

Embolic Stroke of Undetermined Source (ESUS)

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A B S T R A C T

Embolic stroke of undetermined source (ESUS) is a subset of cryptogenic stroke. Recurrence rates are high following ESUS and the optimal treatment to reduce the risk of recurrent stroke depends on the pathophysiology of the index stroke. Because of the composition of emboli, anticoagulants may be a better treatment option than antiplatelet therapy in secondary stroke prevention. This article reviews recent and ongoing clinical trials evaluating antithrombotic treatments in the setting of ESUS, examines differences among the trials, and discusses the implications of anticoagulation in ESUS.

Key words: ESUS, stroke, NOACs, anticoagulation

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INTRODUCTION

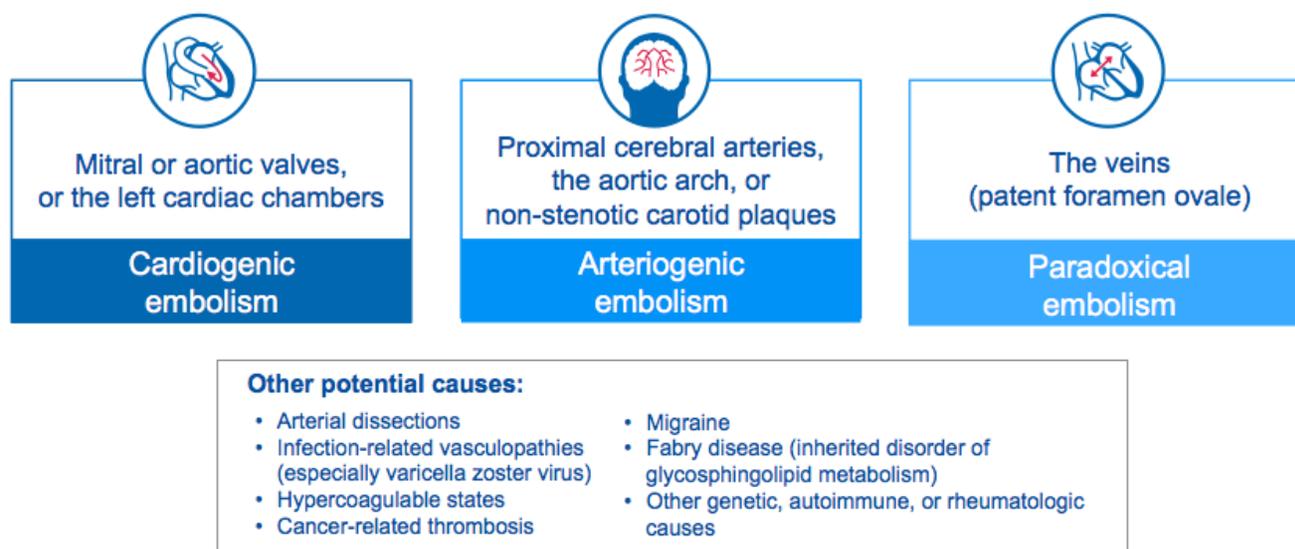
Cryptogenic stroke, which accounts for 25%-33% of ischemic strokes, is poorly defined concerning especially the required diagnostic work-up.^{1,2} A diagnosis of cryptogenic stroke may reflect an incomplete diagnostic assessment, no apparent cause of stroke after an extensive work up, or the presence of multiple possible etiologies.¹ Stroke etiology has implications for secondary prevention treatment strategies and risk for recurrent stroke. Although most cryptogenic strokes are thought to be thromboembolic, guidelines generally recommend aspirin for secondary prevention.^{iii,iv} Embolic stroke of undetermined source (ESUS) is a relatively new clinical concept that strives to refine classification of cryptogenic stroke, as certain types of embolic stroke may respond to a particular treatment strategy (i.e., anticoagulation).^{1,4}

ESUS OVERVIEW: WHAT DO WE KNOW?

ESUS, a subset of cryptogenic stroke, is diagnosed by excluding other etiologies such as cardio-embolic precipitated by atrial fibrillation (AF), small artery disease (lacunar), and occlusive large artery atherosclerosis.¹ ESUS accounts for approximately 17% of ischemic strokes.⁵ Patients with ESUS tend to be relatively young, with an average age of 65 years, and have fewer traditional cardiovascular (CV) risk factors.^{4,5} Data from several national or global stroke registries suggest that cryptogenic stroke in individuals younger than 60 years may be ESUS.⁶ The stroke recurrence rate in ESUS is high. For instance, a systematic review found 4.5% of ESUS patients on antiplatelet therapy had a secondary event during an average follow up of 2.7 years.⁵ According to an analysis of the Athens Stroke Registry, the cumulative five-year probability of recurrence is 29.0%.⁷ Age, but not gender, increases the risk of secondary events, with individuals who are 60-80 years old having more than a

two-fold increase in recurrent stroke compared to those younger than 60. Elderly patients (>80 years) have a three-fold higher risk of secondary events compared to those younger than 60.⁸ Interestingly the CHA₂DS₂-VASc score predicts the risk of stroke recurrence and death in patients with ESUS.⁹

