precede the dysrhythmia of AF [28]. Various ECG, TTE and serum markers have been linked to the definition of AC. These include increased p-wave terminal force in V1 (PTFV1) [29], paroxysmal supraventricular tachycardia (PSVT) [30], premature atrial contraction (PACs) [31], increased PR interval [32], increased left atrial size [33] or volume [34] and elevated NT-proBNP [34]. We recently showed that the prevalence of AC is high in ESUS patients compared to patients with non-embolic stroke (26.6% in ESUS vs. 12.1% in those with large artery disease vs. 16.9% in patients with lacunar stroke;  $p = .001$ ; paper in review). The Cardiovascular Health Study recently showed that in patients with markers of AC, 15.7% experienced stroke during a median 12.9 years of follow up [35]. Collectively, these data make AC a strong etiological consideration in the workup of ESUS patients.

While there is an equipoise in secondary prevention of ESUS with AC, the newly launched ARCADIA (AtRial Cardiopathy and Anti-thrombotic Drugs In Prevention After Cryptogenic Stroke) study is a multicenter, biomarker-driven, randomized, double-blind, phase 3 clinical trial that is currently assessing efficacy of apixaban vs. aspirin in stroke prevention in this population (@ClinicalTrials.gov - estimated end of the study is by mid-2020).

**Paradoxical Embolism:** Paradoxical Embolism via patent foramen ovale (PFO), atrial septal defect and rarely, pulmonary arteriovenous fistula, are also suggested causes in ESUS [2,36], though this has been a longstanding point of controversy [37]. Patients with PFO are known to be younger and have fewer traditional stroke risk factors than those without PFO [38]. Recent studies continued to report similar and even higher PFO prevalence in patients with ESUS that ranges from 25% to 58% [16,39], as compared to the general population (~25%) [40]. The rate of recurrent strokes in patients with PFO and atrial septal aneurysm (ASA) may, however, be lower than what was demonstrated a decade ago (3.0% now vs. 15.2% then) [16,41]. The Risk of Paradoxical Embolism score (ROPE), an index developed to distinguish incidental PFO from PFO related to stroke, shows a ten-fold decrease in stroke recurrence rate (20% to 2%) in younger patients with a pathogenic PFO (large size PFO shunt, ASA) and no vascular risk factors, compared to older patients with PFO and risk factors, suggesting that true paradoxical embolization recurs relatively rarely [42].

In contrast, recent meta-analyses reported a benefit of PFO closure over medical therapy in secondary stroke prevention, and also suggested that presence of pathogenic PFO may be high risk for recurrent strokes [43,44]. Given these trials, it is still questionable whether patients with high risk PFO should still be categorized within the ESUS group or simply included under the stroke of known etiology, based on the classic TOAST criteria [3].

**Other Cardiogenic Causes:** Although the LVEF (left ventricular ejection fraction) cut-off value of 30% is defined as a high-risk cardioembolic source in the original ESUS construct and in the Stop Stroke Study of the Trial of Org 10172 in Acute Stroke Treatment classification system [45,46] there is insufficient evidence to support the predictive capacity of this cut-off value. Hays, *et al.* [47] found that even moderate LV dysfunction (LVEF  $\geq 30\%$ ) independently increased risk of stroke, suggesting that moderate LV dysfunction could lead to thrombosis in the LV cavity. Another study showed that approximately 40% of stroke patients with LV thrombus on contrast-enhanced cardiovascular magnetic resonance (CE-CMR) had LVEF  $\geq 30\%$  [48]. Thus, the current LVEF cut-off value of 30%, which is based on the diagnostic criteria for ESUS, could be suboptimal in detecting all patients at high risk for recurrent cardioembolic stroke.

Clinical entities such as mitral valve disease (prolapse, annular calcification, and valve strands), aortic valve disease (sclerosis, stenosis, and regurgitation), left atrial thrombus, LV aneurysm without thrombus, and atrial septal aneurysm are associated with a modest risk for stroke [49]. It remains unclear whether these diagnoses are directly associated with ischemic stroke or rather reflect complex correlations with other co-morbidities. In conclusion, despite the availability of good diagnostic modalities to identify these cardiac conditions, it is not recommended to routinely screen for these diagnoses as their presence generally does not alter therapy [50]. Studies suggesting the thromboembolic source in ESUS/ cryptogenic stroke are represented in table 1.

Study	Design*	N	Gender (%Female)	Age	Marker measured	Proposed thromboembolic source
Yaghi, <i>et al.</i> [39]	CSS	40	65	Median age 68.5 years (range: 24 - 88)	- 49% had NT-proBNP levels > than 250 pg/mL - 20% had PTFV1 > 5000 $\mu\text{V}\cdot\text{ms}$ on EKG - 5% had severe LAE	Atrial cardiopathy
Kamel, <i>et al.</i> [35]	LCS	121	48	Mean age 68.2 $\pm$ 9.8 years	PTFV1 on EKG	Atrial cardiopathy
Di Tullio, <i>et al.</i> [14]	CCS	40	65	Mean age 65.1 $\pm$ 14.3 years	TEE measuring the thickness and complexity of plaques	Aortic atheromas
Tunick, <i>et al.</i> [51]	CCS	42	38	Mean age 72.0 $\pm$ 1.5 years	TEE measuring the thickness and complexity of plaques	Aortic atheromas
Amarenco, <i>et al.</i> [8]	CCS	250	54.8	Mean age 76.4 $\pm$ 7.9 years	TEE by plaque thickness	Aortic atheromas
Hyafil, <i>et al.</i> [21]	CSS	18	63	Mean age 70 $\pm$ 12 years	AHA type VI plaque	Complicated, Non-stenosing CAP†
Coutinho, <i>et al.</i> [22]	CSS	85	52	Median age 70 years (range: 58 - 79)	Plaque thickness $\geq$ 3 mm	Non-stenosing CAP
Singh, <i>et al.</i> [23]	CSS	35	54.3	Mean age 74.3 $\pm$ 9.6 years	Carotid artery intraplaque hemorrhage	Non-stenosing CAP

**Table 1:** Studies suggesting the thromboembolic source in ESUS/cryptogenic stroke.

\*CSS: Cross Sectional; CCS: Case Control Study; LCS: Longitudinal Cohort Study; #TEE: Transesophageal Echocardiogram; † CAP: Carotid Atherosclerotic Plaque

## Conclusion

Since the introduction of the term ESUS in 2014, multiple research groups have attempted to better define this population and to explore potential contributing etiologies. Many questions remain unexplored. What threshold of quantifiable atherosclerotic burden in the various vascular beds is associated with a high stroke risk? How does underlying etiology influence the clinical outcome in ESUS? Should patients with high risk PFO be eliminated from the ESUS subgroup? If the trials of anticoagulation in ESUS are negative, it may be necessary to redefine the population to better select those that would truly benefit from anticoagulation therapy.

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