Cryptogenic Strokes: Venturing into the Unknown

Julie M. Fussner, BSN, RN, CPHQ, SCRN
Kari D. Moore, MSN, AGACNP-BC
Martha D. Power, APRN, MSN, RN, SCRN
Disclosures

Julie M. Fussner: No actual or potential conflict of interest in relation to this presentation.
Kari D. Moore: Sub-investigator RESPECT ESUS
Martha D. Power: Co-Investigator on the Arcadia study

Objectives

• Identify the most appropriate approach to diagnosing the underlying causes of cryptogenic stroke.
• Discuss the prevalence of atrial fibrillation after cryptogenic stroke and its role in recurrent stroke.
• Identify current guidelines and controversies of management of PFO after cryptogenic stroke.
Cryptogenic Stroke

- Cryptogenic Stroke: Stroke of unknown cause

- Cryptogenic: krɪptˈəʊ dʒəˈnɪk
  - adjective: of unknown or obscure origin
- Crypt: hidden or secret
- Genic: producing or causing

- Embolic stroke of unknown source (ESUS): ¹
  - Subcategory of cryptogenic stroke that selects for patients specifically with non-lacunar infarcts in the absence of an apparent cause such as known atherosclerosis, major cardioembolic source, or other defined etiology


Stroke Impact

- **25.7 Million** people worldwide have had a stroke
  - **6.5 million** die of stroke each year
  - **5 million** are left permanently disabled.

- Ischemic stroke and heart disease are the leading causes of death worldwide with stroke being the 5th leading cause of death in the US
- **~795,000** new or recurrent strokes yearly in the US
- **87%** ischemic; **13%** hemorrhagic
- **A leading cause** of serious long-term disability in the US

Disability Associated With Stroke


Cryptogenic Stroke Incidence in the US

- 690,000 ischemic strokes every year in the US\(^2\)
  - A leading cause of disability in the US and worldwide
- ~200,000 cryptogenic strokes yearly\(^3\)

Diagnostic Evaluation

- TOAST defines cryptogenic stroke (stroke of undetermined etiology) as brain infarction that is not attributable to a definite cardioembolism, large artery atherosclerosis, or small artery disease despite extensive vascular, cardiac, and serologic evaluation.

- ESUS is a subcategory of cryptogenic stroke in patients specifically with non-lacunar infarcts in the absence of an apparent cause such as known atherosclerosis, major cardioembolic source, or other defined etiology.

<table>
<thead>
<tr>
<th>Classification Scheme</th>
<th>Required Workup</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOAST¹</td>
<td>Not specified</td>
</tr>
<tr>
<td>Causative Classification System for Ischemic Stroke (CCS)²</td>
<td>Brain CT/MR, 12-lead ECG, precordial echocardiogram, extra/intravascular imaging</td>
</tr>
<tr>
<td>Embolic Strokes of Undetermined Source (ESUS)³</td>
<td>Brain CT/MR, 12-lead ECG, precordial echocardiogram, extra/intravascular imaging, cardiac monitoring for ≥24 hours</td>
</tr>
<tr>
<td>ASCOD phenotyping⁴</td>
<td>Does not include a cryptogenic stroke category</td>
</tr>
</tbody>
</table>

ASCO(D) = Atherosclerosis, small-vessel disease, cardiac pathology, other causes, dissection


Cryptogenic Stroke Is a Diagnosis of Exclusion*

- Atherosclerotic
- Arteroembolic
- Aortoembolic
- Branch occlusive disease
- Cardioembolic
- Small arterial occlusion
- Other causes
- Paroxysmal atrial fibrillation
- Paroxysmal embolism
- Other causes
- Cancer-related coagulopathy
- Cryptogenic

As new causes of stroke are identified, incidence of cryptogenic stroke are expected to decrease.

