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JACC REVIEW TOPIC OF THE WEEK

Embolic Stroke of Undetermined Source

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ABSTRACT

The term embolic stroke of undetermined source (ESUS) was introduced in 2014 to describe patients with a nonlacunar ischemic stroke and no convincing etiology. The terms ESUS and cryptogenic stroke are not synonyms, as the latter also includes patients with multiple stroke etiologies or incomplete diagnostic work-up. ESUS involves approximately 17% of all ischemic stroke patients, and these patients are typically younger with mild strokes and an annual rate of stroke recurrence of 4% to 5%. It was hypothesized that oral anticoagulation may decrease the risk of stroke recurrence in ESUS, which was tested in 2 large randomized controlled trials: the NAVIGATE ESUS (Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source) and the RE-SPECT ESUS (Dabigatran Etexilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source). The present review discusses the trials of anticoagulation in patients with ESUS, suggests potential explanations for their neutral results, and highlights the rationale that supports ongoing and future research in this population aiming to reduce the associated risk for stroke recurrence.
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The term embolic stroke of undetermined source (ESUS) was introduced in 2014 to describe patients with a nonlacunar ischemic stroke and no convincing etiology (1). The terms ESUS and cryptogenic stroke are not synonyms, as the latter also includes patients with multiple stroke etiologies or incomplete diagnostic work-up. The introduction of the term ESUS facilitated the conduction of randomized controlled trials in this population, as it set criteria to define patients as such, something which was not possible with the original cryptogenic stroke definition (1).

ESUS represents an etiologically heterogeneous group and may be caused by various potential sources of thromboembolism (**Central Illustration, Figure 1**) (2). The most prevalent among them seem to be the left atrium, the left ventricle, and atherosclerotic plaques in the arterial tree supplying the territory of the infarct (3).

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ESUS: AN UNMET CLINICAL NEED AND THE RATIONALE FOR RESEARCH TO IMPROVE OUTCOMES

ESUS represents a large patient group as it involves approximately 17% of all ischemic stroke patients, who are typically younger patients with mild strokes. In addition, these patients have a considerable rate of stroke recurrence of 4% to 5%/year (4,5). Given that nearly 90% of ESUS patients had been treated with antiplatelets, it became obvious that alternative antithrombotic strategies were necessary to reduce recurrent strokes. It was hypothesized that oral anticoagulation may decrease the risk of stroke recurrence in ESUS, which was tested in 2 large randomized controlled trials: NAVIGATE ESUS (Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

ESUS = embolic stroke of undetermined source

PFO = patent foramen ovale

Undetermined Source) and the RE-SPECT ESUS (Dabigatran Etexilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source) (5,6).

AF IN ESUS: LESS IMPORTANT THAN INITIALLY CONCEIVED

Initially, covert atrial fibrillation (AF) was conceived as perhaps the most important underlying mechanism in ESUS patients, especially given that prolonged cardiac rhythm monitoring is not a prerequisite for the definition of ESUS. Randomized controlled trials of prolonged cardiac monitoring like the CRYSTAL-AF (Study of Continuous Cardiac Monitoring to Assess Atrial Fibrillation After Cryptogenic Stroke) (7), EMBRACE (30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event) (8), and Find-AF$_{\text{RANDOMISED}}$ (A Prospective, Randomised, Controlled Study to Determine the Detection of Atrial Fibrillation by Prolonged and Enhanced Holter Monitoring as Compared to Usual Care in Stroke Patients) (9), as well as observational studies (2,4) and meta-analyses (10), showed that AF may be detected in 30% of ESUS patients during long-term follow-up; however, its causal association with the index stroke remains a matter of debate, particularly for episodes of AF that are short-lasting, subclinical, or detected long after stroke (11). The argument of a strong causal association is weakened by emerging evidence showing that:

