Stroke Prevention in Atrial Fibrillation: A 2021 Update

Rakesh Gopinathannair, MD, MA, FAHA, FACC, FHRS
EP Medical Director, Research Medical Center
Director, Cardiac EP Laboratories, The Kansas City Heart Rhythm Institute
Professor of Medicine, University of Missouri-Columbia
Associate Professor of Medicine (Adjunct), University of Louisville

Email: rakesh.gopinathannair@hcahealthcare.com

@drrakeshg1
9/17/2021
Disclosures

• Consultant/speaker: Abbott Medical, Boston Scientific, Pfizer, Zoll Medical

• Physician Advisor: Altathera, PaceMate

None relevant to the content of this presentation
Outline

• Atrial fibrillation: The problem, Prevalence, Impact and Gender differences
• Risk of stroke – Scoring systems
• Stroke Prevention Strategies:
  - Anticoagulation – Guideline Recommendations
  - Novel Oral Anti-Coagulants (NOACs)
  - Gender Differences in Stroke Prevention Strategies
  - Left atrial appendage closure
• Conclusions
AF – A big problem

Trends in AF incidence, Olmsted county, MN

AF – The Problem

• Common – 10% over age 80
• Every hour, 15 patients with AF will have a stroke (15-20% of all strokes)
• Prevalence: ~8 million in North America
• By 2050: ~16 million in America and 33 million worldwide
• 5-times increased risk of stroke (20% of all strokes are due to AF)
• AF accounted for ≈1.5% of strokes in individuals 50-59 years of age and
• ≈23.5% in those 80-89 years of age.
• AF is independently associated with mortality, heart failure, and arrhythmia-induced cardiomyopathy
• Medicare spending for new AF diagnoses has reached $15.7 billion per year

Go AS, et al. AHA Heart Disease and Stroke Statistics, Circulation 2014
Mozaffarian D, et al. AHA Heart Disease and Stroke Statistics, Update Circulation 2015
Burden of Atrial Fibrillation

Atrial Fibrillation Hospitalization Rates/year
Stroke Prevalence Rates/population 2010
Mortality Associated with AFib

Framingham Heart Study, n=5209

The age-adjusted mortality rate attributable to AF was 6.4 per 100 000 people in 2018 (NHLBI data)

Follow-up (y)

Mortality during follow-up (%)
Gender and Stroke Risk in AF

- Stroke risk (RR 1.9) and systemic embolism risk from AF is higher for women
- Remains high in women despite anticoagulation (and despite adequate TTR for warfarin)
- Women were less likely to receive anticoagulation
- Women have worse functional outcome following a stroke
- Mortality after stroke remains same (~23% at 30-days)
- Bleeding risk remains the same (~1% for warfarin)
- Women with AF taking warfarin had ↑ residual risk of CVA/SE compared with men (OR 1.279, 95% CI 1.111 to 1.473, p = 0.001)
- No gender difference in residual risk of CVA/SE was seen in patients receiving NOAC agents (OR 1.146, 95% CI 0.97 to 1.354, p = 0.11)
- Major bleeding was less frequent in women with AF treated with NOAC

Michelena HI et al. Gend Med 2010; 206-217
Thompson LE et al. Am Heart Assoc. 2017;6:e005801
AF - Definitions

• **Paroxysmal**: Recurrent AF (≥ 2 episodes) that terminates spontaneously within 7 days

• **Persistent**: AF sustained beyond 7 days, or lasting <7 days but needing electrical/pharmacological cardioversion

• **Long-standing persistent**: Continuous AF > 1 year duration

• **Permanent**: AF in which cardioversion has either failed or not been attempted

• Overlapping patterns can be seen in the same patient.

