**Reexamination of the embolic stroke of undetermined source (ESUS) concept: A Review**

**Cover title: Reexamination of the ESUS Concept**

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**Word count: 3079**

**Number of Figures and Tables**: 1 Table

**ABSTRACT**

**Importance:** Occult atrial fibrillation (AF) is a leading cause of stroke of unclear etiology. The optimal approach to secondary stroke prevention for these patients remains elusive.

**Observations:** The term embolic stroke of undetermined source (ESUS) was coined to describe ischemic strokes in which the radiographic features demonstrate territorial infarcts resembling those seen in patients with confirmed sources of embolism, but without a clear source of embolism detected. It was assumed that patients with ESUS had a high rate of occult AF and would benefit from treatment with direct oral anticoagulants (DOACs), which are at least as effective as Vitamin K antagonists for secondary stroke prevention in patients with AF, but with a much lower risk of intracerebral hemorrhage. Two recent large randomized trials failed to show superiority of DOACs over aspirin in ESUS patients. These findings prompt a reexamination of the ESUS concept, with the goal of improving specificity for detecting patients with a cardioembolic etiology. Based on the negative trial results, there is renewed interest in the role of long-term cardiac monitoring for AF in patients who fit the current ESUS definition, as well as, the clinical implication of detecting AF. Ongoing trials are exploring these questions.

**Conclusions and Relevance:** Current ESUS definitions do not accurately detect the patients who should be prescribed DOACs, because occult AF is less common than expected in these patients and/or anticoagulants are less beneficial in patients with ESUS but no AF than they are for stroke patients with established AF. More specific criteria to identify patients who may be at higher risk for occult AF and reduce their risk of subsequent stroke have been developed and are being tested in ongoing clinical trials.

**ABBREVIATIONS**

**ESUS:** Embolic Stroke of Undetermined Source

**AF:** Atrial Fibrillation

**VKA:** Vitamin K Antagonists

**DOAC:** Direct Oral Aral AntiCoagulant

**ICH:** IntraCerebral Hemorrhage

**NAVIGATE-ESUS:** New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus Aspirin to Prevent Embolism in Embolic Stroke of Undetermined source

**ISTH:** International Society of Thrombosis and Hemostasis

**HR:** Hazard Ratio

**CI:** Confidence Interval

**COMPASS:** Cardiovascular Outcomes for People Using Anticoagulation Strategies

**RESPECT-ESUS:** Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate *vs.* Acetylsalicylic Acid in Patients with Embolic Stroke of Undetermined Source

**TOAST:** Trial of Org 10172 in Acute Stroke Treatment

**WARSS:** Warfarin-Aspirin Recurrent Stroke Study

**MRI:** Magnetic Resonance Imaging

**DW:** Diffusion-Weighted

**FLAIR:** Fluid Attenuated Inversion Recovery

**ASSERT:** Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial

**CRYSTAL-AF:** Cryptogenic Stroke and underlying Atrial Fibrillation

**ATTICUS:** Apixaban for Treatment of Embolic Stroke of Undetermined Source

ARCADIA: Atrial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke

**INTRODUCTION**

Embolic stroke of undetermined source (ESUS) describes ischemic strokes where the radiographic features are similar to those seen in patients with confirmed embolism sources, such as atrial fibrillation (AF).1 ESUS has been proposed as a subset of cryptogenic strokes, representing a group of patients who considered likely to have a cardiac etiology for their stroke, even though a specific cardiac cause has not been detected. Intensive cardiac monitoring of cryptogenic stroke patients has shown that AF can be detected in up to a third of them over the next 3-years.2 Oral anticoagulation with vitamin K antagonists (VKA) is highly effective compared to antiplatelet therapy in preventing stroke in patients with AF; and direct oral anticoagulants (DOACs) are modestly more effective than VKA with a much lower risk of intracerebral hemorrhage (ICH).3-5 These observations and others led to the hypothesis that DOACs would be more effective than aspirin at preventing recurrent stroke in patients with a recent ESUS. Two large randomized clinical trials tested this hypothesis but failed to establish benefit of DOACs over aspirin (Table). These finding raise questions regarding the usefulness of the ESUS concept for either diagnostic or therapeutic purposes.

The failure of the ESUS studies to establish a group of patients with suspected but unconfirmed AF who benefit from oral anticoagulants has implications for the role of long-term monitoring for AF in patients with stroke, especially those with unclear etiology.

