Cardiac Disease and Stroke

Dawn Kleindorfer, MD
Robert Brear Professor and Chair
Department of Neurology
University of Michigan

Financial Disclosures

• No Financial Disclosures
• Research Funding received from the NIH
OUTLINE

- Ischemic Stroke Background
- Occult afib and other arrhythmias
- ESUS and atrial cardiopathy
- PFO
- Troponin and AIS

Secondary Prevention of Ischemic Stroke

What is the cause of the initial cerebrovascular event?

Other

Specific therapy for specific etiology
Ischemic Stroke Subtypes

- Large Artery
- Small Vessel
- Cardioembolism
- Other
- Cryptogenic

NINCDS Stroke Data Bank:

German Stroke Data Bank

Secondary Prevention of Ischemic Stroke

- What is the cause of the initial cerebrovascular event?
  - Large vessel athero
  - Cardioembolism
  - Small vessel dz

  - Revascularization
  - Antiplatelet agent

  - Anticoagulation
  - Antiplatelet agent

  - Risk factor modification
    - Statin
    - Lifestyle modification
Cardioembolic Stroke Importance

- 15-20% of ischemic stroke
- Worse prognosis than other stroke subtypes
- Larger infarct size
  - Larger sized thromboemboli
  - Abrupt onset of vascular occlusion, no collateral flow developed
- Hemorrhagic transformation more common
  - 51-71% cardioembolic vs 2-21% non

Higher Case Fatality After Cardioembolic Stroke

<table>
<thead>
<tr>
<th>Time after First Stroke</th>
<th>Ischemic Stroke of Uncertain Cause</th>
<th>Ischemic Stroke of Other Cause</th>
<th>Ischemic Stroke of Cardioembolic Cause</th>
<th>Ischemic Stroke of Lacunar Cause</th>
<th>Ischemic Stroke of Basal Ganglia Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 d</td>
<td>4.1 (3.0-5.5)</td>
<td>15.2 (9.0-21.5)</td>
<td>6.9 (4.6-11.4)</td>
<td>7.5 (5.3-11.3)</td>
<td>16.6 (10.7-25.3)</td>
</tr>
<tr>
<td>30 d</td>
<td>6.1 (5.3-14.2)</td>
<td>20.3 (23.5-58.3)</td>
<td>1.1 (0.6-1.8)</td>
<td>14.6 (6.7-10.3)</td>
<td>25.0 (18.5-30.3)</td>
</tr>
<tr>
<td>90 d</td>
<td>8.1 (7.0-14.2)</td>
<td>27.9 (29.5-46.2)</td>
<td>2.8 (1.6-4.9)</td>
<td>21.7 (11.7-39.2)</td>
<td>33.2 (21.2-48.3)</td>
</tr>
<tr>
<td>6 mo</td>
<td>8.1 (6.9-14.2)</td>
<td>40.9 (32.3-61.3)</td>
<td>2.8 (1.6-4.9)</td>
<td>22.6 (15.2-30.2)</td>
<td>41.0 (27.6-58.6)</td>
</tr>
<tr>
<td>1 y</td>
<td>10.0 (7.7-12.9)</td>
<td>53.0 (44.5-61.5)</td>
<td>6.9 (4.1-12.2)</td>
<td>25.0 (18.5-30.3)</td>
<td>52.5 (35.2-69.5)</td>
</tr>
<tr>
<td>2 y</td>
<td>11.0 (10.6-27.6)</td>
<td>61.4 (53.1-66.7)</td>
<td>12.5 (9.0-20.1)</td>
<td>29.0 (25.2-39.5)</td>
<td>62.5 (48.0-76.8)</td>
</tr>
<tr>
<td>5 y</td>
<td>32.2 (31.1-43.8)</td>
<td>90.4 (71.1-88.1)</td>
<td>35.1 (23.6-47.6)</td>
<td>48.6 (40.5-58.0)</td>
<td>73.0 (54.1-86.9)</td>
</tr>
</tbody>
</table>

For 30-day and long-term death rates were significantly different among subtypes (log rank, P<0.0001).
Figure 1: MRI scan of the brain in a patient with embolic stroke; white area indicates the area of the brain where the stroke is located.
AFIB!!!

- The most important and prevalent cause of cardioembolic stroke
- Afib increases risk of stroke five-fold
- Up to 25% of all strokes in the elderly are related to afib
- Inherently treatable!

Decision Support Tool for Afib Patients

Courtesy of Mark Eckman, MD
Etiology?

- 68-year-old man with mild left face and arm weakness and mild neglect
- Risk factors: hypertension, prior smoker
- Neuroimaging: small right cortical infarction
- Carotid ultrasound: no significant stenosis
- EKG: sinus rhythm, normal
- Echo (transthoracic): EF 50%, no major wall motion abnormalities, normal valves, no source
- Labs: LDL 95

ESUS: Are We Missing Paroxysmal Atrial Fibrillation?