• **Non-Valvular AF**: AF in the absence of moderate to severe mitral stenosis, and a mechanical heart valve


A word on Subclinical AF/AF screening

- New-onset device-detected atrial tachyarrhythmias were observed in 23%; 3 times ↑ risk of stroke; more with longer episodes (>5, OR 3.88 vs. <1 min, OR 1.77)
- Temporal relationship: The OR for stroke was the highest within a 5-day period after a qualifying AF episode (>5.5 hrs)
- Number needed to screen to identify 1 treatable new AF case varied by age: 83 for ≥65 years of age, 926 for 60 to 64 years of age, and 1089 for <60 years of age
- ILR screening post-cryptogenic stroke: 30% have AF
- To date, no studies have demonstrated that AF screening reduces mortality or incidence of thromboembolic complications.

Recommendations for screening to detect AF

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opportunistic screening for AF by pulse taking or ECG rhythm strip is recommended in patients ≥65 years of age.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>It is recommended to interrogate pacemakers and implantable cardioverter defibrillators on a regular basis for AHRE.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>When screening for AF it is recommended that:</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>- The individuals undergoing screening are informed about the significance and treatment implications of detecting AF.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- A structured referral platform is organized for screen-positive cases for further physician-led clinical evaluation to confirm the diagnosis of AF and provide optimal management of patients with confirmed AF.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Definite diagnosis of AF in screen-positive cases is established only after physician reviews the single-lead ECG recording of ≥30 s or 12-lead ECG and confirms that it shows AF.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hindricks G et al. ESC 2020 Guidelines. European Heart Journal (2020) 00, 1;125
Belkin MN et al. Circ Arrhythm Electrophysiol. 2018
Stroke Prevention in Atrial Fibrillation
Nonparoxysmal AF was associated with an increased risk of thromboembolism (HR, 1.38 [95% CI, 1.19–1.61]; P<0.001)

The risk of stroke was significantly lower in patients with atrial flutter than in those with AF (HR, 0.69 [95% CI, 0.61–0.79]).
# Bleeding Risk - HASBLED

<table>
<thead>
<tr>
<th>Risk factors and definitions</th>
<th>Points awarded</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H</strong> Uncontrolled hypertension</td>
<td>1</td>
</tr>
<tr>
<td>SBP &gt;160 mmHg</td>
<td></td>
</tr>
<tr>
<td><strong>A</strong> Abnormal renal and/or hepatic function</td>
<td>1 point for each</td>
</tr>
<tr>
<td>Dialysis, transplant, serum creatinine &gt;200 μmol/L, cirrhosis, bilirubin &gt; × 2 upper limit of normal, AST/ALT/ALP &gt;3 × upper limit of normal</td>
<td></td>
</tr>
<tr>
<td><strong>S</strong> Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Previous ischaemic or haemorrhagic* stroke</td>
<td></td>
</tr>
<tr>
<td><strong>B</strong> Bleeding history or predisposition</td>
<td>1</td>
</tr>
<tr>
<td>Previous major haemorrhage or anaemia or severe thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td><strong>L</strong> Labile INR*</td>
<td>1</td>
</tr>
<tr>
<td>TTR &lt;60% in patient receiving VKA</td>
<td></td>
</tr>
<tr>
<td><strong>E</strong> Elderly</td>
<td>1</td>
</tr>
<tr>
<td>Aged &gt;65 years or extreme frailty</td>
<td></td>
</tr>
<tr>
<td><strong>D</strong> Drugs or excessive alcohol drinking</td>
<td>1 point for each</td>
</tr>
<tr>
<td>Concomitant use of antiplatelet or NSAID; and/or excessive* alcohol per week</td>
<td></td>
</tr>
</tbody>
</table>

