DECRYPTING CRYPTOGENIC STROKE
CASE

- 50yoM
- 9/13 left hand numb clumsy
- No past medical history
- Hypercoag panel Neg
- TEE negative
- Loop recorder placed
- Presents to OSH with aphasia 6/14
- New left hemisphere infarcts
- Loop with “possible afib” on it
- Started apixaban
7/14 expressive aphasia and right hand weak
- On apixaban
- New infarct
- Loop recorder
With no afib
Switched to Warfarin
WHAT IS THE ETIOLOGY??
The Unknown
As we know,
There are known knowns.
There are things we know we know.
We also know
There are known unknowns.
That is to say
We know there are some
things
We do not know.
But there are also unknown unknowns,
The ones we don't know
We don't know.

—Donald Rumsfeld, Feb. 12, 2002, Department of Defense news briefing
CRYPTOGENIC STROKE

- TOAST Criteria
  - Large Vessel
  - Cardioembolic
  - Small Vessel
  - Other Known

- Cryptogenic - the known unknowns and the unknown unknowns
Determining the etiology of stroke lets you determine appropriate secondary prevention.
In the literature, usually means stroke with no clearly definable cause even after some type of work up.

This could mean:
1. the cause is reversible and work up was not performed at appropriate time
2. cause of stroke not fully investigated
3. some causes of stroke remain unknown
4. there are multiple concomitant risk factors that force the physician to be unable to determine the final diagnosis
Goals

1. Learn about epidemiology of “cryptogenic” stroke
2. Diagnostic work up
3. Potential etiologies
TYPES OF STROKES

- Intraparenchmal hemorrhage 10%
- Subarachnoid Hemorrhage 3%
- Ischemic 87%
- 2 most common subtypes are LVO and Cryptogenic
Cryptogenic stroke accounts for 23-40% of all stroke. 
~1/3 of strokes are cryptogenic, ~200,000 per year. 
More frequent in younger patients. 
Hard to know what prognosis for recurrence is.
German Stroke Data Bank - 5017 patients, cryptogenic stroke made up 23%, 40% under age 50.

South Korean study found recurrent stroke rate of 30% in cryptogenic patients within 1 year of initial stroke.

Helsinki Young Stroke Registry, age 15-49, followed for 5 years, 807 patients, 267 with cryptogenic stroke. Found to have 3% rate of stroke at 1 year, 8.2% rate at 5 years.
Follow-Up of Transient ischemic attack and stroke patient and Unelucidated Risk factor Evaluation

Studies 722 patients between age 18-50 with first TIA, ischemic stroke or ICH

Patients followed for 9.1 years

226 had undetermined cause of stroke (99 TIAs, 127 Ischemic stroke, no ICH)

Overall, 32% had poor functional outcome (mRS >2)

Ischemic stroke patients had poor outcome 36.5%

TIA patient 16.8%

Stroke in young can cause debilitation
Older patients with cryptogenic stroke are also at increased risk of recurrent stroke and death.

Study from *Neurology* 8/17 pooled patients with cryptogenic stroke from 11 stroke registries in Europe and America.

Ages <60, 60-80, >80, looked at recurrent stroke/TIA and death per 100 patient-years:

- <60: 2.46 and 1.01
- 60-80: 5.76 and 5.23
- >80: 7.88

Patients >80 had ~3-fold higher risk of recurrent event and 8-fold higher risk of death compared to Patients <60.
Study out of South Korea followed 3278 patients with stroke, subtype undetermined in 37%.