The optimal treatment to reduce the risk of recurrent stroke depends on the pathophysiology of the index stroke.¹⁰ The possible sources of ESUS include embolism originating in the mitral or aortic valves, arteries (aortic arch, unstenotic <50% carotid or proximal cerebral arteries plaque), paradoxical embolism; hypercoagulable states; cancer-related thrombosis; and infection-related vasculopathies, among others (Figure 1).⁴ Other cardiogenic sources include moderate left ventricular (LV) systolic or diastolic dysfunction, abnormalities in LV wall motion following a myocardial infarction (MI), and atrial septal aneurysms, among others.¹

Figure 1. Potential Causes of ESUS

Hart et al. *Lancet Neurol* 2014; Nouh et al. *Front Neurol* 2016; Bulwa, Gupta. *Neurol Sci* 2017

Covert AF is relatively common in patients with stroke of undetermined cause. At 12 months, one study evaluating an insertable cardiac monitor (ICM) found AF lasting >30 seconds in 12.4% of patients aged ≥40 years with cryptogenic stroke.¹¹ At 30 days, an event record recorder revealed AF lasting >30 seconds in 16.1% of individuals aged ≥55 years with cryptogenic stroke.¹²

AF is a major risk factor for cardioembolic stroke and, thus, is an exclusion criterion for ESUS. However, current guidelines recommend prolonged rhythm monitoring of 30 days as reasonable within 6 months of the index stroke.¹³ The length of ECG monitoring is impractical for the patients and mainly for the conclusive diagnostic workup

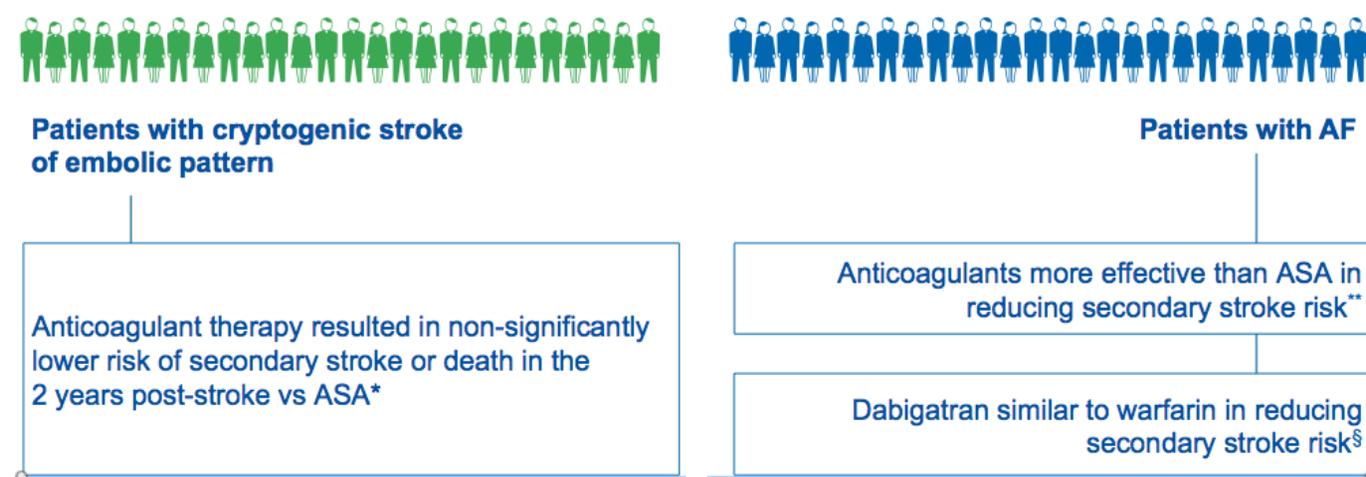
in the end of patient hospitalization. Thus the authors of ESUS definition arbitrarily stated the minimal length of ECG monitoring as 24 hours; however, paroxysmal AF might not occur during this period.¹