**Maximum score**: 9

---

 Stroke Prevention in AF: Guideline Recommendation

• Antithrombotic therapy substantially ↓ stroke risk
• Selection of antithrombotic should be based on stroke risk, irrespective of whether AF is paroxysmal, persistent or permanent
• CHA$_2$DS$_2$–VASC: is recommended for assessment of stroke risk
• For CHA$_2$DS$_2$–VASC score ≥ 2 (men) or ≥ 3, anticoagulation is recommended
• NOACs are recommended in preference to VKAs
• If warfarin is used, a target INR of 2-3 and TTR of ≥70% is recommended
• Renal function should be evaluated prior to initiation of direct thrombin or factor Xa inhibitors and should be re-evaluated at least annually
• For Atrial flutter, similar recommendations apply
• OAC should be considered for stroke prevention in AF patients with a CHA2DS2-VASC score of 1 in men or 2 in women. Treatment should be individualized based on net clinical benefit and consideration of patient values and preferences

Stroke Prevention in AF: Guideline Recommendations

- **Nonvalvular AF and a CHA2DS2-VASc score of 0 (1 in female):** reasonable to omit antithrombotic therapy
- **Nonvalvular AF and a CHA2DS2-VASc score of 1 (2 in female):** OAC should be considered. Treatment should be individualized based on net clinical benefit and consideration of patient values and preferences

- Dabigatran, edoxaban and Rivaroxaban are not recommended in patients with AF and end-stage CKD or hemodialysis
- Dabigatran should not be used in patients with AF and a mechanical heart valve
Stroke reduction in AF patients treated with Warfarin: A meta-analysis

- Risk of stroke/systemic embolism in AF patients = 1.6 for warfarin
- However, TTR ranges from 50-65%

Favors Warfarin

Heterogeneity P=0.13.

ENGAGE AF-TIMI 48
[Edoxaban 60 mg]

ARISTOTLE
[Apixaban]

ROCKET AF
[Rivaroxaban]

RE-LY
[Dabigatran 150 mg]

Combined
[Random Effects Model]
N=58,541

Risk Ratio (95% CI)

0.5 Favors NOAC

1

2 Favors Warfarin

P<0.0001

0.66 (0.53 - 0.82)

0.88 (0.75 - 1.03)

0.80 (0.67 - 0.95)

0.88 (0.75 - 1.02)

0.81 (0.73 - 0.91)

<table>
<thead>
<tr>
<th></th>
<th>RE-LY (Dabigatran)</th>
<th>ROCKET-AF (Rivaroxaban)</th>
<th>ARISTOTLE (Apixaban)</th>
<th>ENGAGE AF TIMI 48 (Edoxaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin vs. OAC (CVA or SE)</td>
<td>1.69 vs. 1.11 p&lt;.001</td>
<td>2.42 vs. 2.12 p=.12 (2.2 vs 1.7 on treatment)</td>
<td>1.60 vs. 1.27 p &lt; .001 NNT = 303</td>
<td>1.80 vs. 1.57 p=.08 (1.5 vs. 1.18 on treatment) *High-dose (60 mg)</td>
</tr>
<tr>
<td>*150 mg shown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Major Bleeding %</strong></td>
<td>3.57 vs. 3.32 p=0.31</td>
<td>3.45 vs. 3.6 p=0.58</td>
<td>3.09 vs. 2.13 p&lt;.001</td>
<td>3.43 vs. 2.75 p&lt;.001</td>
</tr>
<tr>
<td><strong>ICH%</strong></td>
<td>0.74 vs. 0.30 p&lt;.001</td>
<td>0.74 vs. 0.49 p=.019</td>
<td>0.47 vs. 0.24 p&lt; .001</td>
<td>0.85 vs. 0.39 p&lt; .001</td>
</tr>
<tr>
<td><strong>All-cause mortality %/yr</strong></td>
<td>4.13 vs. 3.64 p = 0.051 NNT = 204</td>
<td>4.91 vs. 4.52 p=NS NNT = 238</td>
<td>3.94 vs 3.52 p = 0.05 NNT = 238</td>
<td>4.35 vs. 3.99 p=0.08 NNT = 277</td>
</tr>
<tr>
<td><strong>Conclusion vs. warfarin</strong></td>
<td>Superior efficacy, similar bleeding, less ICH</td>
<td>Non-inferior on efficacy and safety measures</td>
<td>Superior efficacy, less major bleeding and ICH, lower mortality</td>
<td>Non-inferior on efficacy; less bleeding</td>
</tr>
</tbody>
</table>
NOACs: key similarities