1. The rate of AF detection during follow-up in ESUS patients is similar to other non-ESUS stroke patients, as shown in the Find-AF-$_{\text{RANDOMISED}}$ study (9).
2. The rate of occurrence of subclinical atrial fibrillation lasting ≥5 min is similar among older patients with and without history of stroke, as shown in the ASSERT-II (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial) (12). Still, in a large study in Medicare beneficiaries, new diagnoses of AF were more frequent after hospitalization for ischemic stroke than after hospitalization for hemorrhagic stroke or non-stroke conditions (13).
3. ESUS patients are phenotypically different compared with stroke patients with AF, with the former being younger with milder strokes, as shown across registries and trials (2,4–6). In the Athens Stroke Registry, the stroke severity of patients with ESUS was considerably lower in patients with ESUS compared with patients with cardioembolic stroke (National Institute of Health Stroke Scale score 5 vs. 13, respectively) (2). In addition, in the NAVIGATE ESUS and RE-SPECT ESUS trials, the stroke severity of ESUS patients at recruitment was even lower (the median National Institute of Health Stroke Scale score was 1 in both trials) (9,10).
4. The majority of embolic events (stroke or systemic embolism) does not occur proximal to recent episodes of atrial tachycardia or AF, as shown in patients with implantable cardiac monitoring devices in the ASSERT (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial) (14) and TRENDS (A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics) (15) studies.

HIGHLIGHTS

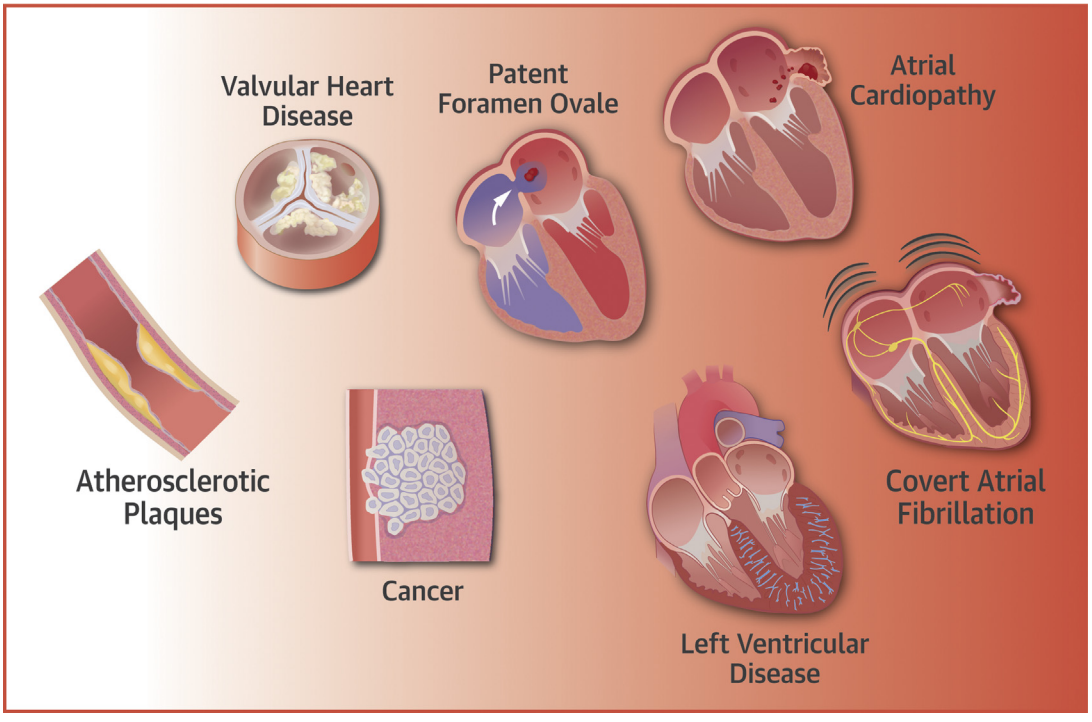
- Covert atrial fibrillation seems to be less important as an ESUS etiology than was initially conceived.
- Potential embolic sources overlap considerably in ESUS, which may explain the neutral trial results.
- Ongoing research investigates ESUS subgroups that may respond better to anticoagulation.
- Combining anticoagulant with antiplatelet warrants further research in ESUS with atherosclerosis.