Here we summarize current data regarding potential causes of ESUS, the implications of detecting AF in this population, the ongoing efforts to identify ESUS patients who are at particularly high risk for occult AF and the efforts to reduce subsequent stroke risk.

***Overview of ESUS Trials***

The New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus Aspirin to Prevent Embolism in Embolic Stroke of Undetermined source (NAVIGATE-ESUS) trial enrolled 7213 subjects with non-lacunar, non-disabling, ischemic stroke without extracranial vessel stenosis >50% or identifiable cardiac source of embolism (AF, left ventricular thrombus, mechanical heart valve, severe mitral stenosis).6 Subjects were randomized to either rivaroxaban 15 mg/day or enteric coated aspirin 100 mg/day. The primary efficacy outcome was first recurrent stroke (ischemic, hemorrhagic, or undefined); the primary safety outcome was major bleeding based on International Society of Thrombosis and Haemostasis (ISTH) criteria.7

NAVIGATE-ESUS failed to demonstrate efficacy or safety of rivaroxaban compared with aspirin in patients with ESUS. The trial was terminated early, after a median follow-up period of 11-months, due to an excess of bleeding in the rivaroxaban group with no offsetting benefit of stroke reduction. The annualized stroke rate in the rivaroxaban group was 5.1% *vs.* 4.8% in the aspirin group (hazard ratio [HR]: 1.07, 95%, confidence interval [CI]: 0.87-1.33). Symptomatic intracranial hemorrhage was 4 times more common in the rivaroxaban group (0.6%/year *vs.* 0.1%/year respectively, HR: 4.02, 95% CI: 1.13-14.2) and ISTH major bleeding was nearly 3-fold increased with rivaroxaban (HR: 2.72, 95% CI: 1.68-4.39).6 The absence of any reduction in stroke, combined with significantly increased major bleeding including ICH, makes rivaroxaban a non-viable treatment for patients with ESUS. Particularly worrisome was the dramatic excess of bleeding despite using a lower than standard dose of rivaroxaban for stroke prevention in AF (15 mg/day *vs.* 20 mg/day). These results contrast with the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial which showed a substantial reduction in stroke, and in mortality, with low dose rivaroxaban in a population with vascular disease8.

The Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate *vs.* Acetylsalicylic Acid in Patients with Embolic Stroke of Undetermined Source (RESPECT-ESUS) trial compared the DOAC dabigatran to aspirin in patients with ESUS.9 The trial was similar in design and inclusion criteria to NAVIGATE-ESUS. Unlike NAVIGATE-ESUS, RESPECT-ESUS required intracranial arterial imaging to rule out high grade symptomatic atherosclerotic stenosis proximal to the index stroke. Subjects (n=5830) were randomized to either dabigatran 150 mg twice/day or non-enteric coated aspirin 100 mg/day, with matching placebo. Dabigatran 110 mg twice/day was administered to subjects over age 75 years or those with creatinine clearance 30-50 ml/min. Both doses of dabigatran are proven effective in preventing stroke in patients with AF,5 in contrast to the non-standard rivaroxaban dose used in NAVIGATE-ESUS. Similar to NAVIGATE-ESUS, the primary efficacy endpoint was recurrent stroke of ischemic, hemorrhagic, or unspecified type, and the primary safety outcome was ISTH major bleeding.

RESPECT-ESUS failed to show a significant reduction in recurrent stroke with dabigatran compared to aspirin (annualized rates of 4.1% *vs*. 4.8%, HR: 0.85, 95% CI: 0.69-1.03). In contrast to the results of NAVIGATE-ESUS, the Kaplan-Meier curves for the primary outcome diverged at about 365 days and an exploratory analysis suggested an advantage of dabigatran after the 1-year benchmark. The annualized rate of ISTH major bleeding with dabigatran (1.7%) and aspirin (1.4%) were similar (HR: 1.19, 95% CI: 0.85-1.66) and the annualized risks of intracranial hemorrhage were identical (0.7% in both arms, HR: 0.98, 95% CI: 0.60-1.60). The risk of ISTH major bleeding on aspirin in RESPECT-ESUS was higher than the risk on aspirin in NAVIGATE-ESUS (1.4%/year *vs*. 0.7%/year, respectively).6, 9 Whether this difference represents chance, the use of enteric coated aspirin in NAVIGATE-ESUS, or a difference in enrolled patient populations is unknown. A subgroup analysis of RESPECT-ESUS suggested an advantage of dabigatran over aspirin in patients older than 75 and in those assigned the lower dose of dabigatran.10

