Beyond Atrial Fibrillation: Unexplained Stroke and Atrial Cardiopathy

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Photo credit: P. Ramakrishnan
Disclosure Information

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BMS-Pfizer Partnership (apixaban)
Roche Diagnostics (NT-proBNP)

FINANCIAL DISCLOSURES
UpToDate
Atrial Cardiopathy and Stroke

- Cryptogenic Stroke/ESUS
- Atrial Fibrillation
- Atrial Cardiopathy
- Therapeutic Implications
Cryptogenic stroke

57 year old man with left arm and hand weakness and numbness
Definition of Cryptogenic Stroke

Ischemic Stroke of Undetermined Origin: Brain infarct not attributed to a definite source of large-vessel atherosclerosis, cardioembolism, or small-vessel disease, in the presence of:

1. extensive cardiac, vascular, hematologic, and serologic evaluation;
2. incomplete evaluation; or
3. evidence of more than one competing cause.

--“TOAST criteria”

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(3) evidence of more than one competing cause.

--“TOAST criteria”
Embolic stroke of undetermined source (ESUS)

Requires full evaluation to establish the following:

- Non-lacunar stroke detected by CT or MRI
- Absence of extracranial or intracranial atherosclerosis causing $\geq 50\%$ luminal stenosis in arteries supplying territory
- No major-risk cardioembolic source of embolism based on TTE and $\geq 24$ hr monitoring (AF/flutter, prosthetic valve, LVEF$<30\%$, etc.)
- No other specific cause identified (dissection, vasculitis, spasm, etc.)

About 1/3 of strokes are of undetermined cause

Etiologic subtypes ("Causes") of ischemic stroke: The Northern Manhattan Stroke Study
ESUS is NOT defined by its size

Cryptogenic stroke
57 year old male economist with no significant past medical history with acute onset of left arm and hand weakness and numbness

Lacunar infarction: small vessel disease
48 year old African American woman with history of untreated hypertension with rapidly progressive right weakness
ESUS is NOT defined by its size

78 year old man with a history of hypertension and rheumatoid arthritis who presented with acute confusion. Evaluated as outpatient. Sent for MRI. Later noted to have a mild left hemiparesis.
ESUS IS characterized by its location

Lacunar infarction: small vessel disease

Cryptogenic strokes
Cryptogenic stroke/ESUS is *NOT* characterized by the presence of risk factors.
The triangle graphs show similar distributions of the 3 main thrombus components—red blood cells (RBCs), fibrin/platelet, and white blood cells (WBCs)—in Trial of Org 10172 in Acute Stroke Treatment (TOAST) groups 1 and 4 and in TOAST groups 2 and 5, respectively.
Potential causes of ESUS

- Migraine
- Genetic disorders
  - Fabry disease
  - CADASIL
  - Collagen mutations
  - Actin mutations
- Vasculopathies
  - Vasculitis
  - Reversible Vasoconstriction Syndrome
  - Inflammation (CRP)
- Infections
  - Syphilis
  - HIV
  - Varicella zoster virus
  - Occult Endocarditis
- Homocysteine
- Sleep apnea
- Hypercoagulable states
  - Factor V Leiden
  - Antiphospholipid antibodies
- Cardiac diseases
- Patent foramen ovale
- Atrial septal aneurysm
- Aortic arch atheroma
- Valvular strands
- Mitral annular calcification

Etc.

“Unknown unknowns”
Potential causes of ESUS

• Migraine
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Etc.

