Embolic Stroke of Undetermined Source (ESUS)

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Disclosures

• UTHSCSA Site-PI for NAVIGATE ESUS
  – Industry sponsored by Bayer

  New Approach riVaroxaban Inhibition of Factor Xa in a Global trial vs Aspirin to prevent Embolism in Embolic Stroke of Undetermined Source
Objectives

• Define ESUS: aka cryptogenic stroke
• Review potential etiologies for ESUS
• Discuss current evidence and guidelines for:
  – interventional therapeutics
  – advanced monitoring techniques
  – pharmacologic treatment of ESUS
• Present ongoing clinical trial of novel oral anticoagulants (NOAC) for stroke prevention
  – NAVIGATE ESUS, RESPECT ESUS, ATTICUS
Major Causes of Ischemic Stroke

- Intracranial Atherosclerosis
- Carotid Plaque with Emboli
- Aortic Arch Plaque
- Cardiogenic Emboli
- Small Artery Disease
- Carotid Stenosis
- Atrial Fibrillation
- Valve Disease
- Ventricular Thrombi
Cryptogenic stroke

• Ischemic stroke of “otherwise undetermined cause”.
• Depends on the extent of diagnostic evaluation
  – The more you look, the more you find
    • TEE
    • Implantable Loop Recorders
    • Hypercoagulable studies
  – Are your findings significant to change treatment
• Nonstandard criteria for “determined cause”.
  – extent of intracranial atherosclerosis
  – PFO size
• An old term that is itself cryptic, vague, and some say has impeded clinical research.
## Frequency of cryptogenic stroke in recent studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N / mean age</th>
<th>% cryptogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASTRAL (2010)</td>
<td>Registry</td>
<td>1633 / 73 yrs</td>
<td>16%</td>
</tr>
<tr>
<td>WARSS (2001)</td>
<td>RCT</td>
<td>2206 / 63 yrs</td>
<td>26%</td>
</tr>
<tr>
<td>PRoFESS (2008)</td>
<td>RCT</td>
<td>20,332 / 66 yrs</td>
<td>16%</td>
</tr>
<tr>
<td>South Korea (2003)</td>
<td>Registry</td>
<td>204 / 67 yrs</td>
<td>18%</td>
</tr>
<tr>
<td>PERFORM (2011)</td>
<td>RCT</td>
<td>19,100 / 67 yrs</td>
<td>22%</td>
</tr>
<tr>
<td>German Stroke Databank (2001)</td>
<td>Registry</td>
<td>5017 / 66 yrs</td>
<td>23%</td>
</tr>
<tr>
<td>Bern Registry (2008)</td>
<td>Registry</td>
<td>1288 / NR</td>
<td>39%</td>
</tr>
<tr>
<td>Besancon (2000)</td>
<td>Registry</td>
<td>1776 / 71 yrs</td>
<td>18%</td>
</tr>
<tr>
<td>Athens Registry (2000)</td>
<td>Registry</td>
<td>885 / 70 yrs</td>
<td>21%</td>
</tr>
<tr>
<td>Mannheim Registry (2012)</td>
<td>Registry</td>
<td>103 / 69 yrs</td>
<td>30%</td>
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</table>
Distribution of ischemic stroke etiologic subtypes

Ischemic Stroke

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

Estimated 300,000 cryptogenic strokes per year in Europe and North America

“..no embolic material was found at the site where blockage must have occurred to account for the brain infarct. In some cases, embolic fragments were found in outlying branches…in the hours and days following embolism, embolic material often undergoes fragmentation, migration and lysis.”

In other words, an open artery supplying the area of infarcted brain is a hallmark of embolism (aka “vanishing occlusions”).
What causes cryptogenic stroke?