Diagnosing Etiology of Stroke

- Medical, family and social history
- Neurologic examination
- Vital signs with blood pressure monitoring
- Routine labs, glucose, lipid panel
- Initial neurovascular assessment
  - CT/MRI, vascular imaging
- Initial cardiac assessment: EKG, continuous telemetry, transthoracic echocardiogram


Potential Etiologies of Cryptogenic Stroke

- Inherited Thrombophilias
- Aortic Arch Atheroma
- Occult Paroxysmal Atrial Fibrillation (AF)
- Patent Foramen Ovale (PFO)
Thrombophilias

- Thrombophilia is defined as the predisposition to form blood clots inappropriately and is characterized by deficiencies and mutations in endogenous anticoagulants or acquired coagulopathies
- May be associated with increased risk of cryptogenic stroke
- Among patients in whom other causes have not been found screening for thrombophilias or coagulopathies may be worthwhile
- The usefulness of screening for thrombophilic states with stroke and TIA is unknown

Aortic Arch Atheroma

- Some evidence from retrospective studies suggests a causal association between atherosclerotic disease of the aortic arch (atheroma or plaque) and increased risk for ischemic stroke
- Aortic arch plaque is independently associated with an increased risk for stroke

References:
TEE Showing Aortic Arch With Very Severe Atherosclerotic Plaque


Atrial Fibrillation

• AF affects >2.7 million Americans
• Prevalence increases with age
• The leading cardiac arrhythmia in the elderly
• In the U.S., 70 000 cases of stroke per year are attributed to AF
• Both persistent and paroxysmal AF are predictors of first as well as recurrent stroke
• Of all AF patients, those with a prior stroke or TIA have the highest relative risk of stroke (risk of 7% - 10% per year)

Occult Paroxysmal Atrial Fibrillation

• Detection of AF is important in the evaluation of patients with otherwise cryptogenic stroke to identify those who might benefit from anticoagulation

• Paroxysmal AF is often asymptomatic, and may not be detected with short-term monitoring

• Technologies available for extended cardiac monitoring include continuous telemetry, ambulatory electrocardiography, serial ECG’s, transtelephonic ECG monitoring, and insertable cardiac monitors.


12-lead ECG Showing AF With a Rapid Ventricular Rate

Copyright © American Heart Association, Inc. All rights reserved.

Risk for Stroke in Patients with AF

Well-established data indicate that AF is associated with a 5-fold increase in the risk for ischemic stroke. Ischemic stroke associated with AF is nearly twice as likely to be fatal as non-AF stroke.

In patients with AF, oral anticoagulants decrease the risk for stroke by 64% compared with placebo.

References:

2016 ESC / EACTS Guidelines for the Management of Atrial Fibrillation

- In patients with TIA or stroke monitoring for atrial fibrillation is recommended by performing an ECG followed by continuous monitoring for at least the first 72 hours.
- In stroke patients monitoring by long-term non-invasive ECG monitors or implanted loop recorders should be considered to document silent atrial fibrillation.
- Interrogate pacemakers and ICDs on a regular basis for atrial high rate episodes (AHRE). Pts with AHRE should undergo further ECG monitoring to document AF before initiation AF therapy.
- Prolonged ECG monitoring seems reasonable in all survivors of an ischaemic stroke without an established diagnosis of AF.

ESC=European Society of Cardiology  EACTS=European Association of Cardio-Thoracic Surgery  EHRA=European Heart Rhythm Association

Endorsed by the European Stroke Organisation
AHA/ASA 2018 Guidelines for the Early Management of Patients with Acute Ischemic Stroke

- Cardiac monitoring is recommended to screen for AF.
- For at least the first 24 hours after acute stroke
- The benefit of prolonged cardiac monitoring to detect AF is uncertain
- In some patients prolonged cardiac monitoring may be reasonable, although the effect on outcomes is uncertain

---

AHA/ASA 2018 Guidelines for the Early Management of Patients with Acute Ischemic Stroke