- 21.2% had negative evaluation
- 10.6% had multiple causes so not able to determine exact mechanism
- 4.8% had incomplete work up
<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate OR (95% CI)</th>
<th>P Value</th>
<th>Multivariate OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>1</td>
<td></td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>60–79</td>
<td>1.82 (1.5–2.22)</td>
<td>&lt;0.001</td>
<td>1.87 (1.46–2.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥80</td>
<td>4.73 (3.51–6.37)</td>
<td>&lt;0.001</td>
<td>3.20 (2.19–4.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>1.53 (1.3–1.8)</td>
<td>&lt;0.001</td>
<td>1.22 (0.95–1.57)</td>
<td>0.119</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>1.09 (0.91–1.3)</td>
<td>0.358</td>
<td></td>
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</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>1.11 (0.93–1.32)</td>
<td>0.234</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>0.73 (0.62–0.86)</td>
<td>&lt;0.001</td>
<td>0.98 (0.76–1.26)</td>
<td>0.870</td>
</tr>
<tr>
<td><strong>Atrial Fibrillation</strong></td>
<td>3.05 (2.5–3.71)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hyperlipidemia</strong></td>
<td>1.13 (0.88–1.45)</td>
<td>0.356</td>
<td></td>
<td></td>
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<tr>
<td><strong>Initial NIHSS score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>1</td>
<td></td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3–6</td>
<td>3.44 (2.27–5.21)</td>
<td>&lt;0.001</td>
<td>3.27 (2.14–5.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥7</td>
<td>31.17 (20.94–46.38)</td>
<td>&lt;0.001</td>
<td>22.20 (14.64–33.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Discharge medication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antithrombotic</strong></td>
<td>0.11 (0.06–0.18)</td>
<td>&lt;0.001</td>
<td>0.15 (0.08–0.30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Statin</strong></td>
<td>1.15 (0.98–1.36)</td>
<td>0.084</td>
<td>2.24 (1.80–2.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Length of stay (d)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6</td>
<td>1</td>
<td></td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6–9</td>
<td>0.95 (0.75–1.21)</td>
<td>0.675</td>
<td>0.97 (0.71–1.33)</td>
<td>0.869</td>
</tr>
<tr>
<td>≥10</td>
<td>3.56 (2.85–4.45)</td>
<td>&lt;0.001</td>
<td>2.39 (1.77–3.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Stroke subtypes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAC</td>
<td>1</td>
<td></td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CE</td>
<td>5.72 (3.97–8.25)</td>
<td>&lt;0.001</td>
<td>1.75 (1.11–2.75)</td>
<td>0.015</td>
</tr>
<tr>
<td>LAA</td>
<td>4.1 (2.85–5.9)</td>
<td>&lt;0.001</td>
<td>1.74 (1.12–2.70)</td>
<td>0.014</td>
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<tr>
<td>SOD</td>
<td>2.85 (1.56–5.22)</td>
<td>&lt;0.001</td>
<td>2.12 (1.02–4.39)</td>
<td>0.044</td>
</tr>
<tr>
<td>UM</td>
<td>3.34 (2.21–5.05)</td>
<td>&lt;0.001</td>
<td>1.83 (1.11–3.02)</td>
<td>0.018</td>
</tr>
<tr>
<td>UN</td>
<td>2.63 (1.8–3.84)</td>
<td>&lt;0.001</td>
<td>1.79 (1.14–2.83)</td>
<td>0.012</td>
</tr>
<tr>
<td>UI</td>
<td>10.18 (6.24–16.61)</td>
<td>&lt;0.001</td>
<td>3.49 (1.81–6.74)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**CE** indicates cardioembolism; CI, confidence interval; LAA, large artery atherosclerosis; LAC, lacune; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; SOD, stroke of other determined etiology; UI, stroke of undetermined etiology because of incomplete evaluation; UM, stroke of undetermined etiology because of multiple causes; UN, stroke of undetermined etiology because of negative evaluation.

