CRYPTOGENIC STROKE

Victor Barredo, M.D.
Neurologist
Baptist and South Miami Hospitals

Disclosures
I have no relevant commercial relationships to disclose.

Stroke Etiologies

<table>
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<tr>
<th>Hemorrhagic Vessel Rupture (15%)</th>
<th>Ischemic Artery Occlusion (85%)</th>
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Breakdown of Ischemic Strokes:
- Atherothrombotic (25-30%)
  Stenotic artery feeding area of infarction
- Cardioembolic (20%)
  A thrombus or other material dislodges from the heart or aortic arch
- Lacunar/Small Vessel (15-20%)
  Small, deep infarct
- Other/Uncommon (5-10%)
- Cryptogenic (25-40%)
  Unknown cause

Small vessel strokes
- Generally due to metabolic disease
  - Hypertension
  - Hyperlipidemia
  - Diabetes
  - Smoking
- Not due to embolic disease
  - The arteries are microscopic, and too small to hold an embolus
- Workup and treatment generally consists of
  - Carotid dopplers
  - Lipids
  - Glucose monitoring
  - Blood pressure control
  - Antiplatelet agents

Adapted from HP Jr, Stroke. Jan 1993; 24; 35-41
Data from NINCDS Stroke Data Bank / Adams Jr. St. Stroke. 1988; 20; 287
Thalamic Lacunar stroke

Embolic Strokes
- Strokes often line up at the watershed distribution or at the cortex
- May be a small shower representing a lysed clot
- May be in one or multiple vascular territories
  - Multiple vascular territories is pathognomonic for emboli or vasculitis
- Infarcts tend to be larger, with more severe symptoms and deficits
  - Aphasia
  - Neglect
  - Field cuts
  - Seizures
- Can cause edema and death

Watershed Distributions
Embolic stroke

Why MRI Matters

- Delayed diagnosis
- Missed diagnosis
- Increased risk from alternative imaging modalities

Patient presents with mild left sided weakness

- Examination shows no cortical signs, only slight left sided weakness.
- Most consistent with lacunar syndrome.
- CT at left is normal.
- MRI at right shows embolic, cortical infarct.
Embolic Stroke Workup

- Carotid Dopplers to rule out artery to artery embolus
- Fasting Lipids
- Blood Sugar
- MRA or CTA of intracranial vessels to rule out stenosis
  - The SAMPRIS trial shows that intracranial angioplasty does not reduce the risk of recurrent stroke
  - Medical management
  - Does give a culprit
- Transesophageal Echocardiogram
  - Rule out thrombus in the left atrial appendage
  - Cannot be seen on 2D surface echo
  - PFO is of no clinical importance most of the time given CLOSURE study.

Cardioembolic Stroke Causes

- Atrial Fibrillation/Flutter
- Low EF
- Cardiac Thrombus or “Smoke”
- Rare Causes:
  - Cardiac Tumor
  - Vegetation on valve
  - Mobile aortic arch atheroma (>3mm)
  - Endocarditis
  - PFO with venous source of embolism

The dilemma of Cryptogenic Stroke

- If all tests are negative (and the patient has no history of Atrial Fibrillation) we now have a cryptogenic stroke
- The patient is at high risk for a recurrent stroke, and hence further disability and death
- The stroke obviously looks embolic in nature, but how to prove it?
  - Paroxysmal atrial fibrillation may only be present for a few minutes a month, but that is enough to cause a devastating stroke.
Cryptogenic Stroke

Why AF Matters

- AF equals 5 fold increase for stroke risk
- Up to 90% of Paroxysmal Atrial Fibrillation (PAF) episodes may be asymptomatic.
- Risk of stroke annually is equal for PAF and permanent AF
- Detection of AF in Cryptogenic Stroke Patients changes treatment
  - Guidelines state change from antiplatelet to OAC

Importance of AF and Stroke

- AF is frequently paroxysmal and asymptomatic, making detection of AF difficult
- 25% of those with AF-associated stroke have no known prior history of AF
- Even in stroke patients with known PAF, 50-70% are in sinus rhythm at time of stroke
- AF is one of the only reasons to use anticoagulation for secondary stroke prevention
  - For almost all other reasons antiplatelet agents are used
  - Anticoagulants have significantly high risk associated with use.

TRENDS Study Subgroup Analysis

Newly Detected AF "NDAF" in Patients with Thromboembolic Events

- 163 patients with previous ischemic stroke/TIA, no known AF, were continuous monitored via pacemaker or ICD
- NDAF > 5 minute duration were found in 28% patients.
- 73% of patients had newly detected AT/AF on <10% of follow-up days
**Post Stroke – Was It Caused by AF?**

- AT/AF burden >5.5 hours on any of 30 prior days appeared to double thromboembolic (TE) risk.
- "35% of all strokes and systemic emboli were preceded by device detected atrial tachyarrhythmia’s.”

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<tr>
<th>AT/AF Burden Status</th>
<th>Annualized TE Rate (95% Confidence Interval)</th>
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<tr>
<td>Low AT/AF burden</td>
<td>1.1 (0.9, 1.4) %</td>
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<tr>
<td>High AT/AF burden</td>
<td>2.4 (1.2, 4.5) %</td>
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2. http://m.theheart.org/article/115346

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**Clinical Impact of NDAF in Stroke Patients**

- Risk of stroke recurrence is 4 times greater among prior stroke patients with NDAF (15.5%) compared to those with either known AF or no AF (3.9%).
- Emphasizes the need for timely detection of AF.