Most patients are prescribed antiplatelet therapy for secondary prevention of cryptogenic stroke. Research has shown that use of a potent antiplatelet agent (e.g., clopidogrel or ticagrelor) or dual antiplatelet therapy does not have a net clinical benefit in secondary prevention of ESUS.^{4,9} The Warfarin-Aspirin Recurrent Stroke Study (WARSS) showed no difference between warfarin and aspirin in reduction of secondary strokes in patients with a noncardioembolic stroke.¹⁴ According to a sub-

group analysis of WARSS, however, warfarin significantly reduced the two-year risk of stroke or death in patients with cryptogenic stroke and no hypertension compared with aspirin.¹⁵ This finding was especially true in the subgroup with a higher level of cardiac failure biomarker

amino terminal pro-B-type natriuretic peptide, NT-proBNP (>750 ng/dl), suggesting a role for anticoagulation in some patients (Figure 2).¹⁶

Figure 2. OAC Effectiveness in Secondary Stroke Prevention



*Sacco et al. Cerebrovasc Dis. 2006;22:4-12. **EAFT Study Group. Lancet. 1993;342:1255-62. §Diener et al. Lancet Neurol. 2010;9:1157-63.

ANTICOAGULATION CLINICAL TRIALS IN ESUS

Histological evidence has shown that thrombi from both cardioembolic and cryptogenic strokes have a higher composition of fibrin compared to noncardioembolic strokes.¹⁷ Anticoagulants are more effective than antiplatelet agents in preventing the formation of thrombus arising from the polymerization of fibrin.³ Non-vitamin-K

oral anticoagulants (NOACs), which target specific aspects of the coagulation cascade, have demonstrated similar or better efficacy with significantly lower intracranial hemorrhage (ICH) in the setting of AF.^{1,4} NOACs are now being evaluated for secondary stroke prevention in ESUS (Table 1).

Table 1. Recent and Ongoing NOAC Trials for Secondary Prevention in ESUS¹⁵⁻²⁰

Trial	No. of Patients	Investigational Drug	Primary Efficacy Outcome	Safety Outcome	Est. Completion
NAVIGATE-ES-US	7,213	Rivaroxaban 15 mg OD	First occurrence of stroke (ischemic or hemorrhagic) or SE	Major bleeding [^]	Terminated early
RE-SPECT ESUS	5,390	Dabigatran 150 or 110 mg BID*	First occurrence of stroke (ischemic, hemorrhagic, unknown)	Major bleeding	October 2018
ATTICUS	~500	Apixaban 5 mg BID	Occurrence of at least one new ischemic lesion at 12 months	MACE Bleeding composite	Unknown
ARCADIA	~1,100	Apixaban 5 mg or 2.5 mg BID*	Recurrent stroke (ischemic, hemorrhagic, or unknown)	ICH Major hemorrhage excluding ICH	2022

*Lower dose of dabigatran for patients aged ≥75 years or with CrCl 30-50 mL/min. Lower dose of apixaban for patients who have at least two of the following: age ≥80 years, body weight ≤60 kg, or CrCl ≥1.5 mg/dL. [^]Based on International Society of Thrombosis and Haemostasis (ISTH) criteria. MACE – Major adverse cardiovascular event. ICH – Intracranial hemorrhage.

NAVIGATE ESUS

The double-blind NAVIGATE ESUS trial randomized 7,213 patients with ESUS to either rivaroxaban (15 mg OD) or aspirin. Eligibility for the trial included having had a non-lacunar ischemic stroke, confirmed by imaging, within six months of screening. Exclusion criteria included occlusive large artery atherosclerosis and AF, with the latter based on a minimum of 20 hours of ECG monitoring. For patients aged 50-59, an additional stroke risk factor, such as hypertension or smoking, was required for enrollment. The median time from stroke to randomization was 37 days. At baseline, the average age of participants was 67 years; the median National Institutes of Health Stroke Scale (NIHSS) score was 1. Patent foramen ovale (PFO) was present in 7% of patients and over the course of the trial, 3% of patients were found to have AF at a median of 5 months after entry, with similar numbers in both the rivaroxaban and control groups.¹⁸ The lower than expected rates of PFO are due to the fact that only 1382 patients in the study had transesophageal echocardiography (TEE) which is not needed by the ESUS criteria. In fact, the PFO rate was 27% in patients who had TEE.