*Variables (age, sex, smoking, initial NIHSS scores, medications at discharge, length of stay, and stroke subtypes), which showed P<0.1 in the univariate analysis, were included in the multivariate analysis.*
The incompletely investigated patient:
Not every patient had carotid imaging
Only TTE or only Holter
The incompletely investigated patient in this series had the highest mortality rate and most likely to have poor outcome at 3 months
Mortality 12.7% within 30 days, 25.5% within 1 year, and 35.7% within 3 years
Poor 3 month Functional Outcome (mRS 3 or higher) 49.6%
Patients in this series who underwent complete work up which was still negative had second lowest poor outcome rate and similar mortality rate compared to other known stroke subtypes.
MRI PROGNOSIS

- Study out of Calgary
- TIA or minor stroke (NIHSS <4)
- Determined to be cryptogenic after standard evaluation
- MRI at 24hrs, then either 30 days or 90 days
- 3 month clinical evaluation
MRI PROGNOSIS

- 333 patients, 207 who had follow up imaging
- 30 day cohort—5 of 76 (6.6%) patients had new lesions on MRI
- 90 day cohort—19 of 131 (14.5%) had new lesions on MRI
- At 90 days for both cohorts, only 4 patients had clinical recurrent stroke (1.2%)

- What else is happening in these people to cause new clinically silent lesions?
AF AND SILENT CEREBRAL INFARCTS (SCI)

- MRI study of 71 patients with AF vs 71 controls

- Number of SCIs, severity of periventricular hyperintensities and deep/subcortical WM hyperintensities were significantly increased in the AF group.

- Higher CHADS2 score associated with more lesions on MRI in the AF group.
Meta-analysis of 11 studies found SCIs in patients with AF 40% of the time on MRI and 22% of the time on CTH.
-AF doubles the risk of SCIs

SCI leads to decreased cognitive performance

-cognitive impairment on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) test was significantly impaired in persistent and paroxysmal AF patients with SCIs compared to controls
Embolic Stroke of Undetermined/Unknown Source—ESUS

A relatively new name

Embolic appearing non-lacunar stroke in patient without proximal artery stenosis or obvious cardioembolic source

The possible sources are subclinical afib, paradoxical embolus from venous side across a PFO, non-occlusive atherosclerotic plaques in the aortic arch, cervical, or cerebral arteries, and inherited thrombophilias

Must consider further work up for these etiologies.
The presumed treatment would be anticoagulation.

Several studies are underway to look at this.
- NavigateESUS—Rivaroxaban vs antiplatelet for ESUS
- RESPECT ESUS—Dabigatran vs antiplatelet for ESUS
- ATTICUS ESUS—Apixaban vs antiplatelet for ESUS

UPMC will be participating in upcoming ARCADIA study for ESUS and atrial cardiopathy with apixaban vs antiplatelet
LACUNAR VS ESUS

Lacunar

ESUS
Basic stuff—
neurovascular imaging, TTE, holter

Minimum Workup
According to guidelines, baseline evaluations, at a minimum, should include:¹¹

- Noncontrast brain CT or brain MRI
- Blood glucose
- Oxygen saturation
- Serum electrolytes/renal function tests
- Complete blood count, including platelet count
- Markers of cardiac ischemia
- Prothrombin time/International Normalized Ratio (INR)
- Activated partial thromboplastin time
- Electrocardiogram
12 lead ECG
- 24hrs or more of telemetry
- TEE if TTE negative
- Screening for hypercoagulability (patients <55)
- MRA/CTA/DSA
- Consider ct chest/abd/pelv

May not be feasible for all patients or centers
POSSIBLE ETIOLOGIES AND WORK UP

- 1. paroxysmal atrial fibrillation
- 2. patent foramen ovale
- 3. aortic arch atheromatous disease
- 4. inherited thrombophilia
Risk of stroke and TIA is thought to be the same in chronic and paroxysmal afib

Current guidelines recommend telemetry for first 24 hours after stroke. Might be reasonable to monitor for 1 month

24hr Holter may be inferior to serial ECG for 3 days in detecting afib

Detection of PAF greatly changes management, very important to detect
HOW DO YOU FIND AF?