On the contrary, covert AF may constitute the main embolic source in specific ESUS subgroups like the elderly. In the RE-SPECT ESUS trial, the subgroup of patients age >75 years had a significant benefit of lower-dose dabigatran over aspirin, which could favor the hypothesis of new-developed or covert AF (6).

POTENTIAL EMBOLIC SOURCES BESIDES AF

The main pathologies that could be etiologically associated with ESUS are presented in **Figure 1**. They could be broadly categorized in 7 embolic sources: atrial cardiopathy, covert AF, left ventricular disease, atherosclerotic plaques, patent foramen ovale (PFO), cardiac valvular disease, and cancer (**Central Illustration**). In a recent analysis of the AF-ESUS study, the 3 most prevalent potential embolic sources were left ventricular disease, arterial disease, and atrial cardiopathy, each being present in nearly one-half of all patients (**Figure 2**) (3). The presence of a potential embolic source in an ESUS patient should not be automatically presumed as its actual cause, given that it may be simply an innocent bystander

CENTRAL ILLUSTRATION **Rationale for Research on Antithrombotic Strategies in ESUS**



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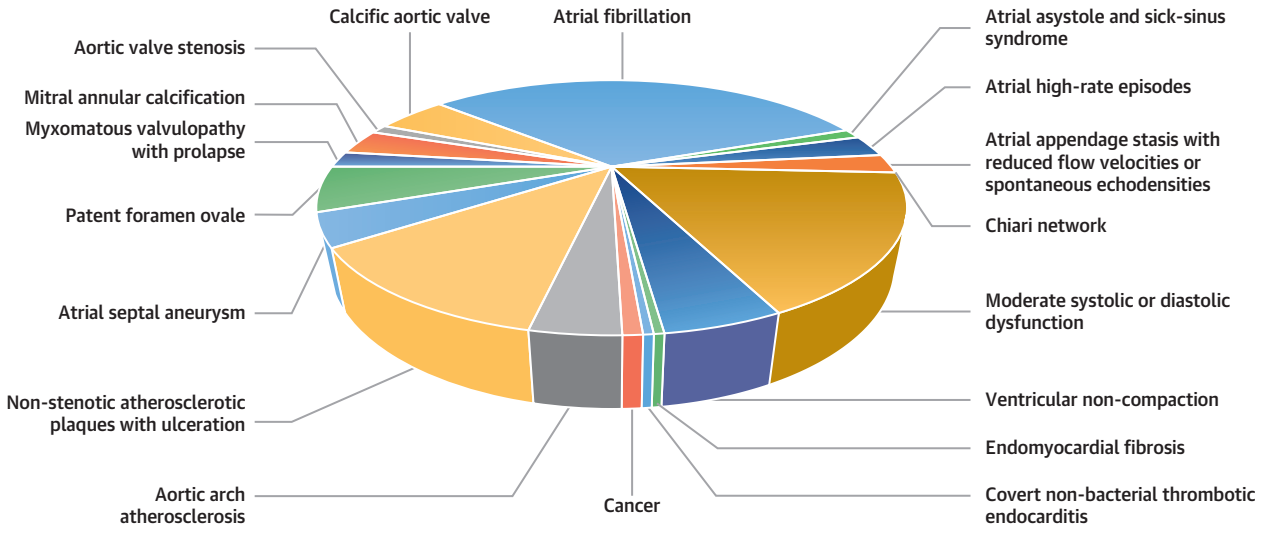
The main pathologies that could be etiologically associated with embolic stroke of undetermined source (ESUS) could be broadly categorized in 7 embolic sources: atrial cardiopathy, covert atrial fibrillation, left ventricular disease, atherosclerotic plaques, patent foramen ovale, cardiac valvular disease, and cancer. For certain embolic sources like atrial cardiopathy and fibrillation, left ventricular disease, PFO, and cancer (drawn toward the red-colored end of the spectrum in the illustration), the main pathophysiological stimulus for thrombogenesis is presumed to be the low blood flow, which predisposes to formation of red thrombi that may respond better to anticoagulation as supported by recent studies and meta-analyses (34,45,46). The ARCADIA trial (AtRial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke) currently investigates whether ESUS patients with atrial cardiopathy respond better to apixaban compared with aspirin for prevention of stroke recurrence (44). On the contrary, in the case of atherosclerotic plaques in the aortic arch, cerebral, and intracranial arteries (drawn towards the white-colored end of the spectrum in the illustration), the main pathophysiological trigger is plaque rupture and subsequent local platelet activation and aggregation leading to formation of white thrombi, which may respond better to antiplatelets. The results of the COMPASS (A Randomized Controlled Trial of Rivaroxaban for the Prevention of Major Cardiovascular Events in Patients With Coronary or Peripheral Artery Disease) trial generate the hypothesis that the combination of low-dose oral anticoagulation and aspirin could further reduce the risk of stroke recurrence in patients with ESUS and atherosclerosis (39,40). However, this should be first assessed in randomized controlled trials before being implemented in routine clinical practice.