- All are noninferior to warfarin for prevention of total stroke and systemic embolism
- All reduce the risk of intracerebral hemorrhage
- Outcomes of major bleeding are generally better than with warfarin
  - Outcome differences may in part be explained by variations in dosing, study design, intrinsic risk, concurrent treatment and other factors
- Reductions in mortality are comparable and appear to be related to lower rates of cardiovascular death and fatal bleeding.
## NOACs in Renal Disease

<table>
<thead>
<tr>
<th>Agent</th>
<th>Standard AF Dose (Prescribing info)</th>
<th>Renal Dosing</th>
<th>Trial and Other Experience</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>150mg Twice Daily (CrCl &gt; 30ml/min)</td>
<td>75mg Twice Daily (CrCl 15-30ml/min)</td>
<td>• RE-LY trial: 150mg or 110mg BID if CrCl &gt; 30ml/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No trial experience in pts w/ CrCl &lt; 30ml/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 75mg dose not studied in RCTs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• European dosage:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 150mg BID if CrCl &gt;50ml/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 110mg BID if CrCl 30-50ml/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Contraindicated if CrCl &lt; 30ml/min</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>20mg Once Daily (CrCl &gt; 50ml/min)</td>
<td>15mg Once Daily (CrCl 15-50ml/min)</td>
<td>• ROCKET-AF trial:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 20mg Daily if CrCl &gt; 50ml/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 15mg Daily if CrCl 30-50ml/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No trial experience in pts w/ CrCl &lt; 30ml/min</td>
</tr>
<tr>
<td>Apixaban</td>
<td>5mg Twice Daily</td>
<td>2.5mg Twice daily if at least 2 of the following:</td>
<td>• ARISTOTLE trial: Renal dose studied as per prescribing information.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 80 y/o, Weight &lt; 60kg, SCr &gt; 1.5ml/dL</td>
<td>• No trial experience in pts w/ CrCl &lt; 25ml/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dosing guidance for ESRD (with or without hemodialysis)</td>
<td>• No trial experience with ESRD patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edoxaban</td>
<td>60mg Once Daily (CrCl 50-95ml/min)</td>
<td>30mg Once Daily (CrCl 15-50ml/min)</td>
<td>• TIMI-ENGAGE: Randomized to 60mg or 30mg Daily</td>
</tr>
<tr>
<td></td>
<td><strong>BLACK BOX WARNING:</strong> Avoid use if CrCl &gt; 95ml/min</td>
<td></td>
<td>• Dose halved if</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• CrCl 30-50ml/min, Weight &lt; 60kg, or</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Concomitant verapamil, quinidine, or dronedarone (strong P-gp inhibitors)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No trial experience in pts w/ CrCl &lt; 30ml/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Worse outcomes in patients with CrCl &gt; 95ml/min</td>
</tr>
</tbody>
</table>

- Among patients with atrial fibrillation and CrCl 25 to 30 mL/min, apixaban caused less bleeding than warfarin
- Even greater reductions in bleeding than in patients with CrCl >30 mL/min.

Stanifer JW. 2020 Apr 28;141(17):1384-1392.
Challenges With Oral Anticoagulation (OAC)

- Bleeding risk
- Drug and diet interactions (VKA)
- Non-adherence
- Issues with monitoring (VKA)

Use of OACs in AF Patients peaks at ~50%, use declines with increasing risk

OAC Adherence

NOACs better than VKA but still ~30% of NOAC patients stop taking the drug at 2 years
Warfarin Ineligible Patient: ROAR Study

- Multicenter study (n=263) of the use of direct oral antagonists (DOACs) in Warfarin ineligible (major bleed or stroke) patients
- 63% (166 of 263) patients had a repeat major bleed on DOACs
- Repeat major bleed was significantly higher in patients with prior gastrointestinal bleeding (74.5% vs. 30%, P < 0.0001)
- Five percent (12 of 263) developed repeat stroke/TE
- 34% (57 of 166) of patients had an intervention to manage repeat major bleed

Left Atrial Appendage: What Does It Do?