- EKGs, Holter monitors, 24hr telemetry had been standard
- Detection was in range of 1-10%
- Can be seen on interrogation of most implantable pacemakers and AICDs
- 2 recent studies in NEJM show that looking for AF longer increases odds of detection
- EMBRACE and CRYSTAL-AF

The NEW ENGLAND JOURNAL of MEDICINE

Atrial Fibrillation in Patients with Cryptogenic Stroke

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 Molinman Rymer, M.D., Vincent Thijs, M.D., Ph.D., Tyson Rogers, M.S., Frank Beckers, Ph.D., Kate Lindborg, Ph.D., and Johannes Brachmann, M.D., for the CRYSTAL-AF Investigators*
EMBRACE

- 572 patients, 55 years or older with cryptogenic stroke
- 30 day event monitor vs conventional 24hr monitor
- Followed for 90 days
- AF recorded in monitor group 16.1% vs 3.2% in control group
- Number needed to screen was 8
CRYSTAL-AF

- 441 patients 40 or older with cryptogenic stroke
- Randomized to insertable cardiac monitor (REVEAL XT) or Conventional treatment
- At 6 months, AF detected in 8.9% of loop patients vs 1.4% in control
- Median time to detection 41 days
- At 12 months 12.4% in loop vs 2.0% in control
- At 36 months 30% vs 3% in control
- Number needed to screen at 6 months = 14, at 12 months = 10, at 36 months = 4.

Safety—5 devices, or 2.4%, explanted due to infection or pocket erosion
- CRYSTAL AF was done with the REVEAL XT

- The Reveal LINQ is the new device

- The LINQ is smaller, easier to implant, downloads information wirelessly

- Both devices are MRI compatible
- Looking longer for AF increases likelihood of finding it
- The majority of patients diagnosed with AF in EMBRACE and CRYSTAL-AF were started on anticoagulation
- Subclinical AF increases risk of stroke, heart failure and death just like symptomatic AF

### Subclinical AF

<table>
<thead>
<tr>
<th>Type of monitoring</th>
<th>Setting</th>
<th>Invasive vs. noninvasive</th>
<th>Duration</th>
<th>Rate of detection of atrial fibrillation, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission ECG</td>
<td>Inpatient</td>
<td>Noninvasive</td>
<td>N/A</td>
<td>2.7</td>
</tr>
<tr>
<td>Inpatient continuous telemetry</td>
<td>Inpatient</td>
<td>Noninvasive</td>
<td>3-5 d</td>
<td>5.5-7.6</td>
</tr>
<tr>
<td>Holter monitor</td>
<td>Outpatient</td>
<td>Noninvasive</td>
<td>24 h</td>
<td>3.2-4.8</td>
</tr>
<tr>
<td>Mobile continuous outpatient telemetry</td>
<td>Outpatient</td>
<td>Noninvasive</td>
<td>7 d</td>
<td>12.5</td>
</tr>
<tr>
<td>Implantable loop recorders</td>
<td>Outpatient</td>
<td>Invasive</td>
<td>21-30 d</td>
<td>16-25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6 mo</td>
<td>9</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>36 mo</td>
<td>30</td>
</tr>
</tbody>
</table>

2016 ESC Guidelines for the Management of Atrial Fibrillation

Guidelines developed by the Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC.

Endorsed by the European Stroke Organisation (ESO)

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>In stroke patients, additional ECG monitoring by long-term non-invasive ECG monitors or <strong>implanted loop recorders</strong> should be considered to document silent atrial fibrillation.</td>
<td>Ila</td>
<td>B</td>
</tr>
</tbody>
</table>
PFO—PATENT FORAMEN OVALE

- Fetal Cardiac development
  - septum Primum
  - septum secundum
- Pathway for placental oxygenated blood to enter left heart
- With first breath pressures change with increase in LA pressure favoring closure of PFO
PFO AND CRYPTOGENIC STROKE

- Lechat et al NEJM 1988; 318:1148-52-evaluation of patients with ischemic stroke
  - PFO present in 56% of patients with no identified cause
  - Present in 40% with risk factors (migraine, MVP, OCPs)
  - Present in 21% of patients with identifiable cause

  - TEE study of 116 patient
  - PFO in 40% with cryptogenic stroke
  - Present in 25% of patients with known etiology
MAJOR CLINICAL TRIALS FOR PFO CLOSURE

- **CLOSURE trial** - used STARFlex device
  - patients 60 or younger with stroke or TIA
  - 5.9% closure vs 7.7% for primary endpoint, P value 0.30.