(16). Although the present review does not aim to discuss thoroughly the available evidence related to the etiological association between the aforementioned embolic sources and ESUS, it will briefly touch upon some recent evidence about the association between ESUS and non-AF pathologies.

The etiologic role of carotid atherosclerotic plaques in patients with ESUS was assessed in several recent studies. In the NAVIGATE ESUS trial and in other studies, carotid plaque was much more often present ipsilateral to the qualifying ischemic stroke than contralateral (17–20). In addition, in the AF-ESUS study, new incident AF was less frequently detected in ESUS patients with ipsilateral carotid plaques compared with those without (21). Similarly, a strong negative association was reported between carotid plaques and PFO in young adults with cryptogenic stroke (22).

The role of atrial cardiopathy in the pathogenesis of ESUS was investigated in several studies during the recent years (23). Several lines of evidence indicate that thrombi may be formed in the diseased left atrium, even in the absence of atrial fibrillation (23). Atrial cardiopathy may be defined using several

FIGURE 1 Distribution of Potential Etiologies of ESUS in the Athens Stroke Registry



Adapted from Ntaios et al. (2). ESUS = embolic stroke of undetermined source.

indices including biomarkers (24–26), cardiac magnetic resonance imaging (27), and electrocardiographic indexes (28–30).

The presumed mechanism of ischemic stroke in patients with PFO is the migration of an embolus from the right to the left atrium. For several decades, observational studies yielded inconsistent results, and later on, the early randomized trials of percutaneous PFO closure failed to show benefit, fueling the controversy about the etiological role of PFO in ESUS (31). However, the recent randomized trials of percutaneous PFO closure yielded impressive results in patients with ESUS who are age <60 years and verified the etiologic association between PFO and ESUS in this patient group (32).