At a pre-defined interim analysis (median follow up of 11 months), the trial was terminated owing to increased bleeding in the rivaroxaban arm without the benefit of lower risk of stroke/systemic embolism (SE). Life-threatening or fatal bleeding occurred in 1.0% of patients treated with rivaroxaban compared to 0.4% of control ($P=0.004$). Symptomatic ICH was also significantly more frequent for rivaroxaban at 0.6% compared to 0.1% for control ($P=0.003$). There was no difference in ischemic stroke rate, with an incidence of 4.7% in each group.¹⁵

RE-SPECT ESUS

RE-SPECT ESUS is a double-blind, event-driven randomized controlled trial evaluating dabigatran 150 or 110 mg BID compared with aspirin in the secondary prevention of stroke. Eligible patients had an ischemic stroke within the previous three months or within six months for those aged ≥ 60 years with an additional stroke risk factor. Inclusion criteria also included a modified Rankin scale of ≤ 3 . Screening also included diagnostic studies to exclude lacunar stroke or major cardioembolic risk factor, such as AF. Patients aged ≥ 75 years or with creatinine clearance (CrCl) 30-50 mL/min are receiving dabigatran 110 mg BID; all other patients randomized to dabigatran are taking the standard dose (150 mg BID).¹⁹ Both doses of dabigatran were proven to be safe and effective for stroke prevention in AF, with a standard dose of 150 mg BID and the lower dose of dabigatran given to patients with high bleeding risk.²⁰ The primary efficacy endpoint of RE-SPECT ESUS is time to first recurrence of stroke (ischemic, hemorrhagic, or unknown). Secondary endpoints include ischemic stroke and a composite of nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death. The primary safety endpoint is time to first major bleeding event.¹⁶ Results are expected to be released in October 2018.

APIXABAN TRIALS

There are two ESUS trials evaluating apixaban in secondary stroke prevention: ATTICUS and ARCADIA. ATTICUS, an open-label study with a planned enrollment of approximately 500 individuals, is comparing apixaban 5mg BID to daily aspirin when initiated within seven days of ESUS. Patients must already have or receive an ICM to participate in the study. The primary outcome is the occurrence of at least one new ischemic lesion as identified by magnetic resonance imaging (MRI) at 12 months. Secondary outcomes include a composite of strokes (ischemic, hemorrhagic, SE), major adverse cardiovascular events (MACE), and bleeding. Trial completion is expected in December 2019.^{4,2,1}

ARCADIA, which began enrolling patients in January 2018, is evaluating apixaban 5 mg BID versus aspirin in patients with a recent cryptogenic stroke and evidence of atrial cardiopathy. A reduced dose (2.5 mg BID) will be given to patients who have two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or known serum creatinine ≥ 1.5 mg/dL. The primary efficacy outcome is recurrent stroke (ischemic, hemorrhagic, or unknown). Secondary outcomes include recurrent ischemic stroke/SE, symptomatic ICH, major hemorrhage excluding ICH, and all-cause mortality. Approximately 1,100 individuals are expected to be enrolled. Study completion is estimated for 2022.^{22,23}

ANTICOAGULATION CLINICAL TRIALS IN ESUS

NAVIGATE-ESUS trial results do not negate the possibility that a NOAC will offer favorable safety and effectiveness for secondary stroke prevention following ESUS. There are several confounders within the trial that could have affected efficacy or safety. For instance, it remains unclear whether the rivaroxaban dose (15 mg) used in NAVIGATE-ESUS diminished the drug's effectiveness in reducing the recurrence of ischemic stroke/SE. In ROCKET AF, the standard dose of rivaroxaban was 20 mg, with 15 mg reserved for patients with CrCl of 30-49 ml/min.²⁴ In NAVIGATE-ESUS, 94% of the rivaroxaban group had normal renal function.¹⁵ The use of a lower-dose drug in patients with normal kidney function may have affected results. Moreover, the once daily dosing regimen with a lower dose may be another factor to consider, since many rivaroxaban trials are now dosing BID to provide 24-hour anticoagulation coverage. The other argument concerns the characteristics of the drug itself, since we do know that the standard dose of rivaroxaban 20mg had the least favourable safety data of all NOACs in subgroup analysis for secondary stroke prevention. There are other potential confounders of the trial results, including time from stroke to randomization, treatment initiation (at least seven days after index stroke). Separately, the investigators noted that the incidence of ICH observed in the aspirin arm was lower than that reported in previous trials. Overall, major bleeding was low at an annualized rate of 1.8% in the rivaroxaban group compared with 0.7% in the aspirin arm.¹⁵

There are several important differences among the various ESUS trials of NOACs, which could affect an investigational drug's ability to demonstrate better outcomes relative to aspirin (the control drug in all of the trials). In addition, it is possible that some causes of ESUS may not be well suited to treatment by OAC. Items that should be considered when assessing ESUS trials include:

