Stroke Prevention in Atrial Fibrillation: Pharmacologic and Non-pharmacologic Options

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Disclosure Statement of Financial Interest
Pradeep Yadav, MD
Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

None

Outline of this talk
Scope of the problem
Anticoagulation options
Non-pharmacologic options
Atrial Fibrillation Epidemiology

- 2010 Global Estimates
  - 20.9 million men
  - 12.6 million women
- 2010 US Prevalence
  - ~2.7-6.1 million
  - Expected to grow to ~5.6-12 million (2050)
- 23.5% of strokes 80-89 years
- > 75,000 strokes/year due to AF

AF is associated with a 1.5- to 1.9-fold mortality risk after adjustment for the preexisting cardiovascular conditions.

2014 AHA/ACC/HRS Treatment Guidelines to Prevent Thromboembolism in Patients with AF

- Assess stroke risk with CHA2DS2-VASc score
  - Score 1: Annual stroke risk 1%, oral anticoagulants or aspirin may be considered
  - Score 2: Annual stroke risk 2%-15%, oral anticoagulants are recommended
  - Higher CHADS2 score predicts worse outcomes (stroke, major bleeding & vascular mortality)
  - Balance benefit vs. bleeding risk
VKA 67% reduction in embolic events

Wolf, PA et al. Circulation 1991;84:527-539

VKA Risk of Intracranial Hemorrhage

- Delayed onset / offset
- Unpredictable dose response
- Narrow therapeutic index
- Drug-drug, food-food interaction
- Problematic monitoring
- High bleeding rate
- Slow reversibility


Mean Time in Therapeutic Range
Around 2/3

What About “Novel” Anticoagulants?

<table>
<thead>
<tr>
<th>Features</th>
<th>Warfarin</th>
<th>NOAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Dosing</td>
<td>Variable</td>
<td>Fixed</td>
</tr>
<tr>
<td>Food effect</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Many</td>
<td>Few</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Half-life</td>
<td>Long</td>
<td>Short</td>
</tr>
<tr>
<td>Antidote</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

POFPS 41st Annual CME Symposium
August 5-7, 2016
“Stroke Prevention in Atrial Fibrillation: Pharmacologic and Non-pharmacologic Options”
Pradeep K. Yadav, M.D.

<table>
<thead>
<tr>
<th>Warfarin vs NOACS</th>
<th>Dabigatran (150 mg)</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reduction in stroke or embolic events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Effect on Bleeding</td>
<td></td>
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</table>

As concluded in the NEJM manuscripts

**Warfarin vs NOACS**

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<tr>
<td><strong>Safety</strong></td>
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</tbody>
</table>

Less intracranial & fatal bleeding

**Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48</td>
<td></td>
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</tbody>
</table>

As concluded in the NEJM manuscripts

Lancet 2014; 383: 955–62
“Stroke Prevention in Atrial Fibrillation: Pharmacologic and Non-pharmacologic Options”
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**Does the guideline prefer one over the other?**

2014 AHA/ACC/HRS Treatment Guidelines to Prevent Thromboembolism in Patients with Non-valvular AF

- CHA2DS2-VASc score of 2 or greater, oral anticoagulants are recommended. Options include warfarin (INR 2.0 to 3.0) (Level of Evidence: A), dabigatran (Level of Evidence: B), rivaroxaban (Level of Evidence: B), or apixaban (Level of Evidence: B).

- For patients with nonvalvular AF unable to maintain a therapeutic INR level with warfarin, use of a direct thrombin or factor Xa inhibitor (dabigatran, rivaroxaban, or apixaban) is recommended (Level of Evidence: C).

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**Despite Increasing NOAC Adoption, Overall Rate of Anticoagulation in High Risk NVAF Patients has Not Improved**

Anticoagulant Use in Patients with NVAF and CHADS2 ≥ 2

![Chart showing total on oral anticoagulation, warfarin, and NOACs from 2011 Q1 to 2013 Q4 from the NCDR Pinnacle Registry.](image)

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**Estimate of persistence to OAC therapy following AF**

![Graph showing proportion of patients on treatment (%)}

<table>
<thead>
<tr>
<th>Years since start of treatment</th>
<th>NOAC</th>
<th>VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>914</td>
<td>1320</td>
</tr>
<tr>
<td>0.5</td>
<td>651</td>
<td>515</td>
</tr>
<tr>
<td>1.0</td>
<td>342</td>
<td>350</td>
</tr>
<tr>
<td>1.5</td>
<td>130</td>
<td>245</td>
</tr>
<tr>
<td>2.0</td>
<td>45</td>
<td>256</td>
</tr>
</tbody>
</table>
Challenges of long term antithrombotic therapy

- Compliance
- Bleeding
- Drug failure
- Drug/Food interactions
- Cost

• If a drug prevents a clot it will have a bleeding risk
• If doesn’t cause bleeding, it probably doesn’t prevent a clot

Major Bleeding Persists across all treatment strategies

% major bleeding

![Graph showing major bleeding across different treatments]

Elderly Falls

- 2012
  - 2.4 million non-fatal falls among older adults treated in ER
    • 722,000 pts hospitalized
- 2011
  - 22,900 older adults died of fall injuries

![CT scan of brain]

CDC National Center for Health Statistics

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What to do with patients who don’t tolerate OAC?