Taken together, the RESPECT-ESUS and NAVIGATE-ESUS trials do not support the use of anticoagulants for secondary prevention in ESUS patients as currently defined. The negative results of these initial trials could reflect that many cases of ESUS are due to embolism from non-stenosing atherosclerotic lesions11, and that anticoagulation offers no advantage over antiplatelet therapy in this pathophysiology. Another possibility is that patients with intermittent AF were screened out by monitoring prior to enrollment, thereby eliminating the ESUS patients most likely to benefit from DOAC. One possible cause for the surprising divergence of the Kaplan-Meier curve in RESPECT-ESUS could be the development of new onset AF over time, in the enrolled participants. Consistent with this idea is the benefit of dabigatran seen in older patients, who are at higher risk for new onset AF.

***ESUS construct***

*Does the ESUS construct remain useful?*

Approximately 1/3 of stroke patients do not fall into a predefined category and were historically classified as having cryptogenic stroke, where no probable cause for stroke was found after a diagnostic evaluation. The cryptogenic stroke construct was used in the Warfarin-Aspirin Recurrent Stroke Study (WARSS) which tested the hypothesis that warfarin better protects from recurrent strokes than aspirin.12 This construct was later modified in the Trial of Org 10172 in Acute Stroke Treatment (TOAST): brain infarction that is neither attributable to a source of definite cardio-embolism, large artery atherosclerosis, small artery disease nor a defined rare cause of brain infarction in patients with competing stroke etiologies (e.g., large artery atherosclerosis and AF).13

Ultimately, the WARSS study did not show benefit for warfarin over aspirin; however, the concept of cryptogenic stroke survived and was promulgated through clinical research that suggested that a substantial subset of these patients may actually constitute missed ‘cardiogenic’ causation, and benefit from anticoagulants.14, 15 More recently, the introduction of the non-vitamin K dependent DOACs with their superior side effect profile over warfarin has reignited interest in testing DOACs in this population.2, 16, 17 In addition, there has been a move to reframe cryptogenic stroke instead as ESUS.18

ESUS is defined as a non-lacunar brain infarction confirmed by imaging, without hemodynamically relevant stenosis (≥50% lumen diameter reduction) in the arterial supply territory, and without an apparent cardioembolic source as determined by transthoracic or transesophageal echocardiography and ≥24-hour electrocardiogram monitoring. Several registries report between 9% and 25% subtypes as ESUS. Patients classified as having ESUS tend to be younger and have a lower prevalence of cardiovascular risk factors. The average ischemic stroke recurrence rate in ESUS patients is approximately 4.5%/year, which was used for power calculations in recently published ESUS trials.19, 20 However, the results from the recent ESUS trials, which did not show a benefit from DOAC use compared to aspirin, have challenged the validity of the ESUS construct.6, 21 These negative results suggest that AF may be less common than anticipated in patients who meet the ESUS definition and suggest that ESUS criteria require optimization to improve specificity for identification of patients with an occult cardiac source of embolism.

For example, the current ESUS definition allows for artery-to-artery embolism from mild to moderate stenosis or even plaque ulcerations from the aortic arch to be considered ESUS. Consequently, ESUS definitions could be refined to help identify those patients where AF – not detected on the initial clinical evaluation – may be a considered as a likely potential cause for stroke *vs.* those where atherogenic emboli are most likely. In addition, the specific role of the atrial arrhythmia in stroke causation remains controversial.22 In the future, enhancing the ESUS definition may include refining the imaging criteria employed for magnetic resonance imaging (MRI) and including cardiac biomarkers of atrial myopathy that may evolve into AF or even act as an embolic source without apparent AF.23, 24 Additionally, it is proposed that the progression of atrial arrhythmias into transient and sustained episodes of AF may increase the risk of stroke recurrence and its prevention with anticoagulation.25