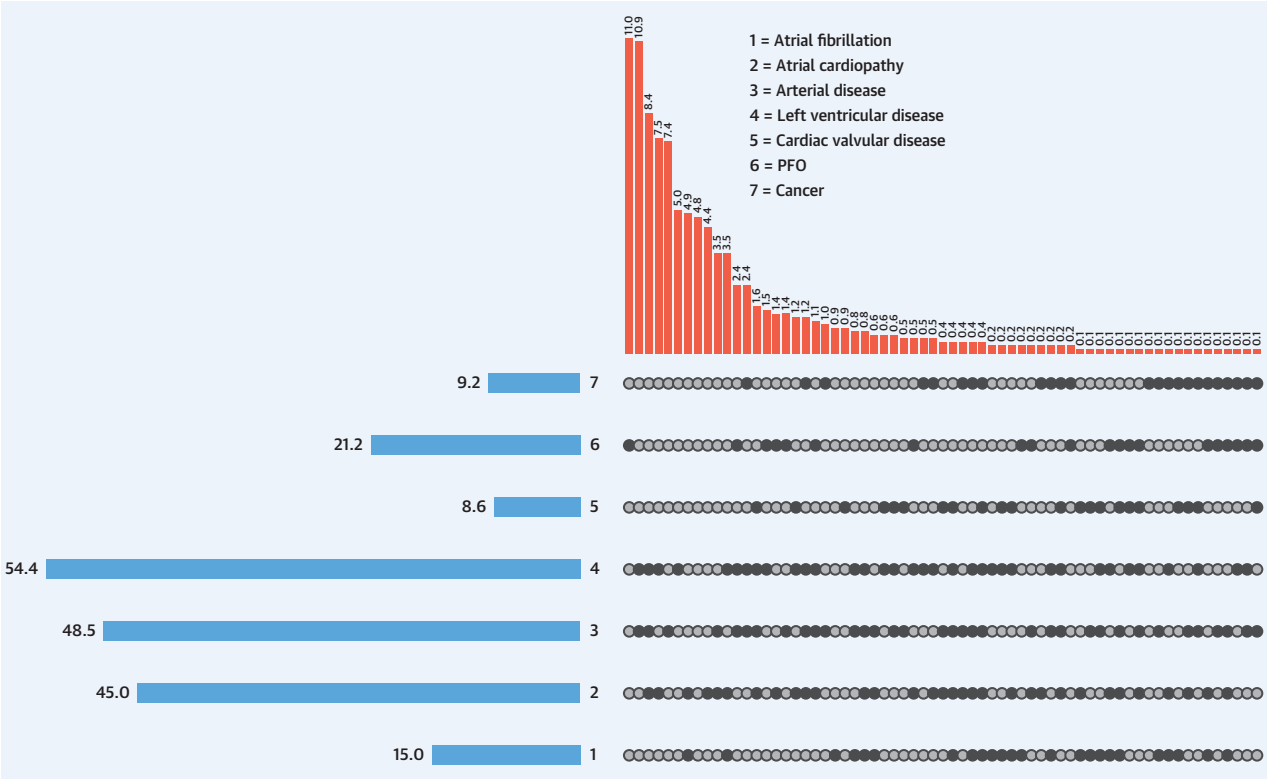
The association between left ventricular disease and ESUS is based on several pathophysiological derangements like low cardiac output, dilated chambers, poor contractility, endothelial dysfunction, and others (33). A recent meta-analysis of randomized controlled trials of oral anticoagulation in patients with heart failure and sinus rhythm showed a large reduction in the risk of stroke in anticoagulant-assigned patients compared with patients assigned to antiplatelets or placebo, further supporting the causal association between left ventricular disease and ESUS (34). Still, the rate of major bleeding was higher in anticoagulant-assigned patients, which offsets any beneficial effect of oral anticoagulation in these patients (34).

Patients with cancer have a substantially increased stroke risk, which varies by cancer stage and type (e.g., it is greatest in patients with lung cancer) (35). This association is mediated by several pathologies like hypercoagulopathy, tumor embolism, mechanical compression of vessels, marantic endocarditis, anemia, radiotherapy, antineoplastic treatment adverse effects, and others (36). Two recent small randomized controlled trials investigated different antithrombotic strategies in patients with cancer and did not show different outcomes; however, these studies were clearly underpowered (37,38). Hence, it is still unclear whether there is any role for anticoagulation in patients with ESUS and cancer.