- Biological and genetic plausibility
- Detection of asymptomatic / occult AF
- Diagnostic dilemma
## AF detection after stroke

<table>
<thead>
<tr>
<th>N</th>
<th>Technique</th>
<th>Prevalence</th>
<th>Predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tayal, 2008</td>
<td>56</td>
<td>MCOT</td>
<td>23% any PAF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n/a</td>
</tr>
<tr>
<td>Ziegler, 2010</td>
<td>163</td>
<td>ICD/PPM</td>
<td>28% PAF/AT &gt;5m</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n/a</td>
</tr>
<tr>
<td>Gaillard, 2010</td>
<td>98</td>
<td>Daily patient-triggered EKG</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;100 PACs 24h Holter Non-lacunar anterior circulation DWI + lesions</td>
</tr>
<tr>
<td>Bhatt, 2011</td>
<td>62</td>
<td>MCOT</td>
<td>24% PAF &gt;30s</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PVC &gt;2m Stroke &gt;TIA Multiple vs. single DWI</td>
</tr>
<tr>
<td>Cotter, 2013</td>
<td>51</td>
<td>ILR</td>
<td>25.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Age Left atrial volume Interatrial block, PACs</td>
</tr>
<tr>
<td>Gladstone, 2014</td>
<td>287</td>
<td>Event Monitor Belt</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Age&gt;75</td>
</tr>
<tr>
<td>CRYSTAL-AF, 2014</td>
<td>225</td>
<td>REVEAL-XT</td>
<td>12% (1 yr)</td>
</tr>
</tbody>
</table>

### Implantable Monitors

- Implanted under skin
- Records up to 3 years
Bottom Line: Look Harder for Occult AFib

- At least 20% of cryptogenic stroke pts have occult AF
- Most AF episodes are asymptomatic
- AF yield increased with longer monitoring duration
  - Unknown optimal duration (forever?)
- AF >6 hours: Doubles 1 yr stroke risk
- Short AF episodes likely predict longer episodes and increased stroke risk
- Treatment options for AFib expanding every day

Is Prolonged Cardiac Monitoring Cost Effective?

- Net gain: 34 quality-adjusted life-years (QALY)
- Cost-utility ratio $13,000 per QALY
- Remained cost-effective over a wide range of model inputs in sensitivity analyses, including changes in the cost and yield of monitoring (even as low as 1%).
Can we identify patients who are highly likely to harbor occult AF?

- Clinical features
  - Age
  - CHADS2Vasc
  - Classic syndromes

- Echocardiographic characteristics
  - Left atrial size

- Radiographic patterns
  - Acute cortical or wedge-shaped infarcts
  - Multiple acute infarcts in >1 territory
  - Prior cortical or cerebellar infarcts

Yes

Yes?
What about self-limited AF?

- Perioperative AF assumed to be self-limited
- Not seen as long-term risk factor for ischemic stroke
- No recommendations for long-term follow-up or management
- But link with long-term stroke is unknown

Epstein et al, *Chest*, 2005
Other atrial arrhythmias <> stroke

Equivalent risks of recurrent stroke, higher risk of bleeding with Rivaroxaban
Other atrial derangements in AF

- AF is associated with many other atrial derangements besides dysrhythmia
  - Endothelial dysfunction
  - Fibrosis
  - Impaired myocyte function
  - Chamber dilatation
- Dysrhythmia = marker for these derangements?


Atrial Cardiopathy

- A commonly used ECG measure of left atrial abnormality (PTFV₁) is associated with stroke risk independently of AF
  - Especially in blacks
Updated hypothesis

- Atrial cardiopathy can cause thromboembolism even in the absence of AF
  - Dysrhythmia that defines AF is a common manifestation of atrial cardiopathy
  - Dysrhythmia in itself increases stroke risk via stasis and remodeling, but is not necessary to cause left atrial thromboembolism

Kamel et al, Stroke, 2016

Proposed StrokeNet ARCADIA Trial

- Primary hypothesis:
  - Apixaban is superior to aspirin for prevention of recurrent stroke or death in patients with cryptogenic stroke and atrial cardiopathy
- Atrial cardiopathy defined as ≥1 of following:
  - PTFV₁ >4000 μV*ms on 12-lead ECG
  - Left atrial size >42 mm in women or >46 mm in men on echocardiogram (mod-to-severe LAE)
  - Serum NT-proBNP >185 pg/mL
Patent Foramen Ovale (PFO)
### Summary of PFO Closure RCTs