*Imaging criteria for cardiogenic embolism*

A refined ESUS definition could include more detailed brain imaging findings that point to cardiac embolization. Diffusion-weighted imaging ( DWI ) on MRI already substantially impacts early stroke diagnosis and therapy and could also aid in stroke causation identification. DWI identifies ischemic lesions in the first hour after stroke onset, even detecting very small lesions because of the superior signal intensity-to-noise ratio. Together with Fluid Attenuated Inversion Recovery (FLAIR) sequences, DWI can also distinguish between chronic and acute lesions.26, 27 Clinically silent, small lesions may influence the diagnosis of stroke subtype in ischemic stroke when multiple lesions are detected on DWI.28 The presence of multiple ischemic lesions suggests embolism from the heart, aortic arch or embolization from the extra- or intra-cranial large arteries (if confined to 1 vascular territory). Multiple infarcts in more than 1 vascular territory, especially bilateral lesions, strongly argue for a proximal source or systemic cause.29 The systematic analysis of DWI MRI patterns in cardiogenic embolism is complicated by the fact that the ‘smoking gun’, such as an atrial thrombus detected by trans-esophageal echocardiography is difficult to establish in the acute stroke setting and later may dissolve and go undetected. Although most experts agree on MRI patterns of proximal or systemic cause, it remains unclear as to how aortic arch atherosclerosis or lower grade large vessel occlusive disease contribute to such patterns. It is conceivable that the analysis of remote and new stroke patterns by comparing FLAIR and DWI sequences may hold further answers. However, solely analyzing the size, shape and location of a lesion does not clarify the stroke etiology.30 For example, even small deep infarcts, which are typically caused by small artery intracranial vascular occlusions, can also be caused by cardiac emboli and have been shown to be increased in patients with AF.31

*Atrial myopathy, atrial fibrillation and embolism*

A higher likelihood of AF may also be signaled by associated cardiac findings. AF occurs when a vulnerable atrial substrate or atrial myopathy, determined by genetic, age-, lifestyle- and disease-related tissue changes, is triggered electrically.32 It is well established that AF causes blood stasis, endothelial dysfunction, hypercoagulability, systemic inflammation, and thus an increased risk of thromboembolism.33-35 In addition, change in heart rhythm from AF to sinus with cardioversion can increase the risk of cardioembolic stroke. However, given the shared cardiovascular risk factors, stroke and AF may be coincidental rather than causally linked in patients with concurrent small and large vessel occlusive disease. This notion is supported by the fact that clinical risk prediction strategies can predict stroke in AF the same way they predict the occurrence of AF after stroke.33, 35 Furthermore, in substantial numbers of strokes with AF, etiology does not appear to be temporally-related and the maintenance of sinus rhythm has not been consistently shown to reduce stroke rates. It should be noted that it is not possible to determine what causes any individual infarct with certainty in the vast majority of cases. Another consideration involves young and otherwise healthy patients with AF, referred to as ‘lone atrial fibrillators’ who do not have a substantially increased risk of stroke, indicating that AF alone is not a sufficient risk factor for thromboembolism.36-38 Nonetheless, for AF patients, having a prior stroke is the most powerful predictor of future stroke39, as well as the degree of benefit from anticoagulation for prevention of future stroke.

The TRENDS40 and Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT)22 studies demonstrate that ischemic stroke might occur without episodes of atrial tachyarrhythmias or AF in the past 30-days, and in many cases in the 6-months prior to the stroke. AF is not infrequently detected only after the occurrence of stroke. However, there does appear to be a relationship between the burden of subclinical AF and stroke: AF burden >5.5 hours/day or episodes lasting >24 hours are associated with higher first-ever stroke risk. Indeed, the temporal relationship is stronger when comparing longer episodes of AF and ischemic stroke.22 Markers of abnormal atrial tissue such as structural dilatation, myocyte and endothelial dysfunction, fibrosis, and inflammation, also play a role in thrombus formation.41 Thus, left atrial thromboembolism likely involves a complex interplay of systemic cardiovascular risk factors, atrial tissue substrate, and arrhythmia with AF representing a marker of progression of the atrial myopathy.25 For these reasons, the mechanistic relationship between AF and stroke is not straightforward and requires additional study.