“Unknown unknowns”
A Brief History of AF and Stroke

• 1970-1980s
  – Association between AF and stroke
• 1980-1990s
  – Warfarin proven superior to aspirin
• 1990-2000s
  – Acceptance of paroxysmal AF as stroke risk
  – Search for optimal method of detecting AF after stroke
• 2000-2010s
  – New oral anticoagulants
  – Improved risk stratification for anticoagulation
  – Identifying minimum AF burden that causes stroke

## Definitions of Atrial Fibrillation

<table>
<thead>
<tr>
<th>Classification</th>
<th>Duration</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Paroxysmal</strong></td>
<td>&lt; 7 days</td>
<td>• May terminate spontaneously or with treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Recurs with variable frequency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Episodes increase in frequency and duration</td>
</tr>
<tr>
<td><strong>Persistent</strong></td>
<td>Continuous 7 days to 12 months</td>
<td>• Both paroxysmal and persistent AF may occur in same patient</td>
</tr>
<tr>
<td><strong>Long-standing persistent</strong></td>
<td>&gt;12 months</td>
<td></td>
</tr>
<tr>
<td><strong>Permanent</strong></td>
<td>&gt;12 months</td>
<td>Represents a therapeutic rather than physiological category</td>
</tr>
<tr>
<td><strong>“Lone AF”</strong></td>
<td>AF in younger patient in absence of disease</td>
<td>This term is of historical interest and should no longer used in therapeutic decision-making</td>
</tr>
</tbody>
</table>
“Occult” Atrial Fibrillation

- Occult AF = AF that eluded detection during the initial stroke evaluation
- Paroxysmal AF that is “difficult” to detect and is only detectable with moderate or long term continuous monitoring
- Episodes may be extremely brief—how brief an episode counts as “ATRIAL FIBRILLATION” is not clear
Why is finding atrial fibrillation so important?

- **Anticoagulation**: ~70% RRR for preventing recurrent stroke vs placebo
- It is the **ONLY** common stroke mechanism for which we have evidence that treatment with anticoagulation works
Challenge of diagnosing AF

- Frequently paroxysmal
- 25% of AF presents with a stroke
- Newly diagnosed AF after stroke:
  - Average AF burden: 1.8 hours per day
  - AF evident on <10% of days

Ziegler, Stroke, 2010
EMBRACE

• 16 stroke centers in Canada
• 572 patients with CS or TIA within prior 6 months
• Age $\geq$ 55 (mean age 73)
• Evaluation negative; 8% underwent TEE
• Comparison of standard (24 hrs) to 30 day event-triggered monitor
• Primary outcome: 30 seconds of AF detected by 90 days

Gladstone DJ et al. NEJM 2014;370:2467-2477.
<table>
<thead>
<tr>
<th></th>
<th>Control (24 hrs) N=285</th>
<th>30 day monitor N=286</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome:</strong> AF &gt; 30 secs</td>
<td>3.2%</td>
<td>16.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Secondary outcome:</strong> AF &gt; 2.5 min</td>
<td>2.5%</td>
<td>9.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Secondary outcome:</strong> any AF</td>
<td>4.7%</td>
<td>19.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Change from antiplatelet to anticoagulant therapy</strong></td>
<td>4.7%</td>
<td>13.6%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Gladstone DJ et al. NEJM 2014;370:2467-2477.
CRystal AF Study

- 441 cryptogenic stroke patients w/o hx AF
- Age >40 (mean age 61)
- 100% underwent TEE
- Comparison: standard monitoring vs. ICM (REVEAL-XT); can reliably detect AF episodes >about 2 min
- Primary endpoint: 30 seconds of AF detected by 6 months;
- Secondary endpoint: AF detected by 12 months

Sanna T et al. NEJM 2014;370:2478.
Primary Endpoint: DETECTION OF AF AT 6 MONTHS

Rate of detection in ICM arm was 8.9% vs 1.4% in control arm.
<table>
<thead>
<tr>
<th></th>
<th>Implantable cardiac monitor (n=221)</th>
<th>Standard care (n=220)</th>
<th>HR for detection of AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 6 months</td>
<td>8.9%</td>
<td>1.4%</td>
<td>6.4 (1.9-21.7)</td>
</tr>
<tr>
<td>At 12 months</td>
<td>12.4%</td>
<td>2.0%</td>
<td>7.3 (2.6-20.8)</td>
</tr>
<tr>
<td>At 36 months</td>
<td>30%</td>
<td>3%</td>
<td>8.8 (3.5-22.2)</td>
</tr>
</tbody>
</table>