THE NAVIGATE ESUS AND RE-SPECT ESUS TRIALS

The 2 recently completed large trials of oral anticoagulation in ESUS concluded that oral anticoagulation was not associated with lower rates of stroke recurrence compared with aspirin (**Table 1**). Interestingly, the event curves in the RE-SPECT ESUS started to diverge after 1 year of follow-up with a positive outcome during the second year in a landmark analysis (6). It is not possible to know whether a similar observation would have been noticed in the NAVIGATE ESUS if the follow-up period was longer, given that patients were followed for a median of 11 months (5).

FIGURE 2 Prevalence of PES and Degree of Their Overlap in the AF-ESUS Study



Each **row** corresponds to a specific potential embolic sources (PES), as described in the legend. **Open cells** indicate absence of the specific PES, whereas **filled cells** correspond to the presence of the specific PES. Each **column** corresponds to a specific combination of PES. The **numbers in the plot** correspond to the proportion of patients in the overall population who have a specific PES **(for the numbers shown at the rows)** or a specific combination of PES **(for the numbers shown at the columns)**. PFO = patent foramen ovale. Reproduced from Ntaios et al. (3).

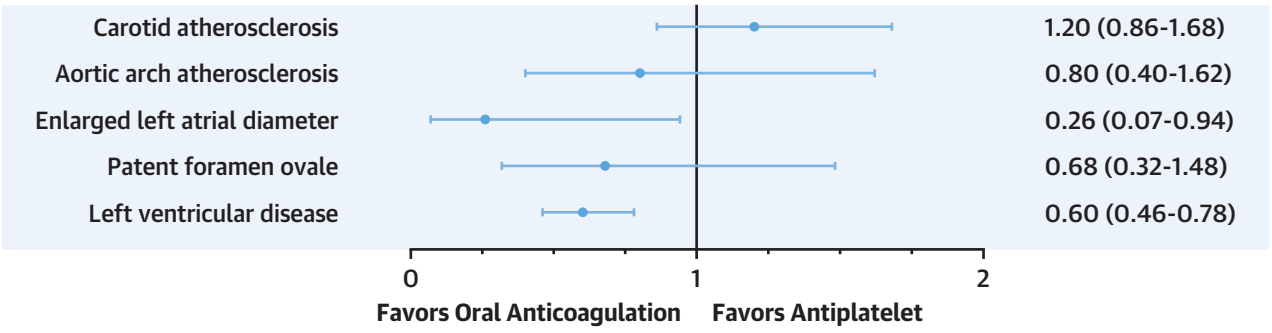
In the NAVIGATE ESUS, there was a significant difference in the rates of major bleeding and intracranial hemorrhage between rivaroxaban- and aspirin-assigned patients, whereas in the RE-SPECT ESUS trial, there was no difference in the rates of these outcomes between dabigatran- and aspirin-assigned patients. However, it should be noted that this inconsistency between the 2 trials was not driven by the safety profile of the oral anticoagulants (i.e., rivaroxaban and dabigatran), but surprisingly, by the safety profile of aspirin in the 2 trials. In particular, the rates of major bleeding were similar between

TABLE 1 Annualized Rates and HRs of the Main Outcomes in the NAVIGATE ESUS and RE-SPECT ESUS Trials

	NAVIGATE ESUS			RE-SPECT ESUS		
	Rivaroxaban (n = 3,609)	Aspirin (n = 3,604)		Dabigatran (n = 2,695)	Aspirin (n = 2,695)	
	Annualized Rate % (Events)	Annualized Rate % (Events)	HR (95% CI)	Annualized Rate % (Events)	Annualized Rate % (Events)	HR (95% CI)
Any stroke	5.1 (171)	4.7 (158)	1.08 (0.87–1.34)	4.1 (177)	4.8 (207)	0.85 (0.69–1.03)
Ischemic stroke	4.7 (158)	4.7 (156)	1.01 (0.81–1.26)	4.0 (172)	4.7 (203)	0.84 (0.60–1.03)
Major bleeding	1.8 (62)	0.7 (23)	2.72 (1.68–3.39)	1.7 (77)	1.4 (64)	1.19 (0.85–1.66)
Intracranial hemorrhage	0.6 (20)	0.1 (5)	4.02 (1.51–10.70)	0.7 (32)	0.7 (32)	0.98 (0.60–1.60)

CI = confidence interval; HR = hazard ratio; NAVIGATE ESUS = Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source; RE-SPECT ESUS = Dabigatran Etexilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source.