Rationale for Left Atrial Appendage Closure

- > 90% of clots in non-valvular AF occur in Left atrial appendage (LAA)
- A more permanent solution
- Not everyone can take OAC
  - LAA closure
    - Does not eliminate risk of stroke
    - Cannot prevent other causes of stroke in patients with atrial fibrillation

LAA Occlusion Devices In US

- Watchman Device Gen II: FDA approved for stroke prevention in March 2015
- Lariat Device: 510K approved for soft tissue apposition since 2009
- Amplatzer Cardiac Plug: 510K approved to close LAA in since 2010
- Atriclip: 510K approved to close LAA in since 2010

Investigational In US
Watchman Left Atrial Appendage Occluder

Being evaluated since 2003
device to undergo rigorous clinical evaluation as an alternative to long term anticoagulants in patients with non-valvular AF

WATCHMAN™ Left Atrial Appendage Closure (LAAC) Device Procedure

- One-time implant that does not need to be replaced
- Performed in a cardiac cath lab/EP suite, does not need hybrid OR
- Performed by a Heart Team
  - IC/EP or IC&EP, TEE, General Anesthesia, WATCHMAN Clinical Specialist
- Transfemoral Access: Catheter advanced to the LAA via the femoral vein
  - (Does not require open heart surgery)
Watchman Device Endothelialization

Case example

TransSeptal Puncture
Posterior and Inferior-Mid
Exchange the TransSeptal Sheath for the Watchman Delivery Sheath

Exchange the Pigtail for the Watchman Device

Open the device
Angiogram

Final position

After care

Suture closure of the common femoral vein
Overnight observation on a telemetry bed
Discharge next day
- Oral anticoagulation (ideally)
- Aspirin + clopidogrel (select cases)
Follow-up in 6 weeks with an imaging study (CT / TEE)
- Discontinue OAC

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Evidence - Most Studied LAAC device

<table>
<thead>
<tr>
<th></th>
<th>PROTECT AF Registry</th>
<th>CAP Registry</th>
<th>PREVAIL Registry</th>
<th>CAP2 Registry</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled</td>
<td>800</td>
<td>566</td>
<td>461</td>
<td>579</td>
<td>2406</td>
</tr>
<tr>
<td>Randomized</td>
<td>707</td>
<td>---</td>
<td>407</td>
<td>---</td>
<td>1114</td>
</tr>
<tr>
<td>WATCHMAN: warfarin</td>
<td>463:244</td>
<td>566</td>
<td>269:138</td>
<td>579</td>
<td>1877:382</td>
</tr>
<tr>
<td>Mean Follow-up</td>
<td>4.0</td>
<td>3.7</td>
<td>2.2</td>
<td>0.58</td>
<td>N/A</td>
</tr>
<tr>
<td>Patient-years</td>
<td>2717</td>
<td>2022</td>
<td>860</td>
<td>332</td>
<td>5931</td>
</tr>
</tbody>
</table>

Favorable Procedural Safety Profile: 7-Day Safety Events

With CT scan for procedure planning: Major clinical events

<table>
<thead>
<tr>
<th>Event</th>
<th>Protect AF n (%)</th>
<th>CAP n (%)</th>
<th>PREVAIL n (%)</th>
<th>CAP2 n (%)</th>
<th>Henry Ford n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardial effusion with cardiac tamponade</td>
<td>13 (2.8)</td>
<td>7 (1.2)</td>
<td>4 (1.5)</td>
<td>8 (1.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Device embolization</td>
<td>3 (0.6)</td>
<td>1 (0.2)</td>
<td>2 (0.7)</td>
<td>0 (0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Pericardial effusion – no intervention</td>
<td>4 (0.9)</td>
<td>5 (0.9)</td>
<td>0 (0.0)</td>
<td>3 (0.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Cardiac perforation (surgical repair)</td>
<td>7 (1.5)</td>
<td>1 (0.2)</td>
<td>1 (0.4)</td>
<td>3 (0.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Device migration</td>
<td>1 (0.2)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Device Thrombus</td>
<td>2 (0.4)</td>
<td>1 (0.2)</td>
<td>1 (0.4)</td>
<td>5 (0.9)</td>
<td>1 (2.4)*</td>
</tr>
</tbody>
</table>