- In the few RCTs of prolonged cardiac monitoring after stroke with clinical end points, no significant benefit of oral anticoagulation for stroke prevention in such patients has been demonstrated.
- All of these studies were underpowered for the secondary clinical end points.
- Thus, the appropriate patient selection criteria for prolonged cardiac monitoring and the clinical benefits of doing so remain uncertain at this time.
Types of Cardiac Monitoring

<table>
<thead>
<tr>
<th>Type of monitoring</th>
<th>Setting</th>
<th>Duration</th>
<th>Rate of AF detection, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission ECG</td>
<td>Inpatient</td>
<td>NA</td>
<td>2.7</td>
</tr>
<tr>
<td>Inpatient continuous telemetry</td>
<td>Inpatient</td>
<td>3-5 days</td>
<td>5.5-7.6</td>
</tr>
<tr>
<td>Holter monitor</td>
<td>Outpatient</td>
<td>24 hours</td>
<td>3.2-4.8</td>
</tr>
<tr>
<td>Holter monitor</td>
<td>Outpatient</td>
<td>48 hours</td>
<td>6.4</td>
</tr>
<tr>
<td>Holter monitor</td>
<td>Outpatient</td>
<td>7 days</td>
<td>12.5</td>
</tr>
<tr>
<td>Mobile continuous outpatient telemetry</td>
<td>Outpatient</td>
<td>21-30 days</td>
<td>16-25</td>
</tr>
<tr>
<td>Implantable cardiac monitor</td>
<td>Outpatient</td>
<td>6 months</td>
<td>9</td>
</tr>
<tr>
<td>Implantable cardiac monitor</td>
<td>Outpatient</td>
<td>36 months</td>
<td>30</td>
</tr>
</tbody>
</table>


Holter Monitor

- Portable external monitor that monitor the cardiac rhythm for 24-48 hours
- Saves all data
- Cumbersome to wear during rehab
- Short period of data

Loop Recorders/Event Monitors

• Worn on the body for up to 30 days
• Often requires activation to record an event
• May require awareness of pt to push event button or change batteries
• Saves events only
• Cumbersome to wear

Figure reproduced with permission from David Darling, MD (http://www.daviddarling.info/encyclopedia/E/event_monitor.html).

Mobile Cardiac Technology

• A monitor worn on the skin that automatically detects, records and transmits abnormal heart rhythms for up to 30 days
• Lasts 7.5 days then changed for a total 30 day recording
• Saves all events
• Waterproof

Figure reproduced with permission from Medtronic, Inc.
Implantable Cardiac Monitors

• A monitor inserted under the skin that automatically detects and records rhythms for up to 3 years.
• Record subcutaneous EKG
• Automatic and patient triggered
• Minimally invasive device insertion procedure

Figures reproduced with permission from Medtronic, Inc.

Choosing a Monitor

• Length of monitoring desired
• Ability of the patient to trigger event monitor, change batteries, keep monitor on
• Feedback system (real time, mail in, reports generated by vendor)
• Patient agreeable to procedure to insert loop recorder
• Cost
• Medical institution/vendor relationships
• Relationships between Provider and Cardiologist
• Patient selection: Would you anticoagulated this patient if you found afib?
Proposed Monitoring Algorithm for Cryptogenic Stroke

• 12 lead EKG and at least 24 hours of telemetry monitoring
• 2-4 weeks of continuous cardiac telemetry
• If stroke considered to be cryptogenic stroke after advanced evaluation: consider prolonged (1-3 years) outpatient loop recording


The Future: Precision Medicine

Apple Heart Study

Apple Heart Study

The Apple Heart Study app uses data from Apple Watch to identify irregular heart rhythms, including those from potentially serious heart conditions such as atrial fibrillation. Apple is conducting this research study in collaboration with Stanford Medicine to improve the technology used to detect and analyze irregular heart rhythms, like atrial fibrillation - a leading cause of stroke.