- Major source or AF-related cardiac thromboembolism (91%) in non-valvular AF
- LAA – source of focal firing & AF triggers in 27% of AF patients undergoing re-do ablation

Left Atrial Appendage: What does it do?

- Conduit, reservoir and neurohormonal
- Major source or AF-related cardiac thromboembolism (91%) in non-valvular AF
- Complex architecture with pectinates facilitate slow conduction and arrhythmogenecity, especially when fibrosis present
- LAA – source of focal firing & AF triggers in 27% of AF patients undergoing re-do ablation

52 year-old Female with Persistent Atrial Fibrillation Undergoing TEE
**WATCHMAN™ Left Atrial Appendage Closure (LAAC) Device Overview**

**Nitinol Frame**
- Radially expands to maintain position in LAA
- Available sizes:
  - 21, 24, 27, 30, 33 mm (diameter)
- 10 Active fixation anchors around device perimeter engage LAA tissue for stability and retention

**160 Micron Membrane**
- Polyethylene terephthalate (PET) cap
- Designed to block emboli from exiting the LAA
LAAC Indications: US vs International

**US (CMS)- WATCHMAN™**
- NVAF
- CHADS2 VASC ≥ 3
- Suitable for short-term warfarin but appropriate rationale exists to seek non-pharmacologic alternative to long-term OAC
- Formal shared decision-making with an independent non-interventional physician

**International**
- LAAC is intended to prevent thrombus embolization from the LAA and reduce the risk of life-threatening bleeding events in patients with NVAF who are eligible for OAC (IIb B)
- Or who have a contraindication to anticoagulant therapy (IIbC)

---

2014 AHA/ACC/HRS AF Guidelines, Circulation. 2014 Apr 10

Section 4.4.1 - Percutaneous Approaches to Occlude the Left Atrial Appendage

Percutaneous LAAO should be considered for those AF patients at an increased risk of stroke who have contraindications to long-term anticoagulation and who are at high risk of thromboembolic events.

Recommendations for occlusion or exclusion of the LAA

LAA occlusion may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment (e.g. intracranial bleeding without a reversible cause).448,449,481,482

Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery.459,483
Rationale to seek non-pharmacologic alternative

- Major bleeding from OAC
- Inability to maintain INR/Non-compliance/refuses OAC
- Medical condition, occupation, or lifestyle placing patient at high risk of major bleeding secondary to trauma
- HASBLED score ≥3
- Fall risk
- CAD patients needing triple therapy
LAA anatomy is complex - Windsock

Endocast

Angiography

TEE

Gross Anatomy

Cardiac CT

Courtesy: Dr Marcus Stoddard

Beigel et al.: JACC Img. 2014;7(12):1251-1265
LAA anatomy is complex - Chicken Wing

Endocast

Gross Anatomy

Angiography

TEE

Cardiac CT

Courtesy: Dr. Marcus Stoddard

Beigel et al.: JACC Img. 2014;7(12):1251-1265
LAA anatomy is complex - Cactus

Endocast

Angiography

TEE

Gross Anatomy

Cardiac CT

Courtesy: Dr. Marcus Stoddard

Beigel et al.: JACC Img. 2014;7(12):1251-1265
LAA Ostial Variations
Efficacy and Safety Data
WATCHMAN Clinical History
Over 2,000 patients with 4,800 patient years follow-up