- **Cardiogenic embolism**
  - unrecognized paroxysmal atrial fibrillation – 15%
  - atrial high-rate episodes
  - left ventricular thrombi
    - remote MI, non-ischemic cardiomyopathies, low EF
  - “*minor-risk cardioembolic sources*”:
    - myxomatous mitral valvulopathy
    - aortic valve disease
    - atrial septal aneurysm, Chiari network, atrial bands
    - mitral annular disease / calcification (MAC)

*Over 70 cardiac disorders have been linked to embolic stroke.*
What causes cryptogenic stroke?  
Mitral annulus calcification (MAC)

- Detected by echocardiography in 10-15% of elderly people; associated with endothelial ulceration.
- Framingham cohort:
- When identified in a stroke patient, MAC is currently not considered to be the likely cause.
What causes cryptogenic stroke? MAC

(A) Punctate calcifications in brain CT scan (arrows). (B) Vertical section of heart with large MAC cavity between left atrium (a) and left ventricle (V). (C) H-E stain of mitral annulus wall embedded with dark spicules of calcium (thick arrow) and paler, amorphous substance (thin arrow). (D) Embolic calcific material in subarachnoid artery.

Mitral annulus calcareous brain emboli.
What causes cryptogenic stroke?

- **Paradoxical embolism**
  - patent foramen ovale (PFO)
    - seen in ~20% of the general population
  - other right to left intra-cardiac shunts
- **Arteriogenic embolism**
  - aortic arch atheroma with ulcerations / thrombi
  - non-stenotic ulcerated cervical carotid atheroma
  - non-stenotic intracranial large artery atheroma
What causes cryptogenic stroke?

**patent foramen ovale**

Inter-atrial conduit for “paradoxical embolism” originating in the venous system but occluding brain arteries.

Present in 23% of the population, and hence usually incidental when found in stroke patients.
Thrombus trapped in a patent foramen ovale viewed from the left atrium
RESPECT Confirms Long-term Safety, Efficacy of PFO Closure for Recurrent Stroke
"To summarize: if you have a stroke and you have a PFO, does this randomized trial show that you'll reduce recurrent stroke by closing?

The answer is no," said moderator Kirtane during the press briefing.

"But if you happen to be a young patient where it's likely to be cryptogenic or if you happen to have features that would predispose you to that, then, at least to my mind, it would make sense based upon these results to close the PFO."
Case Study

- 53 yo RHM with no stroke risk factors except HLP
- presented with sudden onset slurred speech that started improving after 45 min
- On exam, he had some aphasic symptoms in which he was unable to pronounce some words and was noted to have some incorrect word substitution.
- Otherwise exam unremarkable.
Brain MRI

Diffusion

Flair
Work-up

• Imaging:
  – MRA head and neck unremarkable

• EKG:
  – Sinus rhythm with 1st degree A-V block
  – Minimal voltage criteria for LVH, normal variant

• TTE:
  – Left atrium is mildly dilated with otherwise normal
  – LVEF 55-60% with regional wall motion abnormalities.
  – Mild annular calcification (MAC) with mild thickening of the non-coronary leaflet.
  – Interatrial septum is aneurysmal without PFO by color
Further Cardiac Work-up

• TEE
  – The interatrial septum is aneurysmal with evidence of flow across on color flow interrogation, this is consistent with a patent foramen ovale.

• 48 Hour Holter Monitor
  – Single isolated episode 2nd degree AV block was noted, this occurred during usual sleep hours.
  – No pauses >3s or severe bradycardia.
  – No other significant events.
What to do? Treatment Options:

1. Start antiplatelet regiment
   - ie. Aspirin, clopidogrel, or combination therapy
2. Schedule patient for PFO closure.
3. Place an Implantable Loop Recorder
4. Enroll into clinical trial
   - aspirin versus novel oral anticoagulants
What causes cryptogenic stroke?

Atherosclerosis of the aortic arch with thrombi overlying plaques

TEE
Nonobstructive AHA Type VI Plaque  This nonstenosing plaque was detected in a 66-year-old male patient with a cryptogenic stroke ipsilateral to the lesion. The arrowheads on the time-of-flight (TOF) and proton density-weighted (PDW) images point to plaque rupture.