- **RESPECT trial** - use Amplatzer PFO Occluder device
  - patients 18-60 with cryptogenic stroke
  - 9 strokes in closure group vs 16 in medical group (HR 0.49; 95% CI 0.22-1.11; P=0.08)

- **PC trial** – used amplatzer PFO occluder
  - patient 18-60, verified stroke
  - 3.4% in closure vs 5.2% control (HR 0.63; 95% CI 0.24-1.62; P=0.34)
META ANALYSIS OF RCTS OF PFO CLOSURE
EXTENDED FOLLOW UP—POST-HOC ANALYSIS

- Long term follow up of RESPECT group
- Majority of recurrent strokes had known mechanism that PFO closure could not prevent
- For cryptogenic strokes in Amplatzer PFO patients there was a 54% RRR, p=0.042
- If device verified to be in place that reduction went to 70% for cryptogenic stroke recurrence.
- If PFO and ASA, 75% RRR for cryptogenic stroke, HR 0.245, p=0.007
- Do not close PFO outside of research setting
- If recurrent strokes on maximal medical therapy could consider Amplatzer PFO Occluder
NEW DATA

- May 2017
- European Stroke Conference
- 2 studies presented—CLOSE and Gore-REDUCE
- New data regarding PFO closure
663 patients with cryptogenic stroke and PFO + ASA or PFO with large shunt randomized PFO closure vs antiplatelet therapy, and antiplatelet therapy vs anticoagulation

- Followed for 5 years
- PFO closure vs Antiplatelet
  0 vs 4 recurrent strokes (hazard ratio, 0.03; 95% confidence interval [CI], 0 - 0.25; \( P < .001 \))
- Antiplatelet vs Anticoagulation
  7 vs 3 recurrent strokes (hazard ratio, 0.43; 95% CI, 0.1 - 1.45; \( P = .17 \))
- Patients with ASA 2% recurrent strokes, large PFO 0.5% recurrent strokes

Safety:
- Major procedural complications occurred in 14 patients (5.9%) of the closure group. These were AF (\( n = 9 \)), atrial flutter (\( n = 1 \)), supraventricular tachycardia (\( n = 2 \)), air embolism (\( n = 1 \)), and hyperthermia (\( n = 1 \)).
- Increase in AF in the closure group (4.6% vs 0.9%; \( P = .02 \)).
664 patients randomized 2:1 PFO closure vs antiplatelet

Outcomes:
- recurrent stroke 24 months
- new clinical stroke or silent brain infarct on MRI at 24 months
- 6 vs 12 clinical strokes in closure vs medical group

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Closure Group (n = 441)</th>
<th>Medical Group (n = 223)</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized recurrent stroke rate (per 100 person-years)</td>
<td>0.39</td>
<td>1.70</td>
<td>0.23 (0.09 - 0.62)</td>
<td>.001</td>
</tr>
<tr>
<td>Brain infarct present, n (%)</td>
<td>22 (5.7)</td>
<td>20 (11.3)</td>
<td>0.51 (0.29 - 0.91)</td>
<td>.024</td>
</tr>
</tbody>
</table>
These new studies will change practice
The complete data has not been published yet

For patients ischemic stroke with Large PFO or PFO with ASA it might make sense to close PFO

Unclear if this data will apply to small PFO, PFO without ASA, patients with TIA and not ischemic stroke, or patients >60 years old
PELVIS study evaluated young stroke patients with MRV of pelvis to look for pelvic DVT

- 95 patients, 46 cryptogenic, 49 known etiology
- 9 patients found to have pelvic DVT on MRV in cryptogenic arm
- 2 patients found to have pelvic DVT in the other arm

Pelvic DVT found more often in cryptogenic stroke patients but was not significant.

