# Forge AHEAD with stricter criteria in future trials of embolic stroke of undetermined source

**David Z. Rose*, Scott E. Kasner**

**What lurks within the crypt?** With more than 200 known causes of ischemic stroke (Saver, 2016), what should be the minimum workup? Many centers offer high-resolution brain imaging and vessel studies, telemetry monitoring for atrial fibrillation (AF), trans-thoracic and trans-esophageal echocardiography, and a panoply of laboratory tests. Nevertheless, the proportion of strokes that are cryptogenic still ranges from 10–40% (Saver, 2016) which, problematically, includes not only those with an unknown etiology after diagnostic evaluation, but also those with an incomplete workup, as well as those with multiple possible causes (i.e., ipsilateral carotid stenosis with concurrent AF). Such heterogeneity is suboptimal for clinical practice as well as for research, which intends to generate blanket recommendations.

To characterize a subset of cryptogenic stroke patients with an embolic-appearing neuroradiographic pattern, who have had a standardized evaluation, researchers in 2014 created the acronym ESUS: "Embolic Stroke of Undetermined Source" (Hart et al., 2014). Conceptually, a thromboembolic etiology (still unidentified) for patients with ESUS could be presumed in a trial using anticoagulants against antiplatelet therapy. Consequently, two major trials emerged: NAVIGATE ESUS (Hart et al., 2018) (Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients with Recent ESUS) and RE-SPECT ESUS (Diener et al., 2019) (Dabigatran Etexilate for Secondary Stroke Prevention in Patients with ESUS) but neither showed superiority of direct oral anticoagulants over aspirin. In 2017, NAVIGATE ESUS was halted due to excess major bleeding with rivaroxaban (Hart et al., 2018) and in 2018, RE-SPECT ESUS showed similar stroke rates and safety with dabigatran (Granger, 2018). So, currently recommended therapy in 2021 remains as cryptic as its name: a one-size-fits-all daily aspirin, indefinitely – unless the real cause appears later. The concern is, of course, another stroke in the meantime.

**From realization to rejection to renaissance:** Had these ESUS trials been positive instead of negative/neutral, then stroke workup algorithms would be simplified and direct oral anticoagulants prescriptions omnipresent. But alas, the cynics who predicted that ESUS was "a diagnostic entity with fuzzy edges" doubting its value as a therapeutic target (Dennis, 2014) could now substantiate their opinion. Notwithstanding, some neurologists (like us) opine that ESUS modification – not rejection – is the answer: stricter criteria, including only the highest-risk embolic-appearing strokes, after thoroughly excluding even more etiologies. This is the theme of the accompanying article in *Neural Regeneration Research*, "ESUS: Identification of patient subgroups for oral anticoagulation treatment." Authors argue that ESUS workup should routinely include trans-esophageal echocardiography, insertable cardiac monitor, advanced vascular imaging with plaque measurements, and even cardiac magnetic resonance imaging.

We agree. We also believe it is incumbent upon our field to dive deeper into characterizing and understanding the contributors to ESUS. For example, oldest patients with ESUS seem to possess the highest-risk. In RE-SPECT ESUS, patients over 75 years of age (Diener et al., 2019, 2020) had a hazard ratio of 0.63 for recurrent stroke in dabigatran- *versus* aspirin-treated patients, with 95% confidence intervals of 0.43–0.94, and similar trends were observed with age as a continuous variable. Likewise, analysis of CRYSTAL-AF revealed that two factors – older age and a prolonged PR interval on EKG – were independently associated with an increased incidence of AF in cryptogenic stroke (Thijs et al., 2016). While the various underlying contributors to ESUS continue to be explored, it appears that age might be a very strong risk factor for subsequent AF and stroke risk.

Therefore, to promote widespread use of these key, stricter ESUS criteria, we created the mnemonic AHEAD (**Figure 1**): A for Age ≥ 75 years; Head imaging confirming nonlacunar stroke; Echocardiography (including trans-thoracic and trans-esophageal echocardiography) and EKG (including longer-term arrhythmia monitoring like insertable cardiac monitor) to look for cardioembolic source; Arterial studies excluding atherosclerotic stenosis, unfavorable plaque morphology, dissection, vasculitis, or web; and Differential diagnosis including hypercoagulable labs, malignancy screening, and other less common etiologies. The accompanying paper seems well aligned with this approach, along with further studies underway to determine the importance of some of the grayer areas, such as atrial cardiopathy, moderate left ventricular dysfunction, < 50% arterial stenosis, and other potential contributors to ESUS (Siegler et al., 2019).