http://med.stanford.edu/appleheartstudy.html

All of Us Research Program

https://allofus.nih.gov/
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


Is AF just the tip of the Iceberg

- Other arrhythmias
- Enlarged left atrium
- P wave abnormalities on EKG
- Serum biomarkers
- Genetic markers
- Cardiac MRI markers
Left Atrial Appendage Is the Most Common Site of Intracardiac Thrombus Formation in AF

Ongoing Research in ESUS Patients

- Phase III NAVIGATE ESUS evaluating safety and efficacy of rivaroxaban as compared to aspirin for secondary prevention of stroke and systemic embolism in recent ESUS stopped early due to comparable efficacy in treatment arms
  - RESPECT ESUS
  - ARCADIA

Courtesy of Dr. G. Albers; Stanford Stroke Center.

RESPECT ESUS Study

- Randomized, Double-blind, Evaluation in Secondary Stroke Prevention Comparing the EfficaCy and Safety of Dabigatran (110 mg or 150 mg, Oral b.i.d.) Versus Acetylsalicylic Acid (100 mg Oral q.d.) in Patients With Embolic Stroke of Undetermined Source (RESPECT ESUS)
- Primary Outcome Measures: Time to first recurrent stroke (ischemic, hemorrhagic, or unspecified) up to 36 months
- Exclude pt’s with hx afib or > 6 minutes of afib on telemetry

https://clinicaltrials.gov/ct2/show/NCT02239120

ARCADIA Study: AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke

- Randomized, double blind evaluation of either apixaban 5 mg or aspirin 81 mg in in Patients with Embolic Stroke of Undetermined Source (ESUS).
- Unique inclusion criteria: Atrial cardiopathy, defined as ≥1 of the following:
  - PTFV, >5,000 μV*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 Outcome : recurrent stroke of any type.
- Safety outcome: major hemorrhage, ICH, stroke and death

https://clinicaltrials.gov/ct2/show/NCT03192215  NINDS U01 NS095869
Patent Foramen Ovale (PFO)

- PFO is present in 15% to 25% of adults and has been identified as a source for cryptogenic ischemic stroke.
- PFO is an embryonic defect and is characterized by an opening in the septum between the atria; this opening provides a conduit for emboli derived from the deep veins of the pelvis or legs to the brain.
- The prevalence of PFO is higher in young adults with cryptogenic stroke.


TEE: PFO With Mobile Thrombus as Seen Across the PFO

Who Benefits from PFO Closure?

“In patients who have had a stroke, are younger than 60 years of age, and have a PFO with characteristics that are highly likely to allow paradoxical embolism to occur, the effect of closure becomes persuasive.”


Stroke Coordinator Role

- Facilitate and develop a multidisciplinary team to evaluate current practice regarding cryptogenic stroke (CS)
  - Identify Key Stakeholders: Neurologist, vascular neurologist, or neurohospitalist, cardiologist, Nursing, etc. Consider how the patients PCP will be engaged in patient management post discharge
- Implement algorithm for Identification and Diagnostic Evaluation of CS
  - Identify a champion
  - Provider & Nursing Education – Raise awareness, Increase Professional Education to ensure proper and thorough evaluation, Standardize follow up and Continuum of Care
  - Assess and Re-evaluate implementation
  - Transition of care considerations and follow up plan
  - Quality Metrics: Track # of cryptogenic strokes and if algorithm for work up followed
- Patient/Caregiver Education Materials (possible causes CS, Diagnostic testing, CS FAQ Sheet, Discharge Instructions specific to CS)
Example CS Algorithm

Image retrieved from: StrokeAssociation.org/CS

Patient Education Materials

What's at the heart of my cryptogenic stroke?

LINQ Placement Discharge Instruction Sheet

- You may remove the inclusive dressing on the following day after procedure. Allow Dermabond or Steri-Strips to fall off naturally. Keep site clean and dry. Showering/bathing is okay but no submersion in water for 5 to 7 days. Call your physician if swelling, redness, or drainage is noted around incision or if you develop a fever while your incision is healing.

- Follow up appointment should be 6 to 8 weeks following insertion.