Small number of patients evaluated

Could be reasonable to obtain in young patient with PFO and otherwise cryptogenic stroke
ILIAC VEIN DVT
Autopsy study of patients with AA Atheroma -26% of patients with stroke had ulcerated plaque
IMAGING FOR AAA
• Atheromas that are >4mm in thickness, ulcerated or mobile, located at proximal or arch of aorta more likely to cause stroke/TIA
• Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS) trial, aspirin vs warfarin, followed for recurrent stroke/tia
• Patients had TEE
• Plaque >4mm had increased recurrent events (adjusted hazard ratio [HR], 2.12; 95% confidence interval [CI], 1.04 to 4.32)
• Event rates similar for warfarin and aspirin groups in the overall study population (16.4% versus 15.8%; \( P=0.43 \)).
To assess cryptogenic stroke patients, TEE is the gold standard, even though TTE is used as screening.

- TTE identifies abnormality in 0.7% of patients without known cardiac disease
- TTE is basically useless in determining cause of stroke in a young person without heart disease
ARCH TRIAL

- Goal to see what is optimal antithrombotic strategy
- 349 patients, Age >18, mRS <4 with stroke, TIA or peripheral embolism
- Found to have atherosclerotic plaque in thoracic aorta on TEE
- Exclusions: no other cardiac source of embolism, no extracranial or intracranial stenosis, no arterial dissection, no contraindication to anticoagulation, aspirin or plavix.
- Randomized 1:1 to aspirin plus clopidogrel OR warfarin (INR 2-3)
<table>
<thead>
<tr>
<th>Qualifying event</th>
<th>A + C (n=172)</th>
<th>Warfarin (N=177)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>119 (69.2)</td>
<td>131 (74.0)</td>
</tr>
<tr>
<td>Qualifying event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>113 (65.7)</td>
<td>122 (68.9)</td>
</tr>
<tr>
<td>TIA</td>
<td>58 (33.7)</td>
<td>55 (31.1)</td>
</tr>
<tr>
<td>Peripheral Embolus</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
</tbody>
</table>
ARCH RESULTS

- Results:
- Primary endpoint is combination of stroke, MI, peripheral embolism, vascular death, intracranial hemorrhage
- A+C
  - 13 events
- Warfarin
  - 20 events
- Hazard ratio 0.76 (0.30-1.61) P= 0.5
- TTR 67%
- Non-significant 24% reduction in endpoint from dual antiplatelet vs warfarin
ARCH TRIAL

- Stopped for futility after 8 years
- Trouble recruiting patients
- Sample size they thought they needed would be 744 patients per arm
- Actual size was 172 and 177 for A+C and Warfarin respectively

- Still not sure what to do for Arch atheroma
- Unless they have a flopping thrombus, I usually use antiplatelet plus high dose statin
Inherited thrombophilias (e.g., protein C, protein S, or antithrombin III deficiency; factor V Leiden; prothrombin G20210A mutation), and MTHFR

- Rarely contribute to adult stroke
- May play a larger role in pediatric stroke

Studies in younger patients (<55 years of age) have shown an association between prothrombotic genetic variants and ischemic stroke

- Remains controversial in an older population with vascular risk factors

Even in the young, results have been inconsistent

- Small study of cryptogenic stroke patients <50 years of age
  - Increased risk associated with the PT G20210A mutation
  - No significant association with FVL
- 2 other studies of young (<50 years) patients
  - Found no association between ischemic stroke and the FVL, PT G20210A, or MTHFR

The association between APL antibodies and stroke is strongest for young adults (<50 years of age)