- Pilot: Early feasibility with > 6 years of follow up
- PROTECT-AF: Superior to warfarin for primary efficacy, CV death, and all-cause mortality at 4 years\(^1\)
- CAP Registry: Significantly improved safety results\(^2\)
- ASAP: Expected rate of stroke reduced by 77% in patients contraindicated to warfarin\(^3\)
- PREVAIL: Improved success and procedural safety confirmed with new and experienced operators\(^4\)
- CAP2: Currently enrolling up to 1500 patients at ~60 sites
Procedural Success

*PINNACLE FLX (Kar S et al. Circulation, 2021 May 4;143(18):1754-1762)*

- N=400, non-randomized study of WATCHMAN FLX
- CHA2DS2-VASc score was 4.2±1.5
- Success rate ~100%
- Adverse events: 0.5%
- DRT 7/400

Implant success defined as deployment and release of the device into the LAA; no leak ≥ 5 mm
Patient-Level Meta-analysis of PROTECT AF, PREVAIL, and CAP Registries

2406 patients with 5931 patient-years of follow-up (Mean follow-up 2.69 years)

<table>
<thead>
<tr>
<th>Event</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td></td>
<td></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>

Favors WATCHMAN ← Favors warfarin

Holmes DR et al. J Am Coll Cardiol 2015;65:2614–23
### Observed Rates of Major Bleeding Over Time According to Treatment Group

#### Post Procedure Therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Event Rate per 100 pt-yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin + ASA (81mg) daily</td>
<td>10.8 (79/732)</td>
</tr>
<tr>
<td>Clopidogrel (75mg) + ASA (325 mg) daily</td>
<td>5.9 (40/682)</td>
</tr>
</tbody>
</table>

#### Destination Therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Event Rate per 100 pt-yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA (325mg) daily</td>
<td>11.3 (43/382)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rate Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.96</td>
</tr>
<tr>
<td>Post Procedure</td>
<td>0.49</td>
</tr>
<tr>
<td>Destination</td>
<td>0.28</td>
</tr>
</tbody>
</table>

*if leak >5mm, patients remained on warfarin + ASA until seal documented, skipping the clopidogrel + ASA pharmacotherapy

---

Overall period defined as after randomization to the end of follow-up; post-procedural period as >7 days after randomization to the end of follow-up; destination therapy period as beyond 180 days post-randomization, when patients assigned to LAA closure were eligible to receive aspirin alone.
LAAC in Patients with Absolute OAC Contraindication

- ASAP Study (Multicenter observational; n=150)
- Warfarin ineligible (hemorrhagic/bleeding tendencies in 93%); CHADS2VASC 4.4 ±1.7

ASAP –TOO RCT prematurely terminated due to poor enrollment

<table>
<thead>
<tr>
<th>Event</th>
<th>Events/Patient-Years*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy</td>
<td>8/175.0 (4.6%)</td>
</tr>
<tr>
<td>Death, all cause</td>
<td>9/180.0 (5.0%)</td>
</tr>
<tr>
<td>All stroke</td>
<td>4/176.0 (2.3%)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>3/176.9 (1.7%)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>1/179.1 (0.6%)</td>
</tr>
</tbody>
</table>

Cost-Effectiveness

**Central Illustration** Warfarin Versus NOACs Versus LAAC: Cumulative Cost and Time to Cost-Effectiveness Following Treatment Initiation.

<table>
<thead>
<tr>
<th></th>
<th>Time to Clinical Effectiveness (Incremental QALYs)</th>
<th>Time to Cost-Effectiveness (Cost per QALY)</th>
<th>Time to Dominance (More Effective, Less Costly)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAAC vs. warfarin</td>
<td>Year 3 (0.015)</td>
<td>Year 7 ($42,994/QALY)</td>
<td>Year 10</td>
</tr>
<tr>
<td>NOACs vs. warfarin</td>
<td>Year 1 (0.008)</td>
<td>Year 16 ($48,446/QALY)</td>
<td>N/A</td>
</tr>
<tr>
<td>LAAC vs. NOACs</td>
<td>Year 5 (0.007)</td>
<td>Year 5 (Dominant)</td>
<td>Year 5</td>
</tr>
</tbody>
</table>

Asmarats L et al. Cardiac interventions today
May/June 2018 Vol. 12, No. 3
1. Useful for shallow LAA with wide ostium
2. Amulet IDE trial (ClinicalTrials.gov #: NCT02879448)
**AMULET IDE Trial**

- The Amulet occluder was non-inferior for safety and effectiveness of stroke prevention for NVAF compared with the Watchman device, and superior for LAA occlusion (↓ leaks).