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**Ziegler Paper**

**Topic: Intermittent and symptom-based monitoring**

- Data from 574 AT500 IPG patients were analyzed retrospectively over 1 year, with intermittent monitoring simulated by analyzing data from randomly selected days.
- "Intermittent and symptom-based monitoring is highly inaccurate for identifying patients with any or long-duration AT/AF and for assessing AT/AF burden."

Example: Quarterly Holter recording detects AF in 54% of the patients with AF, and is correct 29% of the time in ruling out AF in patients.

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**Baptist Health South Florida**

Combining Medical Education
How AF is Detected in Cryptogenic Stroke Patients
The more you look, the more AF you find

- N = 145
- Acute stroke or TIA and no history of AF
- 24-hour Holter recording if normal ECG
- 7-day event monitor if normal Holter

Incremental % AF Detection

SURPRISE Study
Updated Results

Methods:
- 85 patients with cryptogenic stroke/TIA and no AF on 24-hour telemetry were implanted with Reveal XT
- All patients had a minimum of 6 months of monitoring

Results:
- 14 of 85 (16.5%) of patients diagnosed with AF
  - Median time from stroke onset to first recorded event - 98 days
  - Average AF burden was 2 hours per day monitored
  - CHADS2-Vasc in AF group was 4.14 vs. 3.24 in no AF (p=0.03)

Incidence of Atrial Fibrillation detected by Implantable Loop Recorders in Unexplained Stroke

Methods:
- 65 patients with cryptogenic stroke implanted
- Patient workup included vascular & cardiac imaging, at least 24 hours of cardiac rhythm monitoring

Results:
- AF was identified in 25.5% (13) patients
  - Median time to AF detection after implant was 48 days
  - Median duration of first detected AF episode was 6 minutes
  - AF was associated with increasing age (p = 0.018), interarterial conduction block (p = 0.02), left atrial volume (p = 0.02) and the occurrence of atrial premature contractions on preceding external monitoring (p = 0.03)
  - Clinical action (OAC) was taken on all patients where AF was detected

Cotter et al, Neurology, 2013; 80 (14)
Occult Atrial Fibrillation in Cryptogenic Stroke
Detection by 7-day ECG vs. ICM

Methods:
- 60 patients with cryptogenic stroke implanted
- Compared ICM to 7-day Holter monitor
- Patient workup included Cerebral imagining, ECG, 72 hour telemetry, 24-hour Holter, TEE

Results:
- AF was identified in 17% (10) patients
- Average time to detection 64 days post-stroke
- Yield of ICM (17%) vs. 7-day ECG (1.7%) significantly higher p=0.0077


Insertable Cardiac Event Recorder in Detection of Atrial Fibrillation After Cryptogenic Stroke: An Audit Report
Etgen et al., 2013

Methods
- Patient work-up included MRI, 12-lead ECG, 24-72 hr. bedside telemetry, 24-hr Holter, TEE, computed tomography/MRI angiography
- 22 patients with cryptogenic stroke and eligible for oral anticoagulation were implanted with Reveal XT
- AF defined as episode ≥6 minutes

Results
- AF detected in 27.3% (6) patients
- Average time to detection post-stroke was 161 days


Patient Pathway for Acute Stroke
Reimbursement
Cryptogenic Stroke – Appropriate Diagnosis Coding

- "Cryptogenic stroke" usually refers to strokes with no clearly definable cause even after extensive workup.
- Although atrial fibrillation (AF) may be suspected in these patients, it can’t be assigned as a diagnosis code until the diagnosis is established.
- Diagnosis coding for cardiac monitoring insertion depends on the circumstances:
  - Inpatient (during the same admission as the acute stroke)
    - The acute stroke is the principal diagnosis code
  - Outpatient (after discharge from the acute stroke admission)
    - If a specific symptom or sign is present that necessitated the device insertion/test/procedure, that should be used as the principal diagnosis code; however, these patients are usually asymptomatic
    - If the patient has residuals from the stroke, a code from category 438.XX (late effects of cerebrovascular disease) is appropriate as the principal diagnosis code
    - If the patient has no residuals from the stroke, code V12.54 (personal history of stroke or TIA w/o residual deficits) is appropriate as the principal diagnosis code
    - Code V12.54 can also be used as secondary diagnosis codes if a specific symptom or sign is coded as the principal diagnosis

ICMs are Underutilized

- ICMs are recommended by clinical guidelines; yet significantly underutilized

Up to 3 in 4 patients who met appropriate criteria for ICM implantation did not receive one
Cardiac Diagnostics Landscape

24-Hour Holter: 2.5 Million
Event Recorder: 1.5 Million
14-30 Day "MCOT": 250,000
Insertable Cardiac Monitor: 25,000

Source: Frost & Sullivan report: North American Cardiac Monitoring and Diagnostic Services Markets

Symptoms and Intermittent Monitoring
The Tip of the AF Iceberg

Conclusion

- Embolic strokes have a specific appearance on a diagnostic MRI
- With no known hx of AF, the workup is usually negative, leaving us with a diagnosis of cryptogenic stroke
- The yield of diagnosing AF in these patients can be quite high if proper protocol is followed
- An enthusiastic and cooperative partnership between a neurologist and cardiologist is imperative
Thank you