- Your LINQ Loop Recorder was synced to the "My Care Link Monitor" remote monitoring device by the Cath Lab staff after the LINQ was inserted.

- The "My Care Link Monitor" is in the white box from Cath Lab and needs to go with you upon discharge.

- You will want to plug the monitor in the wall next to where you sleep. It will automatically download and send information to your physician every night at 1am. You should not have to do anything with the monitor unless notified by the Physician and/or Medtronic.

- Unless you are going on vacation or are away for more than a right or two, it is okay to travel without the monitor. All of the data will then download when you return home.

- If you are going to a rehab facility prior to going home, take the monitor with you and plug it in the wall next to the bed there. Make sure to take home with you upon discharge from Rehab.

- If you have any questions about your Monitor or LINQ device please...
Case Study

75 year old LHWF with h/o uncontrolled HTN, 30 pack year tobacco abuse, breast cancer, vertigo, and lightheadedness with change in position for many years presented to the ED with worsening vertigo – “overwhelming dizziness” and “legs felt like jelly”. States if she didn’t sit down felt like she would pass out. Symptoms resolved after 30 minutes. No other associated symptoms. In the last 3 months she has also had spells of talking “gibberish” lasting 5 minutes. No prior stroke or seizure. BP on arrival to ER 216/92. BP at home has been running SBP 150’s up to 190’s.

**Home medications:** Amitriptyline, Atenolol, Chlorthalidone

**Vital Signs:** 216/92, 85, 18, 97.7, 100% RA

**Diagnostic Work Up:**
- EKG – NSR, Telemetry in hospital x 48 hours negative for arrhythmia
- Neurologic exam Normal and NIHSS 0
- CTH – old lacunar infarct right thalamus. No acute findings
- CTA COW – 3.0 mm R M1 saccular aneurysm
- CTA Neck – minimal soft plaque bilateral proximal ICAs

**Labwork:** CBC – normal, Glucose 136, CMP normal, Troponin normal, PT/PTT/INR normal, A1c 5.9, TSH 3.310, Trig 213, T. Chol 229, LDL 154, HDL 32, UA negative, RPR - nonreactive

- **MRI Brain** – Stroke 2 different vascular territories
  - L MCA
  - L PCA - thalamus

- **TEE** – LA and RA normal size, LAA normal, No thrombus, EF 55-65%, Mild MR, Aortic arch with moderate atherosclerosis. No ASD, PFO, VSD. No vegetation.
Medical Decision Making for Secondary Stroke Prevention:

Multidisciplinary Team
- Hospitalist
- Cardiology
- Stroke Neurology
- Patient/Family
- Nursing

Medical Management and Ongoing evaluation:
athero in aortic arch a possibility for etiology; plaque immobile without ulceration/thrombus, felt not to be high probability for etiology.

Stroke etiology determined to be cryptogenic - with her age and prevalence of a-fib it was determined additional monitoring for PAF was needed:

Started on aspirin 325 mg daily, high dose statins with goal LDL < 70, aggressive BP management with goal BP < 130/80 and implantable loop recorder placed to monitor for occult PAF.

Follow up with PCP, Cardiology, and Neurology

Conclusions: Management of Cryptogenic Stroke

- Cryptogenic stroke is a diagnosis of exclusion

- The proportion of patients with cryptogenic stroke decreases based on the extent of the evaluation

- Long-term monitoring studies of patients with otherwise cryptogenic stroke find that between one-fifth and one-third have paroxysmal AF and are at risk for cardioembolic stroke

- The ability to better discern causes of cryptogenic stroke has profound implications in terms of secondary stroke prevention and patient outcomes
Conclusions Continued:

• Cryptogenic stroke patients without documented atrial fibrillation may have other mechanisms for stroke.

• The Stroke Coordinator plays a key role in facilitating the development of a focused multidisciplinary team, as well as implementation of evidence based protocols and education unique to the cryptogenic stroke population.

AHA/ASA Cryptogenic Stroke Resources

StrokeAssociation.org/CS