| Mnemonic **AHEAD** for strict ESUS75 | Rationale |
|---|---|
| **A** Age ≥75 years | • Older ESUS patients may benefit more from anticoagulation |
| **H** Head imaging | CT or MRI brain to identify:<br>• embolic-appearing infarcts,<br>• superficial/cortical involvement, or<br>• size>1.5 cm,<br>• and exclude a subcortical lacune due to hypertensive emergency, diabetes, hyperlipidemia and other small-vessel disease risk factors |
| **E** EKG and Echo | Long-term EKG monitoring/recording to exclude patients with:<br>• paroxysmal/occult atrial fibrillation, or<br>• other arrhythmias<br>Transthoracic plus Transesophageal echocardiography to exclude:<br>• Atrial/ventricular thrombi or masses,<br>• infectious/inflammatory valvular vegetations, and<br>• Patent foramen ovale and atrial septal aneurysm (with bubble study) |
| **A** Arterial imaging | CTA, MRA, CUS/TCD, or DSA to exclude:<br>• intra/extra-cranial atherosclerosis (by stenosis or by morphology),<br>• intra/extra-cranial dissection,<br>• carotid web,<br>• significant aortic arch atheroma, or<br>• primary/secondary cerebral vasculitis/vasculopathy (with spinal tap) |
| **D** Differential Diagnosis | When appropriate, serum and urine tests to exclude:<br>• hypercoagulable states,<br>• toxicology for drugs of abuse, or<br>• genetic screening for mitochondrial disease or leukoencephalopathies<br>pan-CT (chest/abdomen/pelvis) to exclude:<br>• primary malignancy,<br>• metastatic disease or cancer recurrence,<br>• other etiologies |

**Figure 1** | **AHEAD mnemonic for ESUS75.**
The mnemonic AHEAD was created to identify a subgroup of ESUS patients who are 75 years of age or older and also to recall the ESUS major criteria: Head imaging showing nonlacunar stroke, Echo/EKG without cardioembolic source, Arterial studies excluding atherosclerosis, dissection, vasculopathy or vasculitis, and Differential Diagnosis to consider rarer causes such as hypercoagulable state, malignancy, mitochondrial disease, etc. It may be reasonable to consider anticoagulation instead of antiplatelet therapy, or low-dose anticoagulant twice-a-day plus antiplatelet for this subgroup, termed "ESUS75." CT: Computed tomography; CTA: computed tomography angiogram; CUS: carotid ultrasound; DSA: digital subtraction angiography; EKG: electrocardiogram; MRA: magnetic resonance angiogram; MRI: magnetic resonance imaging; TCD: transcranial Doppler.

Potentially, by checking off boxes using the AHEAD paradigm, this adapted classification – which we termed "ESUS75" – could reveal a primary, pre-specified benefit of anticoagulation over antiplatelet therapy. In an ESUS75 trial, subjects would be enrolled using a streamlined process (AHEAD) with stricter, key criteria and therefore could stand the most to gain. Specifically, the use of insertable cardiac monitor (the E within the AHEAD paradigm for EKG monitoring) is an example of how this strict definition of ESUS75 may avoid two diagnostic pitfalls: "anchoring bias" (focusing solely upon ESUS without a thorough differential) and "premature closure" (disregarding other

testing modalities or opportunities to find alternate etiologies such as AF) (Rose et al., 2016). The hazard of these biases is that suboptimal treatment may ensue: aspirin in patients who, if found to have AF, could instead have received anticoagulation or left atrial appendage closure to prevent stroke, and ablation or rate-control medications to help with palpitations and other symptoms (Brachmann et al., 2016).

Curiously, Kaplan-Meier curves in RE-SPECT ESUS revealed a late divergence after one year for superiority with dabigatran over aspirin if the follow up had been longer (Granger, 2018; Diener et al., 2019, 2020). Conceivably, this divergence may be a result of a gradual accumulation of AF in an ESUS population at high risk of developing it anyway. Theoretically, this "pre-AF" subgroup would respond more favorably to anticoagulation than antiplatelet for secondary stroke prevention. Cumulatively, obviously, subjects become older over time, and hence, anticoagulation may be validated in an ESUS75 trial with only elderly participants.

**Is ESUS75 worthwhile and sensible as a clinical construct for both research and practical purposes?** The annualized stroke recurrence rate in ESUS was found to be 4.5% (Ntaios et al., 2015; Hart et al., 2017), yet in hindsight, the overrepresentation of younger patients (mean age 65 years) (Ntaios et al., 2015; Hart et al., 2017), may have led to the underwhelming ESUS trial results. Hence, ESUS75 would address that limitation. Moreover, in both aforementioned ESUS trials the elderly represented sizable subgroups: about 20% of subjects were ≥ 75 (Dennis, 2014; Hart et al., 2018; Diener et al., 2019, 2020). Mathematically, as ESUS represents 17% of all strokes (Hart et al., 2014), and about 20% are ≥ 75, then ESUS75 represents 3.4% of all strokes (400,000 people worldwide) annually. Enrolling a tiny fraction of this amount should be more than sufficient for a new trial.

**Forging AHEAD:** Naturally, there is meaningful psychological benefit of uncovering the stroke etiology for the anxious patient. Nobody with a stroke wants to be told, "I don't know what caused this," which is essentially what cryptogenic patients hear. Indeed, there is comfort in knowing the name of the cause of one's stroke, as well as the estimates of future stroke risk, and the options for treatment to maximize risk reduction. It is a relief to be extracted from the apprehensive diagnostic limbo of cryptogenic stroke.

As for the future, we expect that the ESUS75 concept may indeed be further refined, especially as more comprehensive testing evolves that may reclassify new events into another etiological category. The ending to the saga of these "tales of the crypt-ogenic strokes" has yet to be written, but the future looks less mysterious when we forge AHEAD together.

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