Dee Dee Wang et al. Manuscript accepted in JACC Interventions
Meta-Analysis Shows Comparable Primary Efficacy Results to Warfarin

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>0.79 (0.42, 1.07)</td>
<td>0.22</td>
</tr>
<tr>
<td>All stroke or SE</td>
<td>1.02 (0.42, 1.07)</td>
<td>0.94</td>
</tr>
<tr>
<td>Ischemic stroke or SE</td>
<td>1.95 (0.42, 1.37)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.22 (0.42, 1.37)</td>
<td>0.004</td>
</tr>
<tr>
<td>Ischemic stroke or SE &gt; 7 days</td>
<td>1.56 (0.42, 1.37)</td>
<td>0.21</td>
</tr>
<tr>
<td>CV/unexplained death</td>
<td>0.48 (0.26, 0.90)</td>
<td>0.006</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.73 (0.42, 1.07)</td>
<td>0.07</td>
</tr>
<tr>
<td>Major bleed, all</td>
<td>1.00 (0.42, 1.07)</td>
<td>0.38</td>
</tr>
<tr>
<td>Major bleeding, non procedure-related</td>
<td>0.51 (0.26, 0.90)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

PROTECT AF: Final, 5-Year Primary Efficacy Events Consistent with 4-Year Results

<table>
<thead>
<tr>
<th>Event</th>
<th>Rate (per 100 Pts-Yrs)</th>
<th>Rate Ratio (95% CI)</th>
<th>Posterior Non-inferiority</th>
<th>Probability Superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy</td>
<td>2.2</td>
<td>3.7</td>
<td>0.61 (0.42, 1.07)</td>
<td>&gt;99.9%</td>
</tr>
<tr>
<td>Stroke (all)</td>
<td>1.5</td>
<td>2.2</td>
<td>0.68 (0.42, 1.37)</td>
<td>99.9%</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>0.2</td>
<td>0.0</td>
<td>N/A</td>
<td>--</td>
</tr>
<tr>
<td>Death (CV/unexplained)</td>
<td>1.0</td>
<td>2.3</td>
<td>0.44 (0.26, 0.90)</td>
<td>&gt;99.9%</td>
</tr>
</tbody>
</table>

Watchman versus Coumadin

- Safe and mature procedure: few early but no late events
- At least as effective as Coumadin in patients non-valvular AF
  - Non-inferior and superior for preventing the combined outcome of stroke, systemic embolization, and cardiovascular death
  - Superior for cardiovascular and all-cause mortality
The WATCHMAN Device is indicated to reduce the risk of thromboembolism from the LAA in patients with non-valvular atrial fibrillation who:

- Are at increased risk for stroke and systemic embolism based on CHADS2 or CHA2DS2-VASc scores and are recommended for anticoagulation therapy;
- Are deemed to be suitable for warfarin; and
- Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.

**WATCHMAN™ FDA Indications for Use**
March 2015

**CMS NCD Feb 2016**

- CHADS2 score ≥ 2 or (ischemia attack/thromboembolism) or CHA2DS2-VASc score ≥ 3
- A formal shared decision making interaction with an independent non-interventional physician
- A suitability for short-term warfarin but deemed unable to take long term oral anticoagulation

**Optimal Indication of LAA Closure**

Non rheumatic AF with a CHADS-VASc ≥ 2 with challenges With oral anticoagulants
Ideal patient for LAA closure

• Not necessarily a first line treatment
• Ideal for patients
  – Who cannot take long term anticoagulants
  – Compliance issues
  – Don’t want to take long term anticoagulants: life style issues
  – Patients who have stroke on anticoagulants

Should all patients with CHADS2 score be offered LAA closure

Based on the data all patients should informed about both options

Shared decision making

Penn State Hershey’s Program

Done in the cath / EP lab

TEE \(\rightarrow\) CT for pre procedure planning

3 D print, bench testing for difficult anatomies

Center for Structural Heart Disease

TAVR
MitraClip (Percutaneous Mitral Valve Repair)
Valvuloplasty, ASD, PFO closure

LAA closure (Watchman)
Alcohol Septal Ablation
Paravalvular Leak Closure
Shared decision with appropriate rationale

Risk of stroke
Vs
Long term risk of bleeding

Slide courtesy: Dr. Saibal Kar, TVT 2016

Thank You

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