CRYSTAL AF: Recurrent Stroke/TIA

Study was not powered for this endpoint
EMBRACE/CRYSTAL AF

- 30 day MCOT superior to standard monitoring
- Insertable Cardiac Monitor (ICM) is superior to standard monitoring
- Detection of AF changes management
- Unanswered:
  - 30 day MCOT vs. ICM
  - Does long-term monitoring reduce risk of stroke
## CRYSTAL AF

**Implantable cardiac monitor (n=221)** | **Standard care (n=220)** | **HR for detection of AF**
--- | --- | ---
At 6 months | 8.9% | 1.4% | 6.4 (1.9-21.7)
At 12 months | 12.4% | 2.0% | 7.3 (2.6-20.8)
At 36 months | 30% | 3% | 8.8 (3.5-22.2)

**ONLY 30%! What else is out there?**

Questioning the traditional concept of atrial fibrillation as mechanism of stroke

- No clear temporal relationship between AF and stroke
  - Studies of implanted cardiac electronic devices (ASSERT/TRENDS)
  - Brief asymptomatic episodes of AF are common
  - Even runs of AF as short as 20 seconds are associated with stroke risk
  - >90% of strokes occur more than 30 days apart from an episode of AF

Questioning the traditional concept of atrial fibrillation as mechanism of stroke

• No clear temporal relationship between AF and stroke

• Ectopy may lead to stroke before AF

• Genetic mutations associated with AF associated with stroke prior to development of AF

• Electromechanical dissociation between EKG and atrial contraction (esp LAA) in patients with PAF
  Warraich HJ et al. Stroke. 2014;45:1481-1484

Atrial Fibrillation and Mechanisms of Stroke
Time for a New Model

Hooman Kamel, MD; Peter M. Okin, MD; Mitchell S.V. Elkind, MD, MS; Costantino Iadecola, MD

- Mechanisms of atrial dysfunction and thromboembolism
  - Myocardial fibrosis
  - Impaired myocyte function
  - Stasis
  - Endothelial dysfunction
  - Chamber dilatation
  - Inflammation
  - Thrombophilia
  - Left atrial appendage dysfunction

Traditional model of AF and stroke

- Vascular risk factors
- Abnormal atrial substrate
- Non-atrial stroke mechanisms
- Stroke
- Atrial fibrillation
Proposed new model of AF and stroke

Paroxysmal Supraventricular Tachycardia and the Risk of Ischemic Stroke

Deidentified data provided by states to AHRQ Healthcare Cost and Utilization Project (HCUP)

All non-federal hospitals in California for 2009
N= 4,806,830 eligible patients
N= 14,121 (0.29%) diagnosed with PSVT without AF
N=14,402 (0.30%) experienced stroke

Adj HR 2.10, 95% CI 1.69–2.62


*Figure.* Cumulative rates of ischemic stroke are shown according to whether or not patients had a preexisting diagnosis of paroxysmal supraventricular tachycardia (PSVT).
P wave Terminal Force in EKG lead V1 reflects left atrial electrical and structural properties

### Associations between P-Wave Terminal Force in Electrocardiogram Lead V₁ and Incident Ischemic Stroke Subtypes (n=1107)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unadj</th>
<th>Adj</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ischemic stroke</td>
<td>1.24 (1.07-1.42)</td>
<td>1.20 (1.03-1.39)</td>
</tr>
<tr>
<td>Ischemic stroke subtypes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptogenic or cardioembolic</td>
<td>1.31 (1.10-1.55)</td>
<td>1.31 (1.08-1.58)</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>1.29 (0.99-1.68)</td>
<td>1.29 (0.96-1.72)</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>1.32 (1.07-1.62)</td>
<td>1.23 (0.97-1.56)</td>
</tr>
<tr>
<td>Non-cardioembolic</td>
<td>1.14 (0.94-1.40)</td>
<td>1.14 (0.92-1.40)</td>
</tr>
</tbody>
</table>

Results are reported as the hazard ratio (95% CI) for each 1-standard deviation increase in PTFV1. Adjusted model includes age, sex, race, education, smoking status, diabetes, hypertension, lipid levels, atrial fibrillation, and heart failure.