***Role of long-term monitoring***

AF is responsible for a third of all ischemic strokes,42 and AF diagnosis in the post-stroke setting mandates a change in management from antiplatelet to anticoagulant therapy.43 However, the often paroxysmal and asymptomatic nature of AF can make diagnosis challenging.44 Incidence of asymptomatic AF exceeds 90% in some studies, demonstrating the need for cardiac monitoring to ensure accurate detection.45, 46 Multiple factors affect detection rates including patient characteristics, the extent of evaluation for other stroke mechanisms, the definition of AF, the AF density/burden, and most importantly the duration and intensity of monitoring. Studies using short-term external monitors and an AF duration threshold of <30 seconds for diagnosis are approximately twice as likely to “find AF” than those using a duration threshold of >30 seconds.47-49 Observational studies using insertable cardiac monitors for up to 3-years demonstrated higher rates of AF detection compared to 30 days of external monitoring.49-51 A meta-analysis of 31 prospective studies showed that studies with monitoring lasting ≤72 hours detected AF in 5.1%, whereas monitoring lasting ≥7 days detected AF in 15%.52 The Cryptogenic Stroke and underlying Atrial Fibrillation (CRYSTAL-AF) randomized study demonstrated a 30.0% AF detection rate at 36-months in patients using an insertable cardiac monitor compared to 3.0% in patients randomized to routine follow-up.53, 54 When assessing the odds of AF detection in multiple studies comparing various monitoring techniques in a cryptogenic stroke population, long-term monitoring was associated with a 7.3-fold increased odds of AF detection.52 The superiority in diagnostic yield may be even greater outside of the clinical trial setting where AF detection rates at 1-year were found to be 32% higher than that observed in CRYSTAL-AF.55

***On-going trials***

Current research aims to define subgroups of ESUS patients that may benefit from anticoagulant therapy. The AF-ESUS score was derived to identify patients with ESUS at high risk of post-stroke AF detection.56 If validated on a large scale, high risk patients might be targeted for longer-term cardiac monitoring following the index stroke. High risk ESUS patients might also comprise the study population for a renewed randomized trial to test anticoagulation *vs.* antiplatelet therapy. As mentioned before, regardless of AF, changes in atrial tissue itself may be the primary inciting factor for stroke for a subgroup of ESUS patients. Therefore unlike RESPECT-ESUS and NAVIGATE-ESUS, the ongoing randomized trial of Apixaban for Treatment of Embolic Stroke of Undetermined Source (ATTICUS) will be enriched with factors that have been associated with cardioembolic stroke.57 (see Table) In addition to standard ESUS criteria, participants must also have at least 1 of the following factors: left atrial size >45mm, spontaneous echo contrast in the left atrial appendage, left atrial appendage flow velocity ≤0.2m/s, atrial high rate episodes, CHADS2VA2Sc ≥4, or PFO. The primary endpoint will be the occurrence of at least 1 new ischemic lesion identified by MRI at 12-months compared to baseline. Similarly, the Atrial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke (ARCADIA) study (Table) is enrolling ESUS patients with evidence of atrial cardiopathy, defined as ≥ 1 of the following markers: P-wave terminal force >5000 µV × ms in ECG lead V1, serum NT-proBNP > 250 pg/mL, and left atrial diameter index ≥ 3 cm/m2 on echocardiogram.58

Inclusion of specific atrial parameters of diastolic dysfunction will help to test the hypothesis that atrial cardiopathy is the mechanistic underpinning of a subset of ESUS that may be responsive to anticoagulant therapy. Preliminary research has shown a similar burden of atrial fibrosis among patients with ESUS and those with AF.59, 60 The relationship between atrial fibrosis and stroke among patients with AF is well established.61 In addition, several observational studies have shown left atrial volume index to be associated with cardioembolic stroke and/or subsequent detection of AF among patients with ESUS.62, 63 Further investigation into mechanistic pathways including the role of biomarkers is warranted to inform optimal treatment of these patients.64

**Conclusions and Relevance**

The failure of NAVIGATE-ESUS and RESPECT-ESUS to show a benefit among patients who received DOACs over aspirin indicates that occult AF may be less common that expected in these patients and that the definition of ESUS lacks specificity for cardioembolic stroke etiologies. Since the response to antithrombotic therapies may differ for atherogenic *vs.* cardiac emboli, a refined definition of ESUS should attempt to separate these important subgroups. These negative trial results suggest long-term monitoring is important in patients with ESUS to document AF prior to initiating anticoagulation. It is also important to clarify the efficacy of anticoagulants in stroke patients when a limited duration of AF is detected by long-term monitors many months after a stroke of unclear etiology. Ongoing trials are attempting to identify ESUS patients who are at particularly high risk for occult AF and reduce their risk of subsequent stroke.

**ACKNOWLEDGEMENTS**

The authors would like to thank Dr. Swathi Seshadri and Dr. Amy Molan for help with manuscript preparation.