Thromboembolic Causes of ESUS

- Thrombus trapped in a patent foramen ovale
- Thrombus overlying an ulceration on a carotid artery plaque
- Myxomatous mitral valve with small thrombi attached to a roughened surface
- Thrombus removed from aortic arch during surgery from a patient with leg embolus
“At the same time as this rather long list of sources of embolus is given, it must be made clear that in many cases, although the diagnosis of cerebral embolism seems beyond question, no source for the embolus can be found after most careful search.”

• NINDS Stroke Data Bank carried-out at 4 academic hospitals in the mid-1980s.
• 1805 patients hospitalized for acute ischemic stroke evaluated by the investigators.
• Of infarcts of undetermined cause (40% of all strokes), 67% had features supportive of embolism.
• “There is ample evidence for many occult sources of embolism, the difficulty resides in proving their existence, and their role in first and recurrent stroke.”
Causes of cryptogenic stroke: key concepts

• Most are thromboembolic (not AFib)
• Cannot diagnose the source with confidence in individual patients because
  – potential sources occur with sufficient frequency in elderly patients that cause-effect is statistically unclear
    • i.e., dilated left atrium, MAC, non-occlusive carotid stenosis, intracranial athero, etc…
  – sophisticated diagnostic testing of limited availability and expensive
    • Implantable Loop Recorders
Advanced Monitoring for ESUS

- 274 consecutive stroke unit (Barcelona) admissions with ischemic stroke or TIA.
- 32% (n= 89) had non-lacunar ischemia, no known heart disease, and no atherosclerotic stenosis ≥50%.
- The 89 patients (mean age = 70 yrs) underwent transesophageal echocardiography and prolonged ECG monitoring:
  - 4 paroxysmal atrial fibrillation
  - 24 aortic arch plaque (mobile or >4mm in thickness)
  - 13 moderate/severe left ventricular systolic dysfunction
  - 5 patent foramen ovale with atrial septal aneurysms
  - 3 “valve disease”
Prolonged Ambulatory Cardiac Monitoring Improves the Detection and Treatment of Atrial Fibrillation in Patients with Cryptogenic Stroke

• Methods
  • cryptogenic stroke within 6 months
  • patients >55 yrs-old
  • 572 patients from 16 sites in Canadian Stroke Consortium
  • 2009-2012 (~ 1 participant / month / site)
  • Event-triggered 30-day loop recorder (82% completed >3 wks)

• Results:
  - AF > 30 sec in 15%
  - AF > 2.5 min in 10%

Purpose: To evaluate if enhanced (dedicated ECG lab analysis) and prolonged Holter monitoring would detect AF more often than GL standard AF detection (≥24-hour continuous ECG Monitoring) in patients with ischemic stroke.

Trial Design: Randomized 1:1, controlled, multicenter trial. Patients were 60 years of age and older with a history of ischemic stroke and were within 7 days or less of the onset of ischemic stroke symptoms. They were in sinus rhythm at admission and had no AF history. Randomized within a median time of 3 days from stroke symptoms. Repeated 10-day Holter-ECG monitoring (0, 3, 6 months). N= 398.

Primary Endpoint: New A Fib or flutter of ≥ 30 seconds found within 6 months and before the recurrence of stroke. Secondary: AF and recurrent stroke after 12 months

<table>
<thead>
<tr>
<th>Trial Results</th>
<th>6 months</th>
<th>P</th>
<th>AF 12 months</th>
<th>P</th>
<th>Stroke 12 months</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive Monitoring</td>
<td>13.5%</td>
<td>0.002</td>
<td>13.5%</td>
<td>0.02</td>
<td>2.5%</td>
<td>0.28</td>
</tr>
<tr>
<td>Standard-of-care Monitoring</td>
<td>4.5%</td>
<td></td>
<td>6.1%</td>
<td></td>
<td>4.5%</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: For this patient population, intensive 10-day Holter-ECG monitoring was better than standard-of-care for AF detection.
Duration of Atrial Fibrillation in the Intervention Arm