FIGURE 3 Comparison Between Oral Anticoagulation and Antiplatelet Treatment in Patients With ESUC/Cryptogenic Stroke and Underlying Potential Embolic Source



Hazard ratios and 95% confidence intervals are obtained from an exploratory subgroup analysis of the NAVIGATE ESUS trial for patients with carotid atherosclerosis (17); from a systematic review and meta-analysis including the NAVIGATE ESUS (Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source) trial for patients with aortic arch atherosclerosis (47); from an exploratory subgroup analysis of the NAVIGATE ESUS trial for patients with enlarged left atrial diameter (>4.6 cm) (45); from a systematic review and meta-analysis including the NAVIGATE ESUS trial for patients with patent foramen ovale (46); and from a systematic review and meta-analysis including the NAVIGATE ESUS trial for patients with heart failure and sinus rhythm (34).

rivaroxaban- and dabigatran-assigned patients (1.8% and 1.7%/year, respectively) (**Table 1**). On the contrary, the rates of major bleeding in patients assigned to aspirin in the NAVIGATE ESUS were lower compared with patients assigned to aspirin in the RE-SPECT ESUS trial (0.7% and 1.4%/year, respectively) (**Table 1**). Aspirin was in enteric-coated form in the NAVIGATE ESUS and in plain form in the RE-SPECT ESUS trial (5,6). There is no strong evidence in the published data comparing enteric-coated and plain aspirin that could convincingly explain this difference in the outcomes of major bleeding. Therefore, it is unclear whether this difference was caused by some difference in the safety profile of the 2 forms of aspirin or was just a play of chance.

WHY WERE THE ESUS TRIALS NEUTRAL?

A possible explanation for the lack of a beneficial effect of oral anticoagulation compared with aspirin in ESUS patients may be the overlap of potential embolic sources in this population (3). In the AF-ESUS study, 65% of patients had >1 potential embolic source, whereas only 29.7% and 4.8% had a single source or none, respectively (3). In 31.1% of patients, there were ≥3 potential embolic sources present (3). On average, each patient had 2 potential embolic sources (3). For certain embolic sources (like atrial cardiopathy, left ventricular disease, PFO, and cancer), the main pathophysiological stimulus for thrombogenesis is presumed to be low blood flow, which predisposes to formation of red thrombi that may respond better to anticoagulation (11). On the contrary, for other embolic sources like aortic arch, cervical, or intracranial atherosclerosis, plaque ulceration triggers the formation of white thrombi that may respond better to aspirin (11). In this context, it may be hypothesized that treating an ESUS patient with anticoagulants rather than aspirin may just result in exchanging red thrombi for white, without any meaningful change in the overall thromboembolic burden and, hence, stroke rates.

DIRECTIONS OF ONGOING AND FUTURE RESEARCH ON ESUS

The COMPASS (A Randomized Controlled Trial of Rivaroxaban for the Prevention of Major Cardiovascular Events in Patients With Coronary or Peripheral Artery Disease) trial provided important information about the role of the combination of low-dose oral anticoagulation and aspirin in patients with stable atherosclerotic disease (39). The combination of low-dose rivaroxaban plus aspirin was associated with a large reduction of stroke risk compared with aspirin as monotherapy both in the overall population (0.7% vs. 1.4%, respectively; hazard ratio [HR]: 0.51; 95% confidence interval [CI]: 0.38 to 0.68) (39), as well as in patients with previous stroke (1.4% vs. 3.4%, respectively; HR: 0.42; 95% CI: 0.19 to 0.92) (40). This was especially evident in cardioembolic strokes and ESUS (41). Although the rate of major bleeding was increased in patients assigned to rivaroxaban/aspirin compared with aspirin (3.1% vs. 1.9%, respectively;