**DISCLOSURES**

**GA:** Consultant for iSchemaView, Genentech, and Johnson & Johnson; equity in iSchemaView. **AJC:** Institutional funding form Bayer, Boehringer Ingelheim, Daiichi Sankyo and Pfizer/BMS and personal consulting fees from Abbott, Bayer, Boehringer Ingelheim, Boston Scientific, Daiichi Sankyo, Medtronic and Pfizer/BMS. **JB:** Institutional funding from Abbott, Bayer, Biotronik, BSC, Boehringer Ingelheim, Daiichi Sankyo, Novartis and Pfizer/BMS and personal consulting fees from Abbott, Bayer, Medtronic and Pfizer/BMS. **SG:** Funding from Sanofi, Pfizer, Bristol Myers Squibb and Ono Pharma, Nakatani Foundation for Advancement of Measuring Technologies in Biomedical Engineering, and Vehicle Racing Commemorative Foundation; grant-in-aid for MEXT/JSPS KAKENHI 19H03661, AMED grant number A368TS. **SHH:** Consulting fees from Bayer Healthcare, BI, BMS, Boston Scientific, Daiichi Sankyo, Gilead, Johnson & Johnson, Medtronic, Pfizer, Sanofi Aventis, Servier, Zoll and lecture fees from Bayer Healthcare, BI, BMS, Daiichi Sankyo, Pfizer, Sanofi Aventis, and Medtronic. **RB:** Consulting fees, paid steering committee membership, promotional speaking, and research funding from Medtronic, Boehringer-Ingelheim, Pfizer, Bristol Myers Squibb, Abbott, Amag Pharma, Abbvie. **PRK:** Equity interest in Biotelemetry; consultant to Medtronic, Boehringer-Ingelheim, Pfizer, BMS, Daiichi, and Johnson and Johnson (Janssen). **CBG:** Research and consulting funding from Medtronic, Boehringer-Ingelheim, Pfizer, Bristol Myers Squibb, Janssen, Bayer, Daiichi Sankyo, and Boston Scientific. **DK:** Medtronic Advisory Board, member of the stroke focus group, lecture fees, travel grants, and grants from Medtronic and the Danish Research Foundation, St. Jude Medical now Abbott for research grant and travel grants, Boehringer Ingelheim Advisory Board Member, lecture fees. **PF:** No disclosures. **RP:** Receives research support from AHA, Pfizer and Abbott Inc; on ad board for Medtronic and Abbott; royalties from UpToDate. **EH:** Research support from Abbott, Bristol Myers Squibb, Janssen, and Medtronic; consulting fees from Bayer, Bristol Myers Squibb, Janssen, Medtronic, and Pfizer.

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**Table 1. ESUS TRIALS SUMMARY**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Trials**  | **Patients enrolled**  | **Intervention/Treatments** | **Primary Outcome(s)** | **Results** |
| **NAVIGATE- ESUS**  | 7213  | Drug: rivaroxabanDrug: acetylsalicylic acid (aspirin)Other: rivaroxaban-placeboOther: aspirin-placebo | 1. Incidence rate of the composite efficacy Outcome (includes ischemic, hemorrhagic, undefined, TIA and systemic embolism)2. Incidence rate of a major bleeding event according to ISTH criteria  | Study halted early due to no efficacy improvement over aspirin at an interim analysis concluding very little chance of showing overall benefit if study were completed |
| **RESPECT- ESUS** | 5390  | Drug: optional aspirin as comedicationDrug: placebo to aspirinDrug: placebo to optional aspirin as comedicationDrug: placebo to dabigatran etexilateDrug: aspirinDrug: dabigatran etexilate | 1. Adjudicated recurrent stroke (ischemic, hemorrhagic, or unspecified)2. First major bleed defined according to ISTH criteria | No benefit of anticoagulation for secondary stroke prevention in the overall ESUS population |
| **ARCADIA** | 1100 (estimated) | Drug: apixabanDrug: aspirin | 1. Incidence of recurrent stroke (ischemic, hemorrhagic, or of unclear type) | Estimated primary outcome January 2022 / trial completion April 2022 |
| **ATTICUS** | 352  | Drug: apixabanDrug: aspirin | 1. Occurrence of at least one new ischemic lesion identified by MRI | Primary outcome completed August 2020 / estimated trial completion December 2022 |

**Abbreviations:** ESUS, embolic stroke of undetermined source; ISTH, International Society on Thrombosis and Hemostasis; MRI, magnetic resonance imaging; TIA, transient ischemic attack