- **Dosing.** As mentioned above, NAVIGATE-ESUS used a rivaroxaban dose (15 mg) that has not been rigorously evaluated in clinical trials. ROCKET-AF was not designed to provide statistical assessment of the safety and effectiveness of 15 mg of rivaroxaban in patients with AF. ARCADIA uses a similar dosing protocol as that used in ARISTOTLE: 5 mg BID as the standard dose and a reduced dose (2.5 mg) for certain patients.^{19,20,26} Similar to ROCKET-AF, ARISTOTLE did not fully evaluate the safety and efficacy of the two different doses in prevention of AF-related stroke. Comparatively, RE-SPECT ESUS uses the two doses of dabigatran (150 and 110 mg) that demonstrated similar or superior reduction of ischemic stroke in patients with AF in the RE-LY trial.^{16,17}
- **Covert AF.** NAVIGATE-ESUS excluded patients with an ICM and no ECG monitoring was mandated after patient enrollment. Despite this, 3% of the cohort was found to have AF during the course of the study.¹⁵ In RE-SPECT ESUS and ARCADIA, additional ECG monitoring, including an ICM, may be used at the physician's discretion.^{16,19-20} ATTICUS specifies use of an ICM or daily ECG monitoring in its protocol.⁴
- **PFO.** It is unclear whether the percentage of patients with PFO could have affected efficacy outcomes in NAVIGATE-ESUS or will affect outcomes in the ongoing ESUS trials. Although PFO is included in the definition of ESUS, it is unknown whether thrombi originating from PFO are more amenable to anticoagulation or an antiplatelet therapy. A meta-analysis comparing outcomes for OAC and antiplatelet for secondary prophylaxis in the setting cryptogenic stroke and PFO showed low overall event rates that favored use of OAC. However, there was no significant difference between the two treatment strategies.²⁷
- **Arterogenic emboli.** It is possible that other sources of ESUS, such as subclinical atherosclerosis in large vessels supplying the brain or in the aortic arch, may not respond well to OAC. In a post-hoc analysis of the SOCRATES trial, patients diagnosed with ESUS and with subclinical atherosclerosis in large vessels randomized to the ticagrelor arm had a significant reduction in recurrent stroke compared to those in the aspirin group. There was no between-group difference for individuals with ESUS and without subclinical atherosclerosis in large vessels.²⁸ It may be that antiplatelet therapy is a better secondary prevention strategy to stabilize plaque and prevent

thrombus formation in patients with stenosis <50% in large vessels supplying the brain or with aortic arch atheroma.⁹

- **Safety.** The ESUS trials have differing safety endpoints: major bleeding based on ISTH criteria (NAVIGATE-ESUS), time to first major bleed (RE-SPECT ESUS), bleeding composite (ATTICUS), and ICH and major hemorrhage excluding ICH (ARCADIA). All of these trials assume low rates of bleeding.¹⁵⁻²⁰

IMPLICATIONS FOR ANTICOAGULATION IN ESUS

RE-SPECT ESUS is expected to report results in October 2018. If results show a benefit for dabigatran over aspirin in secondary stroke prevention in ESUS, it is possible that prolonged ECG monitoring to detect covert AF will become obsolete in many cases since dabigatran is approved for use as stroke prophylaxis in AF. ATTICUS may have similar implications for use of apixaban but results from this small trial (~500 patients) are more likely to add to the body of evidence rather than precipitate a change in clinical practice.

Evidence from ARCADIA may provide insight into the effectiveness of a biomarker-driven treatment strategy. More recently, a registry of patients with acute ischemic stroke found that elevated troponin levels were associated with ESUS but not noncardioembolic strokes.²⁹ In ARCADIA, one of the criteria defining atrial cardiopathy is NT-pro BNP >250 pg/mL.²⁰ Results and sub-group analysis may have implications for the optimal antithrombotic strategy for secondary stroke prevention.

It may be that the recommended diagnostic work-up to establish a diagnosis of ESUS will be expanded to include longer than 24-hour ECG monitoring, biomarkers as NT-proBNP, or some additional diagnostic methods to assist in choosing the most appropriate secondary stroke prevention treatment. For instance, contrast-enhanced cardiac magnetic resonance imaging may provide useful information for detection of thrombi (e.g., LV thrombus) that would be suitable for anticoagulation.³⁰

CONCLUSION

ESUS comprises approximately 17% of ischemic strokes and is associated with a high recurrence rate. The goal is to tailor secondary stroke prevention strategies based on the most likely mechanism of the index stroke. The clinical construct of ESUS and associated clinical trials are tangible steps in ascertaining the optimal antithrombotic strategy for a given patient. Although NAVIGATE-ESUS was stopped prematurely, the ongoing ESUS studies should help answer several remaining questions in this area, such as NOAC dosing, frequency and type of bleeding events in the ESUS patient population, and NOACs' role in secondary prevention.

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