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**Disclosures**  
- NIH- U01 NS062835 (Co-PI) POINT  
- DMCs for Daiichi-Sankyo, Schering-Plough Research Institute and Novartis  
- Advisory Board for AstraZeneca

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**Distribution of Ischemic Stroke Subtypes**

- **Ischemic Stroke**
  - 35% Large Artery Atherosclerosis
  - 20% Small Artery Disease "lacunes"
  - 15% Recognized Cardiogenic Embolism
  - 5% Unusual (e.g. dissections, arteritis)
  - 25% Cryptogenic

**Cryptogenic Stroke**

- The cause, criteria for diagnosis, and treatment are enigmas
- The source cannot be diagnosed with confidence in individual patients because potential sources occur with sufficient frequency in elderly patients that cause-effect is statistically unclear and sophisticated diagnostic testing of limited availability and expensive
- Many are likely cardioembolic, yet current guidelines recommend antiplatelet drugs
- NOACs are effective and safer than warfarin for AF
- Perhaps NOACs would be more effective than antiplatelet drugs for cryptogenic stroke

**Cryptogenic Stroke**

- A group of interested neurologists decided to tackle the definition, causes and treatment of cryptogenic stroke
- The group began discussions
- The group proposes that most cryptogenic strokes are emotional strokes of unknown source, either cardiogenic, arteriogenic, or paradoxical, so the ESUS International Working Group was born
Major Causes of Ischemic Stroke

Thromboembolism plays a role embolism ischemic strokes.

Atherosclerosis is Widespread at Autopsy

Cryptogenic Stroke: current

- An ischemic stroke of “otherwise undetermined cause”
- Depends on the extent of diagnostic evaluation (the harder you look, the more you find)
- No standard criteria for “determined cause”
- It is an old term that is itself cryptic, vague and has impeded clinical research
- So, this description defines what it isn’t, and we want to know what it is!

ESUS: proposed

- It is proposed that ESUS replace cryptogenic stroke
  - Embolic strokes of undetermined source are defined as non-lacunar brain infarcts without proximal arterial stenoses or cardioembolic sources with a clear indication for anticoagulation
  - Because emboli consist mainly of thrombus, it is likely that anticoagulants will reduce recurrent brain ischemia more effectively than antiplatelet agents. Randomized trials testing direct-acting oral anticoagulants for secondary prevention are warranted
Diagnostic Criteria for Embolic Stroke of Undetermined Source (ESUS) must be sufficient to:

- Demonstrate acute brain infarct on neuroimaging that is non-lacunar
- Demonstrate absence of occlusive proximal atherosclerosis
- Demonstrate no major-risk cardioembolic source

Diagnostic Studies Required for ESUS

- Brain CT* or MRI to demonstrate non-lacunar stroke (*visualization usually requires delayed imaging >24 hrs after onset)
- Imaging of both extracranial and intracranial arteries supplying the area of the infarct (conventional, MR, or CT angiography, or transcranial Doppler ultrasonography)
- Exclude major cardioembolic source (12-lead EKG, cardiac monitoring >24 hours with automated rhythm detection, echocardiography)

ESUS in Summary: A novel construct

- Most cryptogenic strokes are embolic (cardiogenic, arteriogenic, paradoxic)
- Extensive diagnostic efforts to define the specific cause are often futile and may be unnecessary
- ESUS (embolic strokes of undetermined source) is a new, clinically useful construct
- For secondary prevention of ESUS, anticoagulants are likely to be more efficacious than antiplatelet drugs

Embolic strokes of undetermined source: The case for a new clinical construct

Cryptogenic Stroke / ESUS International Working Group

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Lancet Neurol 2014 (in press April 2014)
The ESUS group then discussed treatment trials for ESUS with the FDA

- The FDA enthusiastically supported a comparison of NOACs vs. ASA
  - 20-30% of ischemic strokes
  - No previous trials to define optimal care
  - High likelihood that anticoagulants effective
  - Widespread equipoise for anticoagulant vs. aspirin for secondary prevention
  - Enthusiasm high in the stroke research community
- The ESUS group has contributed to launching two large trials comparing NOACs to aspirin

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**Randomized Evaluation in Secondary stroke Prevention Comparing the Thrombin inhibitor dabigatran etexilate versus ASA in Embolic Stroke of Undetermined Source (ESUS)**

- ~20% of ischemic strokes have been categorized in recent studies as ESUS

**Diagnostic Pathway**: assess with MRI/CT to rule out lacunae; carotid U/S and ≥24 hour rhythm monitoring to rule out AF

**Index ischemic stroke (ESUS)**

- Modified Rankin score ≤3, age ≥60 or 50–59 with additional risk factors. Includes TIA with pathological imaging evidence.
- All patients receive dabigatran 150 mg BID, unless ≥75 years or CrCl <50 mL/min. These patients receive dabigatran 110 mg BID.

**Primary endpoint: stroke**

**Event-driven: 350**

- **Primary endpoint: stroke**
  - 30-day follow-up
  - 0 days – 3 months
  - 0.5–3 years

- **Placebo (matching ASA)**
  - **ASA (100 mg OD)**
  - **Placebo (matching dabigatran)**
  - **Dabigatran (150 or 110 mg BID)**

- **End of treatment**
  - **n=3000**
  - **n=3000**

- **Secondary endpoint: systemic embolism**

**Trial design**

- Phase 3
- Parallel group design
- Double-blind
- Randomized

**Inclusion criteria**

- Patients with ischemic stroke of undetermined source
- Patients aged ≥18 years
- Patients with a mRS ≤3
- Patients with an age ≥60 or 50–59 with additional risk factors

**Exclusion criteria**

- Patients with a mRS >3
- Patients with an age <18 years
- Patients with a contraindication to antithrombotic therapy
- Patients with a history of severe bleeding
- Patients with a history of thromboembolic events

**Key points**

- **RE-SPECT ESUS**
  - Study of secondary stroke prevention
  - Comparing the Thrombin inhibitor dabigatran etexilate versus ASA in Embolic Stroke of Undetermined Source (ESUS)
  - Randomized
  - Event-driven: 350