HR: 1.70; 95% CI: 1.40 to 2.05), the net clinical benefit outcome (defined as cardiovascular death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into critical organ) favored the rivaroxaban/aspirin combination (4.7% vs. 5.9%, respectively; HR: 0.80; 95% CI: 0.70 to 0.91) (39). An adequately powered randomized controlled trial is definitely warranted to test the hypothesis that the combination of low-dose oral anticoagulation and aspirin could decrease the risk of stroke recurrence in patients with ESUS and aortic arch, cervical, or intracranial atherosclerosis. In addition, the putative superior safety profile of oral factor XIa inhibitors suggests that they could represent a promising strategy for stroke prevention in patients with ESUS and atherosclerosis as an add-on therapy to antiplatelet treatment (42). The ongoing AXIOMATIC (A Global, Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of BMS-986177, an Oral Factor XIa Inhibitor, for the Prevention of New Ischemic Stroke or New Covert Brain Infarction in Patients Receiving Aspirin and Clopidogrel Following Acute Ischemic Stroke or Transient Ischemic Attack) trial investigates the role of oral Factor XIa Inhibitor (BMS-986177) for secondary stroke prevention in patients with acute ischemic stroke or transient ischemic attack and atherosclerosis proximal to the affected brain area (43).

For ESUS patients without atherosclerotic lesions, it seems rational to hypothesize that oral anticoagulation could reduce the risk of stroke recurrence, given the high prevalence of pathologies that tend to generate red thrombi, like atrial cardiopathy and fibrillation, left ventricular disease, PFO, and cancer (3). Recent evidence suggests that anticoagulation may reduce stroke risk in patients with atrial cardiopathy (44) or left ventricular disease (34) (**Figure 3**). In this context, the ongoing ARCADIA (AtRial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke) trial currently investigates whether ESUS patients with atrial cardiopathy respond better to apixaban compared with aspirin for prevention of stroke recurrence (44).

THE END OF THE BEGINNING

Six years after the inception of the ESUS concept, the publication of the 2 ESUS trials marks the end of the beginning of the ESUS trajectory: although neutral, they provided important information about this large stroke population that is characterized by no convincing etiology, a distinct and reproducible phenotype, and considerable stroke risk.

There is reasonable rationale for ongoing and future research toward tailoring the antithrombotic strategy according to patient characteristics: 1) anticoagulation in ESUS patients with pathologies that tend to generate red thrombi, like atrial cardiopathy, or with a high risk for covert AF, like the elderly; and 2) combining low-dose anticoagulation with antiplatelets in ESUS patients with atherosclerosis. In the meantime, the ESUS concept may need to be revised to accommodate recent evidence that evolved our understanding about: 1) which strokes are indeed "undetermined"; and 2) which diagnostic work-up is indeed "proper." With regard to the former, it seems rational to remove patients with PFO and age below 60 years and no other potential embolic sources, as the robust evidence of the large benefit of PFO closure that emerged from several well-conducted randomized controlled trials presumes a causal association (32). On the contrary, patients with PFO and age >60 years should not be removed from the ESUS population, as there is no evidence that PFO closure is superior to antithrombotic therapy in this age group. With regard to the latter, there is ongoing discussion about the role of more intensive diagnostic work-up in patients with ESUS (e.g., prolonged cardiac monitoring, sophisticated imaging of the atherosclerotic plaque with magnetic resonance imaging, and others).

The high prevalence of ESUS patients, the considerable stroke risk, the availability of sophisticated diagnostic modalities, the establishment of novel antithrombotic strategies (like the combination of low-dose rivaroxaban/aspirin), and the development of novel classes of oral anticoagulants (like the FXIa inhibitors) highlight ESUS as an important priority in stroke research in the coming years.

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