Common causes of venous thrombosis are unlikely to cause stroke
- Activated Protein C resistance/Factor V Leiden
- Protein C, Protein S, Antithrombin III
- Prothrombin mutation
- This “typical” hypercoagulable panel is low yield in arterial stroke
- These tests are more high yield in CVT

In young patients without known etiology/risk factors anticardiolipin and lupus anticoagulant are high yield
- Should also order beta-2 glycoproteins

MTHFR and homocysteine are not helpful—DO NOT ORDER

Testing in the acute phase can be misleading—need to repeat at 12 weeks
Testing should be done off of heparin or warfarin or NOAC
This is not clear.

Recommendations I have seen from Heme many times in past:
- If heterozygous (or homozygous) for FVL and no prior clot then aspirin
- If positive for LAC/APL and no prior clot then aspirin
- If LAC/APL persistently positive and no prior clot then aspirin or clopidogrel
- If recurrent events sometimes clopidogrel or anticoagulation

The utility of ordering these studies for arterial stroke is low for the most part.
15% of cancer patients had thromboembolic complication during the course of treatment

Stroke in cancer patients can be unrelated to cancer (conventional stroke mechanism), cancer-related (hypercoagulable state), or treatment related

Cancer leading to venous thromboembolism is well known

Thrombophlebitis migrans may appear months or years before malignancy is discovered

Could cryptogenic stroke be related to undetected malignancy
Study out of South Korea, looked at patients with neurologic symptoms, DWI lesion, sufficient diagnostic work up, and D-Dimer.

They excluded all cases that were not cryptogenic.

They divided them into cryptogenic strokes with active cancer (diagnosis in 6 months previous), and cryptogenic without active cancer.

348 patients, 71 in active cancer group, 277 in just cryptogenic group.
The two cryptogenic groups were compared with a Cancer-control group that did not have stroke.

Plasma levels of D-dimer were significantly higher in the cancer-stroke group than in the cancer control group.

D-dimer levels were 20x higher in cancer-stroke group than in non-cancer cryptogenic group.

Cancer-stroke group also had different infarct pattern on MRI, multiple infarcts in multiple vascular territories.

The non-cancer cryptogenic group usually had single or multiple lesions in a single vascular territory.
OCCULT CANCER
10 patients in the non-cancer stroke group who had elevated d-dimer and characteristic MRI pattern

All 10 were found to have occult malignancy during hospitalization
Stroke, cancer, cancer treatment can all cause D-dimer elevation so it isn’t very specific by itself.

Another study following cancer patients with MCA stroke used TCD monitoring for embolic signals.

Patients without conventional stroke mechanisms were more likely to have embolic signal on TCD.

Embolic signals also more likely to be found in patients with elevated D-dimer.

Elevated D-dimer and presence of adenocarcinoma more likely to have embolic signals.

D-dimer levels decreased with use of anticoagulation.
What must you do?
- Vessel imaging, LDL, hgba1c for all
- TTE for almost everyone, TEE for some, cardiac MRI/CCTA not very often
- Telemetry, holter on d/c, 30 day event monitor with autotrigger algorithm, consider loop recorder
- Hypercoagulable panel—usually only for younger patient or venous thrombosis
- CT chest/abd/pelv—if suspicion for occult malignancy is high
The number of strokes that are “cryptogenic” is high
Cryptogenic stroke seen more often in young people
Young people are likely to be debilitated by stroke and have recurrence of stroke
Determining mechanism of stroke leads to changes in secondary prevention
Work up for AF, PFO treatment, Aortic arch atheroma or inherited thrombophilia may lead to decreased recurrent cryptogenic stroke

The ideal treatment for ESUS is currently being studied
THANK YOU

ANY QUESTIONS?
REFERENCES

References

- Bernstein R, Sanna T, Diener H, Passman RS, et al. CRYSTAL AF-preliminary data, not yet published
REFERENCES