Stroke Prevention in Atrial Fibrillation

Anil Gehi, MD
Associate Professor of Medicine
Cardiac Electrophysiology
anilgehi@med.unc.edu
Four pillars of AF management:

• Stroke prevention
• Slow / reverse AF progression
• Control the heart rate
• Consider a rhythm control strategy
Case #1

- 72 year-old woman with high blood pressure, osteoporosis, pacemaker
- Noted on routine pacemaker check to have atrial fibrillation
- Most episodes about 10 minutes, some up to 10 hours – patient unaware
- Takes aspirin
- No history of bleeding
Case #2

- 46 year-old woman with diabetes
- Urgent care visit for “heart fluttering”
- Found to have atrial fibrillation on EKG
- Episode resolved on its own within 24 hours
- Recalls similar episode last year lasting 2-3 hours
Case #3

- 61 year-old man
- Noted by primary care provider to have irregular heart rhythm
- Atrial fibrillation on EKG
- Unclear how long has been going on
- Patient notes increased fatigue, less energy over last few months
Case #4

- 83 year-old man with congestive heart failure, atrial fibrillation
- Takes apixaban (Eliquis) to prevent stroke
- Presented to ER with weakness, low blood pressure
- Hospitalized for anemia, found to have bleeding ulcer
- Required blood transfusion
Stroke in AFib
Left atrial appendage thrombus (clot)
Signs of stroke

Spot a stroke: Warning signs and symptoms

- Face drooping
- Arm weakness
- Speech difficulty
- Time to call 911
Who is at risk for stroke?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure (or LV dysfunction)</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension BP&gt;140/90 or treated hypertension on medication</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Prior Stroke or TIA or Thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease (e.g. MI, PVD, Aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74 years</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (female gender)</td>
<td>1</td>
</tr>
</tbody>
</table>
## Risk for stroke: CHA$_2$DS$_2$-VASc score

<table>
<thead>
<tr>
<th>CHA$_2$DS$_2$-VASc score</th>
<th>Annual risk for stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>1</td>
<td>1.3%</td>
</tr>
<tr>
<td>2</td>
<td>2.2%</td>
</tr>
<tr>
<td>3</td>
<td>3.2%</td>
</tr>
<tr>
<td>4</td>
<td>4.0%</td>
</tr>
<tr>
<td>5</td>
<td>6.7%</td>
</tr>
<tr>
<td>6-9</td>
<td>&gt;8-9%</td>
</tr>
</tbody>
</table>
Why do AFib patients get clots? It’s complicated…

Risk **not** dependent on how much Afib you have

**Figure 2.** Observed rates of ischemic stroke according to risk category.
Time of stroke not necessarily during Afib episode
# Recommendations for stroke prevention

<table>
<thead>
<tr>
<th>Risk Profile</th>
<th>Recommended Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH(_A^2)DS(_2)-VASc=0</td>
<td>Nothing</td>
</tr>
<tr>
<td>CH(_A^2)DS(_2)-VASc=1 men</td>
<td>“Reasonable” anticoagulation</td>
</tr>
<tr>
<td>CH(_A^2)DS(_2)-VASc=2 women</td>
<td>Novel anticoagulants preferred to warfarin*</td>
</tr>
<tr>
<td>CH(_A^2)DS(_2)-VASc &gt; 2 men</td>
<td>“Recommend” anticoagulation</td>
</tr>
<tr>
<td>CH(_A^2)DS(_2)-VASc &gt; 3 women</td>
<td>Novel anticoagulants preferred to warfarin*</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>Percutaneous LAA occlusion</td>
</tr>
<tr>
<td>Moderate-severe mitral stenosis</td>
<td>Warfarin: INR 2.0-3.0</td>
</tr>
<tr>
<td>Mechanical Valve</td>
<td>Warfarin + aspirin: INR 2.0-3.0 AV</td>
</tr>
<tr>
<td></td>
<td>Warfarin + aspirin: INR 2.5-3.5 MVR</td>
</tr>
</tbody>
</table>

Dialysis patients: warfarin or “alternative” apixaban

Distinguish “antiplatelets” and “anticoagulants”