- 30s - 6 minutes: 8 cases
- 6 minutes - 6 hours: 5 cases
- 6 to 24 hours: 3 cases
- > 24 hours: 9 cases

Duration of longest AF episode
Implantable Loop Recorder
Original Article

Cryptogenic Stroke and Underlying Atrial Fibrillation

Tommaso Sanna, M.D., Hans-Christoph Diener, M.D., Ph.D., Rod S. Passman, M.D., M.S.C.E., Vincenzo Di Lazzaro, M.D., Richard A. Bernstein, M.D., Ph.D., Carlos A. Morillo, M.D., Marilyn Mollman Rymer, M.D., Vincent Thijs, M.D., Ph.D., Tyson Rogers, M.S., Frank Beckers, Ph.D., Kate Lindborg, Ph.D., Johannes Brachmann, M.D., for the CRYSTALAF Investigators

N Engl J Med
Volume 370(26):2478-2486
June 26, 2014
Time to First Detection (CRYSTAL AF)

Number of ILRs needed to detect first episode of AF:
A. 14 for 6 months
B. 10 for 12 months
C. 4 for 36 months
A new perspective on Embolic Strokes of Undetermined Source

• Most cryptogenic strokes are embolic:
  – cardioembolic, arteriogenic, paradoxical

• New, clinically useful, construct:
  – embolic strokes of undetermined source (ESUS)

• For secondary prevention of ESUS, newer anticoagulants are likely to be more efficacious than antiplatelet therapy.

• Long term cardiac monitoring may identify atrial fibrillation but does not identify a cause in the majority of ESUS cases.
What is the evidence that anticoagulants will importantly reduce recurrent stroke in patients with ESUS?

Cardiogenic emboli?
Paradoxical emboli?
Arteriogenic emboli?
Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) 
(NEJM 2012; 366: 1859)

• 2305 pts with left ventricular ejection fraction (LVEF) ≤35% randomized (double-blind) to warfarin INR target 2-3.5 vs. aspirin 325mg/d.

• Cohort characteristics:
  – Time-in-therapeutic range = 63%;
  – 87% heart failure; mean LVEF = 25%; atrial fib excluded.
  – Mean age = 61 y/o; 80% men
  – mean BP =124/74 mmHg
  – 13% prior stroke/TIA
  – mean follow-up = 3.5 yrs.
## WARCEF Results

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Aspirin</th>
<th>Relative risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N = 1142</strong></td>
<td><strong>N = 1163</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All deaths and all strokes</td>
<td>302</td>
<td>320</td>
<td></td>
</tr>
<tr>
<td>All deaths</td>
<td>268 (6.6%/yr)</td>
<td>263 (6.5%/yr)</td>
<td></td>
</tr>
<tr>
<td>Ischemic strokes</td>
<td>29 (0.7%/yr)</td>
<td>55 (1.4%/yr)</td>
<td>48% 0.005</td>
</tr>
<tr>
<td>Intracerebral hemorrhages</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>66</td>
<td>31</td>
<td>&lt;0.001</td>
</tr>
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Warfarin-Aspirin Recurrent Stroke Study (WARSS)

NEJM 2001; 345: 1444.

• 1990s RCT involving pts with recent ischemic stroke (<3 mo) of all etiologies except recognized cardioembolic.

• Warfarin (target INR 1.4-2.8; mean = 1.9) vs. ASA 325 mg/d.

• 26% of 2206 participants deemed “cryptogenic”:
  – ~5.8%/yr recurrent stroke
  – HR 0.92 with warfarin vs. ASA

• Cryptogenic with embolic features (n=338):
  – 2-yr rate of recurrent stroke or death:
    • 12% warfarin vs. 18% ASA.
Relationship between achieved INR and stroke rate: WARSS (non-cardioembolic) vs. ATRIA (atrial fibrillation cohort)

WARSS
(non-cardioembolic ischemic stroke)
NEJM 2001; 345: 1450.