Background

N-terminal pro-B-type natriuretic peptide (NT-proBNP)

- released by ventricles and atria in response to stretch and increased volume
- increased in heart failure, structural heart disease, and other situations of cardiac strain.

Cardiac troponin T (cTnT)

- Indicator of cardiac injury
- May be elevated with subclinical myocardial injury and structural heart disease.
  - Highly-sensitive assay can detect concentrations >10 times lower than conventional assays used for the detection of acute cardiac ischemia.

Both NT-proBNP and cTnT:

- Associated with subclinical cardiac dysfunction
- May be associated with stroke risk through direct (embolism, impaired cerebral perfusion) and indirect (shared risk factors) mechanisms.

NT proBNP and incident ischemic stroke in the Cardiovascular Health Study (n= 4034)
Adjusted for demographics, risk factors and potential mediators (AF, CHF, LVH)

ElkindMS et al. AAN 2013
Left Atrial Appendage Is the Most Common Site of Intracardiac Thrombus Formation in AF
LAA Morphologies

Chicken wing

Windsock

Cactus

Cauliflower

Non-chicken wing morphologies associated with stroke risk in AF

Prevalence of Prior Stroke/TIA According to Different LAA Morphologies and in Chicken Wing Versus Non–Chicken Wing Morphologies


http://dx.doi.org/10.1016/j.jacc.2012.04.032
“Atrial cardiopathy” as a cause of stroke

Atrial fibrillation
  Chronic AF
  Paroxysmal AF
  Occult AF

Other arrhythmias
  Enlarged left atrium
  P wave abnormalities on EKG
  Serum biomarkers of cardiac dysfunction
  Genetic markers of atrial fibrillation
  Gene expression profiles
  Cardiac MRI markers
  Others?
Treating unselected ESUS patients with anticoagulation has not been effective

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>N</th>
<th>Primary outcome</th>
<th>Annual rate on DOAC</th>
<th>Annual rate on AP</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAVIGATE ESUS</td>
<td>Rivaroxaban</td>
<td>7213</td>
<td>Recurrent stroke/systemic embolism</td>
<td>5.1%</td>
<td>4.8%</td>
<td>1.07 (0.87-1.33)</td>
</tr>
<tr>
<td>RESPECT ESUS</td>
<td>Dabigatran</td>
<td>5390</td>
<td>First recurrent stroke</td>
<td>4.1%</td>
<td>4.8%</td>
<td>0.85 (0.69-1.03)</td>
</tr>
</tbody>
</table>

Lumpers vs Splitters:
Time to Deconstruct ESUS!

Figure 2. Potential Occult Sources of Currently Unexplained Ischemic Stroke, Their Overlap, and Their Expected Response to Antithrombotic Drugs

- Silent myocardial infarction
- Atrial cardiopathy without atrial fibrillation
- Subclinical atrial fibrillation
- Patent foramen ovale
- Occult cancer
- Known cancer
- Nonatherosclerotic vasculopathies
- Large-artery atherosclerosis without luminal stenosis
- Undiagnosed aortic atherosclerosis

Need for randomized trials of anticoagulant vs antiplatelet drugs
Need for randomized clinical trials of various antiplatelet drugs, including combination therapies

Warfarin-Aspirin Recurrent Stroke Study Primary Endpoint

Kaplan-Meier Analyses of the Time to Recurrent Ischemic Stroke or Death According to Treatment Assignment