- **Antiplatelets**
  - Aspirin
  - Clopidogrel (Plavix)
  - Prasugrel (Effient)
  - Ticagrelor (Brilinta)

  *Little benefit for stroke prevention in Afib*

- **Anticoagulants**
  - Warfarin (Coumadin)
  - Dabigatran (Pradaxa)
  - Rivaroxaban (Xarelto)
  - Apixaban (Eliquis)
  - Edoxaban (Savaysa)

  *Major benefit for stroke prevention in Afib*
“Thin the blood” to prevent clots
Occlude the left atrial appendage to prevent clots
Dr. Karl Paul Link
Recognized possible medical use
Started being used in humans in 1954
Early recipient: 1955 (heart attack)
Warfarin only helps in narrow "therapeutic range"

Only INR > 2.0 confers protection

Hylek et al., NEJM 2003; 349: 1019-26
Comparison of warfarin with newer agents

<table>
<thead>
<tr>
<th>Study</th>
<th>NOAC (events)</th>
<th>Warfarin (events)</th>
<th>RR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY*</td>
<td>375/6076</td>
<td>397/6022</td>
<td>0.94 (0.82–1.07)</td>
<td>0.34</td>
</tr>
<tr>
<td>ROCKET AF†</td>
<td>395/7111</td>
<td>386/7125</td>
<td>1.03 (0.90–1.18)</td>
<td>0.72</td>
</tr>
<tr>
<td>ARISTOTLE‡</td>
<td>327/9088</td>
<td>462/9052</td>
<td>0.71 (0.61–0.81)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48§</td>
<td>444/7012</td>
<td>557/7012</td>
<td>0.80 (0.71–0.90)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Combined (random)</td>
<td>1541/29287</td>
<td>1802/29211</td>
<td>0.86 (0.73–1.00)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

**Figure 3: Major bleeding**

Data are n/N, unless otherwise indicated. Heterogeneity: I²=83%; p=0.001. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.
Comparison of warfarin with newer agents

**Figure 2: Secondary efficacy and safety outcomes**

Data are n/N, unless otherwise indicated. Heterogeneity: ischaemic stroke $I^2=32\%$, $p=0.22$; haemorrhagic stroke $I^2=34\%$, $p=0.21$; myocardial infarction $I^2=48\%$, $p=0.13$; all-cause mortality $I^2=0\%$, $p=0.81$; intracranial haemorrhage $I^2=32\%$, $p=0.22$; gastrointestinal bleeding $I^2=74\%$, $p=0.009$. NOAC=new oral anticoagulant. RR=risk ratio.
Stroke Relative Risk Reduction

- Placebo: 22%
- Placebo: 64%
- Warfarin: 36%
- Warfarin: 12%*
- Rivaroxaban: 21%
- Apixaban: 12%*
- Edoxaban: 12%*

* Not significant
How do these anticoagulants compare to warfarin with respect to bleeding?

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Bleeding</strong></td>
<td>Similar</td>
<td>Similar</td>
<td>Lower</td>
<td>Lower</td>
</tr>
<tr>
<td><strong>Intracranial Bleeding</strong></td>
<td>Lower</td>
<td>Lower</td>
<td>Lower</td>
<td>Lower</td>
</tr>
<tr>
<td><strong>Gastrointestinal Bleeding</strong></td>
<td>Higher</td>
<td>Higher</td>
<td>Similar</td>
<td>Higher</td>
</tr>
</tbody>
</table>
What about patients with bleeding problems?

• Signs, symptoms of possible internal bleeding:
  – Pale skin or rapid, weak pulse
  – GI bleeding – bright red or black (“tarry”) stool
  – Vomiting blood – bright red or dark brown (“coffee grounds”)
  – Tender, swollen, bruised, or hard areas with bruising underneath the skin
  – Blood stained urine
  – Vaginal bleeding
  – Coughing blood
  – Headache with confusion, drowsy, faint
Anticoagulants (especially newer agents) are relatively safe
Stop other unnecessary blood thinners (antiplatelets)