ATRIA
(atrial fibrillation)
NEJM 2003
Guidelines for Antithrombotic Therapy for Secondary Prevention of Cryptogenic Stroke

• 2008 American College of Chest Physicians:
  – antiplatelet therapy.

• 2008 American Heart Association:
  – antiplatelet therapy.

• European Stroke Organization guideline, 2011 American Heart Association revised guideline, 2012 American College of Chest Physicians guideline, and 2010 Canadian Best Practice Recommendations for Stroke Care
  – do not comment specifically on cryptogenic stroke, but recommend antiplatelet therapy for patients with non-cardioembolic ischemic stroke

• None advocate for anticoagulants
The large and consistent reduction in intracranial hemorrhage, both intracerebral bleeds and subdural hematomas, is the most important advantage of the direct acting oral anti-coagulants (DOACs) over warfarin in elderly atrial fibrillation patients.
DOACs vs. warfarin phase III RCTs in atrial fib: Intracerebral hemorrhage

- Dabigatran 110 mg BID: $P < .001$
- Dabigatran 150 mg BID: $P < .001$
- Rivaroxaban 20 mg QD: $P = .024$
- Apixaban 5 mg BID: $P < .001$
- Edoxaban 60 mg QD: $P < 0.001$
- Edoxaban 30 mg QD: $P < 0.001$

ESUS: An important unmet medical need warranting an RCT

- 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.
NAVIGATE ESUS:

New Approach to rivaroxaban Inhibition of Factor Xa in a Global trial vs Aspirin to prevent Embolism in Embolic Stroke of Undetermined Source

Study Design
ESUS trial design

Prospective, randomized, double-blind, active-comparator, event-driven, superiority, phase III study

Patients with recent ischemic stroke and:
1. visualized by brain CT or MRI that is not lacunar (subcortical infarct ≤1.5 cm)
2. absence of cervical carotid atherosclerotic artery stenosis ≥50% or occlusion
3. no atrial fibrillation after ≥ 24 hours cardiac rhythm monitoring
4. no intra-cardiac thrombus on transthoracic echocardiography
5. no other specific etiology for cause of stroke (eg, arteritis, dissection, migraine/vasospasm, drug abuse)

Age ≥ 18 years (max 10% patients <60 years)

Target RRR 30%; superiority w/ 90% power α=0.05
Enrollment ~24 months; minimum treatment ~12 months; study duration ~36 months
Estimated mean treatment duration 18 - 24 months;

% ~7,000
Rivaroxaban 15 mg od n ~ 3,500

ASA 100 mg od n ~ 3,500

Day 1
Randomization

1 month post study drug observation period

Efficacy Cut-off Date 30±7 days EOS

Expected timelines:
First patient randomized: December 2014
Last patient randomized: December 2016
Last patient last visit: December 2017
Topline results Q1 2018

2 substudies included in protocol
- MRI substudy to look at covert strokes
- Biomarker / genetics substudy to identify biomarkers linked with ESUS, recurrent stroke and treatment response
Study Objectives

**Primary efficacy outcome:**
Composite of the first occurrence of all recurrent strokes (ischemic, hemorrhagic, and undefined stroke, and TIA with positive neuroimaging), and systemic embolic events

**Secondary efficacy outcomes:**
1) CV death (including death due to haemorrhage), recurrent stroke, systemic embolism, MI
2) All-cause mortality
3) Individual components of the primary and secondary efficacy outcomes stroke, CV death, MI) as well as ischemic stroke, disabling strokes (Rankin 4 and 5)

**Primary safety outcome:**
ISTH major bleeding

**Secondary safety outcome:**
1) Life-threatening bleeding
2) Clinically relevant non-major bleeding
3) Intracranial hemorrhage
ESUS – Choice of Dose: 15 mg OD