No. At Risk

<table>
<thead>
<tr>
<th></th>
<th>Days after Randomization</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
<td>90</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1,103</td>
<td>1,047</td>
</tr>
<tr>
<td></td>
<td>1,013</td>
<td>998</td>
</tr>
<tr>
<td></td>
<td>972</td>
<td>956</td>
</tr>
<tr>
<td></td>
<td>939</td>
<td>924</td>
</tr>
<tr>
<td></td>
<td>900</td>
<td>885</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1,103</td>
<td>1,057</td>
</tr>
<tr>
<td></td>
<td>1,032</td>
<td>1,004</td>
</tr>
<tr>
<td></td>
<td>984</td>
<td>974</td>
</tr>
<tr>
<td></td>
<td>951</td>
<td>932</td>
</tr>
<tr>
<td></td>
<td>900</td>
<td></td>
</tr>
</tbody>
</table>

n = 2,206

WARSS/APASS: Effect of warfarin vs aspirin on recurrent stroke/death among those with elevated NT-proBNP

NT-proBNP ≤ 750 pg/ml

NT-proBNP > 750 pg/ml

The AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke randomized trial: Rationale and methods

Hooman Kamel\textsuperscript{1}, WT Longstreth Jr\textsuperscript{2,3,4}, David L Tirschwell\textsuperscript{2}, Richard A Kronmal\textsuperscript{5}, Joseph P Broderick\textsuperscript{6}, Yuko Y Palesch\textsuperscript{7}, Caitlyn Meinzer\textsuperscript{7}, Catherine Dillon\textsuperscript{7}, Irene Ewing\textsuperscript{6}, Judith A Spilker\textsuperscript{6}, Marco R Di Tullio\textsuperscript{8}, Eldad A Hod\textsuperscript{9}, Elsayed Z Soliman\textsuperscript{10}, Seemant Chaturvedi\textsuperscript{11}, Claudia S Moy\textsuperscript{12}, Scott Janis\textsuperscript{12} and Mitchell SV Elkind\textsuperscript{13,14}; on behalf of the ARCADIA Investigators
ARCADIA
AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke
(Elkind/Kamel/Longstreth/Tirschwell)
NINDS U01 NS095869

- Multicenter, randomized, active control trial of apixaban vs aspirin for patients with unexplained stroke AND atrial cardiopathy
- NIH-funded (StrokeNet mechanism)
- Industry supported (providing drug and assays)

Primary hypothesis:
- Apixaban superior to aspirin for preventing recurrent stroke in patients with cryptogenic stroke and atrial cardiopathy
Key inclusion criteria

- Age ≥45 years
- Clinical diagnosis of ESUS (Embolic stroke of undetermined source)
- Stroke onset >3 days and <180 days prior.
- Atrial cardiopathy, defined as ≥1 of the following:
  - $\text{PTFV}_1 > 5,000 \ \text{µV} \cdot \text{ms}$ on 12-lead ECG (ECG criterion).
  - Serum NT-proBNP > 250 pg/mL (BNP criterion).
  - Left atrial size index ≥3 cm/m² on echocardiogram (i.e., severe left atrial enlargement) (Echocardiographic criterion).

Primary outcomes:

- Efficacy: recurrent stroke of any type.
- Safety: major hemorrhage, intracranial hemorrhage, stroke and death
Status Update 8/10/2021

• ~2626 patients screened
• 704 patients with ESUS/atrial cardiopathy randomized
• 145 sites in US and Canada
• Adding up to 30 more in US and Canada
• ARCADIA Cognition and Subclinical infarcts (CSI) funded ancillary study

Target screen 4400 patients
Randomize 1100 patients with ESUS/atrial cardiopathy
Why neurologists won’t care about AF in the future...

- Suitable biomarkers may replace AF as a target of therapy
- These have the advantage of being measured at a single point in time
- Avoid the need for long-term monitoring
- Trials are needed to determine if a biomarker-driven strategy can determine which patients with atrial cardiopathy warrant anticoagulation.
A Less Brief History of AF and Stroke

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  – Association between AF and stroke
• 1980-1990s
  – Warfarin proven superior to aspirin
• 1990-2000s
  – Acceptance of paroxysmal AF as stroke risk
  – Search for optimal method of detecting AF after stroke
• 2000-2010s
  – New oral anticoagulants
  – Improved risk stratification for anticoagulation
  – Identifying minimum AF burden that causes stroke
• 2010-2020?
  – Atrial cardiopathies

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