**Figure 3.** Hazard ratios (HRs) for the risk of nonfatal (n=12,191) and fatal (n=1,381) bleeding associated with the use of warfarin, aspirin, clopidogrel, and combinations of these drugs. CI indicates confidence interval.
Left atrial appendage occlusion (Watchman)
Left atrial appendage occlusion (Watchman)
Left atrial appendage occlusion as good as warfarin

**FIGURE 2** PROTECT AF/PREVAIL Combined: Meta-Analysis Shows Comparable Primary Efficacy Results to Warfarin

<table>
<thead>
<tr>
<th>Event</th>
<th>HR</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>0.79</td>
<td>0.22</td>
</tr>
<tr>
<td>All stroke or SE</td>
<td>1.02</td>
<td>0.94</td>
</tr>
<tr>
<td>Ischemic stroke or SE</td>
<td>1.95</td>
<td>0.05</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.22</td>
<td>0.004</td>
</tr>
<tr>
<td>Ischemic stroke or SE &gt; 7 days</td>
<td>1.56</td>
<td>0.21</td>
</tr>
<tr>
<td>CV/unexplained death</td>
<td>0.48</td>
<td>0.006</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.73</td>
<td>0.07</td>
</tr>
<tr>
<td>Major bleed, all</td>
<td>1.00</td>
<td>0.98</td>
</tr>
<tr>
<td>Major bleeding, non procedure-related</td>
<td>0.51</td>
<td>0.002</td>
</tr>
</tbody>
</table>

The combined data set of all PROTECT AF and PREVAIL Watchman patients versus chronic warfarin patients documented: 1) similarity in overall stroke or systemic embolism; 2) ischemic stroke slightly increased with Watchman but hemorrhagic stroke significantly decreased with warfarin; and 3) all-cause mortality and major nonprocedural bleeding both significantly improved with Watchman. CI = confidence interval; CV = cardiovascular; HR = hazard ratio; SE = systemic embolism; other abbreviations as in Figure 1.
Procedural safety

Patients With Safety Event (%)

- PROTECT AF 1st Half: 9.9%
- PROTECT AF 2nd Half: 4.8%
- CAP: 4.1%
- PREVAIL: 4.1%
- CAP2: 3.8%
- EWOLUTION*: 2.8%
Bottom line

- Preventing strokes is critical
- AFib patients are at risk for clots in the left atrial appendage
- Use CHA$_2$D$_2$-VaSC to determine your risk
- Non-warfarin blood thinners are preferred if possible
- Patients who cannot take blood thinners should be considered for appendage occlusion
- Watch for bleeding, watch for stroke
- **DOING SOMETHING IS MUCH BETTER THAN DOING NOTHING**
Case #1

- 72 year-old woman with high blood pressure, osteoporosis, pacemaker
- Noted on routine pacemaker check to have atrial fibrillation
- Most episodes about 10 minutes, some up to 10 hours – patient unaware
- Takes aspirin
- No history of bleeding
Case #1

• CHA₂D₂-VaSC: 3
• Recommend: stop aspirin, take anticoagulant
• Chose apixaban
Case #2

- 46 year-old woman with diabetes
- Urgent care visit for “heart fluttering”
- Found to have atrial fibrillation on EKG
- Episode resolved on its own within 24 hours
- Recalls similar episode last year lasting 2-3 hours
Case #2

- CHA$_2$D$_2$-VaSC: 2
- Recommend: consider anticoagulant
- Chose dabigatran
Case #3

• 61 year-old man
• Noted by primary care provider to have irregular heart rhythm
• Atrial fibrillation on EKG
• Unclear how long has been going on
• Patient notes increased fatigue, less energy over last few months
Case #3

- $\text{CHA}_2\text{D}_2$-VaSC: 0
- Recommend: no therapy
Case #4

- 83 year-old man with congestive heart failure, atrial fibrillation
- Takes apixaban (eliquis) to prevent stroke
- Presented to ER with weakness, low blood pressure
- Hospitalized for anemia, found to have bleeding ulcer
- Required blood transfusion
Case #4

-CHA$_2$D$_2$-VaSC: 3
-Episode of major bleeding (not reversible)
-Recommend: left atrial appendage occlusion
Questions?