- 20 mg is the approved dose for prevention of stroke, which includes embolic stroke, in AF patients (ROCKET AF)
- ESUS is a vulnerable population for ICH
- 15 mg dose selected based on the following considerations
  - should lead to less bleeding than 20 mg
  - should provide sufficient efficacy
    - modelling data shows overlap with 20 mg
    - effective and safe in ROCKET AF in moderate renal impairment and J-ROCKET normal/mild renal impairment
- No dose adjustment for moderate renal impairment planned, as 15 mg safe and efficacious in ROCKET AF
- Rivaroxaban 15 mg OD is expected to provide the best benefit/risk in patients with ESUS by balancing efficacy and bleeding
Choice of Comparator: Aspirin 100 mg

- Current stroke guidelines recommend antiplatelet therapy for patients with non-cardioembolic ischemic stroke
  
- ASA – most frequently used
  - Meta-regression analysis of placebo controlled studies indicate 15% RRR for recurrent stroke
  - Similar efficacy over dose range 50 – 325 mg, limited data for <75 mg

- Clopidogrel and ASA + dipyridamole are used and are the preference in some countries, but there is no clear difference in available data
  - Stroke subgroup of CAPRIE did no show a difference between clopidogrel and ASA
  - In PRoFESS study, ASA + dipyridamole failed to show non-inferiority versus clopidogrel

→ ASA 100 mg regarded as the best comparator in a worldwide double-blind trial and was also used in other stroke studies (eg, PERFORM)

Inclusion Criteria

1. Embolic stroke of undetermined source defined as:
   • Recent ischemic stroke (including TIA with positive neuroimaging) visualized by brain CT or MRI to be not lacunar (subcortical infarct ≤ 1.5 cm), and
   • Absence of cervical carotid atherosclerotic stenosis (or vertebral and basilar artery stenosis in case of posterior circulation stroke), that is ≥ 50%, or occlusion in arteries supplying the area of ischemia in CT or MR angiography or ultrasound, and
   • No history of AF, no documented AF on 12-lead ECG or episode of AF lasting 6 minutes or longer detected during at least 24 hours of ECG monitoring (Holter or telemetry), and
   • No intra-cardiac thrombus on transthoracic echocardiography, and
   • No other specific cause of stroke known or identified by routine clinical care (e.g., arteritis, dissection, migraine / vasospasm, drug abuse)
Additional Inclusion Criteria

2. Time from recent ischemic stroke to randomization and first study medication intake (and only if the investigator regards it as safe to initiate therapy with an anticoagulant) between 7 days and 6 months except:
   - in case of minor strokes (NIHSS ≤ 3), study medication may be initiated as early as 3 days after stroke onset.
   - in case of intravenous thrombolysis treatment or hemorrhagic transformation seen on the qualifying CT or MRI, study medication will not be initiated before 10 days after the acute stroke event unless a repeat CT or MRI scan performed before randomization documents the absence of no new or extension of hemorrhage.

3. All planned diagnostic tests for stroke evaluation must be completed. Brain imaging and 24-hour cardiac monitoring must be repeated if new symptoms of stroke/TIA occurred after the initial stroke evaluation, as does 24-hour cardiac monitoring if symptoms suggestive of AF occur.

4. Age ≥18 years

5. For patients with age < 60 years at least one of the following risk factors: stroke or TIA prior to index stroke, diabetes, hypertension, and heart failure

6. Written informed consent
Main exclusion criteria

1. Severe disabling stroke (modified Rankin score ≥ 4 at screening)
2. If imaging of intracranial arteries is performed by CT or MR angiography or transcranial Doppler: ≥ 50% luminal stenosis in arteries supplying the area of ischemia
3. Patient with patent foramen ovale with plans for closure
4. Known serious infection or inflammatory disease that may be the cause of stroke
5. Patient has or is intended to receive an implantable ECG loop recorder
6. Indication for chronic anticoagulation or antiplatelet therapy
7. eGFR < 30 mL/min/1.73m²
8. Active bleeding, major bleeding within last 6 months, history of primary intracranial hemorrhage or high risk for serious bleeding contraindicating anticoagulant or antiplatelet therapy
THANK YOU