<table>
<thead>
<tr>
<th>CLOSURE</th>
<th>TC</th>
<th>RESPECT</th>
<th>Gore</th>
<th>CLOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion</td>
<td>PFO+CIS</td>
<td>PFO+CIS or TIA or peripheral embolism</td>
<td>PFO+CIS</td>
<td>PFO +C.0X</td>
</tr>
<tr>
<td>Follow Up</td>
<td>2 years</td>
<td>4 years</td>
<td>2 years</td>
<td>3yrs</td>
</tr>
<tr>
<td>Primary EP</td>
<td>Stroke/TIA/death</td>
<td>Stroke/TIA/death/peripheral embolism</td>
<td>Stroke/death</td>
<td>Clinical recurrent stroke, all stroke (including silent)</td>
</tr>
<tr>
<td>Technical Success Rate</td>
<td>89%</td>
<td>96%</td>
<td>96%</td>
<td>94%</td>
</tr>
<tr>
<td>Medical Arm</td>
<td>Local PI discretion</td>
<td>Local PI discretion</td>
<td>Local PI discretion</td>
<td>Standardized options, must tx post closure</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.78 (p=0.37)</td>
<td>0.63 (p=0.34)</td>
<td>0.49 (0.08)</td>
<td>0.29 (0.04)</td>
</tr>
<tr>
<td>Device</td>
<td>StarFlex</td>
<td>Amplatz</td>
<td>Amplatz</td>
<td>Helex Septal Occluder</td>
</tr>
</tbody>
</table>
PFO caveats

- Thorough evaluation for other causes needed
- Data is very limited for those over 65
- Best data is for those “high-risk” PFOs, with atrial septal aneurysms and/or larger shunts
- Complications are still not infrequent during procedure
  - 4.9% in <65yo, 10.9% in >65yo
Elevated troponin independently increases risk of mortality within a population

• 85% of AIS had troponin measured
• 20% of those were abnormal
• Mortality risk even after adjusting for CAD/CHF and concurrent MI

Troponin Elevations in Acute Ischemic Stroke

- 85% of AIS had troponin measured
- 20% of those were abnormal
- Mortality risk even after adjusting for CAD/CHF and concurrent MI

Troponin and Cause of Death

- Troponin only associated with cardiac causes of death
- Even after excluding AMI
- “Dose Effect” the higher the troponin, the higher the mortality
- Even after adjusting for cardiac hx or MI

### Table 3. Multivariate Odds After AIS in Those With Complete Cardiac Evaluation, Excluding Those With Concurrent AMI (Ref=139/1377)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dead by 1 yr OR (95% CI)</th>
<th>Dead by 3 yr OR (95% CI)</th>
<th>Dead by 5 yr OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>3.45 (2.11-5.64)</td>
<td>3.06 (1.44-6.47)</td>
<td>2.91 (1.26-6.71)</td>
</tr>
<tr>
<td>Age (per 10-yr increase)</td>
<td>1.59 (1.23-2.07)</td>
<td>1.80 (1.33-2.43)</td>
<td>1.95 (1.70-2.27)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.96 (0.56-1.67)</td>
<td>1.34 (0.66-2.69)</td>
<td>1.36 (0.85-2.14)</td>
</tr>
<tr>
<td>Hx of cardiac disease</td>
<td>1.46 (0.93-2.28)</td>
<td>1.02 (0.69-1.50)</td>
<td>1.36 (0.97-1.89)</td>
</tr>
<tr>
<td>Hx of diabetes mellitus</td>
<td>0.61 (0.36-1.03)</td>
<td>1.04 (0.74-1.47)</td>
<td>1.16 (0.80-1.67)</td>
</tr>
<tr>
<td>Hx of CVD</td>
<td>0.99 (0.54-1.82)</td>
<td>1.29 (0.70-2.32)</td>
<td>1.73 (1.11-2.69)</td>
</tr>
<tr>
<td>Hx of dementia</td>
<td>1.29 (0.73-2.31)</td>
<td>1.25 (0.80-1.96)</td>
<td>1.75 (1.11-2.74)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.41 (0.73-2.71)</td>
<td>1.68 (1.04-2.71)</td>
<td>2.04 (1.38-3.01)</td>
</tr>
<tr>
<td>mRS 0-1</td>
<td>0.56 (0.34-0.93)</td>
<td>0.51 (0.35-0.75)</td>
<td>0.37 (0.24-0.55)</td>
</tr>
<tr>
<td>NIHSS (5-point increase)</td>
<td>1.91 (1.59-2.27)</td>
<td>1.55 (1.40-1.72)</td>
<td>1.44 (1.20-1.72)</td>
</tr>
</tbody>
</table>

ASA indicates acute ischemic stroke; AMI, acute myocardial infarction; CI, confidence interval; CVD, chronic renal disease; Hx, History; mRS, modified Rankin scale; OR, odds ratio; and NIHSS, retrospective National Institutes of Health stroke score.

*Statistically significant.
Troponin and Recurrence

- 2,334 IS patients
- 20% with abnormal troponin
- 13% with recurrent IS
- After adjustment for sociodemographics, stroke severity and vascular risk factors:
  - Elevated troponin associated with increased risk of recurrence HR 1.5 (1.1, 2.0)

Summary

- Cardiac disease and stroke are tightly linked and of great public health importance
- Looking for occult afib is very important
  - Changes treatment decisions
  - Atrial cardiopathy may be important?
- PFO closure may be reasonable for young patients with cryptogenic stroke
- Troponin elevations in the acute setting are likely prognostic indicators of badness