- Procedure-related complications were higher with the Amulet device (pericardial effusions and device embolization) and decreased with operator experience.
Conclusions

- AF in increasing in incidence and prevalence
- Substantially increases risk of stroke and thromboembolism (accounts for ~20% for all strokes)
- Highly effective therapies are available to prevent or reduce the risk for stroke in patients with AF
- NOACs are preferred over warfarin for stroke prevention in non-valvular AF
- Compared to warfarin, target specific oral anticoagulants are: a) at least as good at preventing stroke, b) substantially reduce risk of intracranial hemorrhage, and c) may be associated with improved survival
- Many issues need to be considered: Bleeding risk, renal disease, drug interactions, cost, compliance, patient preferences etc.
Conclusions

- A significant proportion of NVAF patients who need OAC are either not on it or cannot take it long-term
- LAA is primary source for NVAF-related thromboembolism
- Percutaneous LAAC is an established alternative to anticoagulation in patients with NVAF at high risk for bleeding or having contraindications to OAC
- WATCHMAN™ and Amulet ™: FDA-approved percutaneous LAAC devices in the US
- Indication: Moderate to high risk of stroke with appropriate rationale to seek alternative to long-term anticoagulation
- Randomized trials have proved efficacy and safety of Watchman compared to warfarin → Equivalent for total stroke; superior for hemorrhagic stroke and cardiovascular mortality. Amulet equivalent to watchman for efficacy & safety
Thank you!

Contact Info:
Email: rakesh.gopinathannair@hcahealthcare.com
Twitter: @drrakeshg1
Cell: 301-641-6062
www.kcheartrhythm.com
Supplementary Slides
1. Advantageous in patients with absolute contraindication to OAC
2. Electrical isolation of LAA may provide arrhythmic benefit
AMAZE trial: Evaluating the efficacy of LAA ligation along with pulmonary vein isolation for long-standing persistent AF
<table>
<thead>
<tr>
<th>Device</th>
<th>Advantages</th>
<th>Limitations</th>
<th>Current status</th>
<th>Future</th>
</tr>
</thead>
<tbody>
<tr>
<td>WATCHMAN</td>
<td>- Most data</td>
<td>- Unsuitable for shallow, wide appendage</td>
<td>FDA approved</td>
<td>- Trial comparing against NOACs (OCCLUSION-AF)</td>
</tr>
<tr>
<td></td>
<td>- 2 Randomized studies and registry data</td>
<td>- Need for OAC or DAPT post-op</td>
<td>CE Mark</td>
<td>- Management of leaks and DRT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Use with DAPT only</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(In absolute OAC CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Post-AF ablation (OPTION)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Alternative to OAC as first line (CHAMPION-AF)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Post-TAVR (WATCH-TAVR)</td>
</tr>
<tr>
<td>AMULET</td>
<td>- Shallow, wide appendages</td>
<td>- DAPT post-op</td>
<td>CE Mark FDA Approved</td>
<td>- AMULET-IDE (LBCT at ESC2021)</td>
</tr>
<tr>
<td></td>
<td>- Lobe &amp; Disc design can account for ostial variation</td>
<td></td>
<td></td>
<td>CATALYST (Alternative to OAC as first line )</td>
</tr>
<tr>
<td>LARIAT</td>
<td>- Can be used in patients with absolute CI to OAC</td>
<td></td>
<td>FDA 510 K FDA safety communication</td>
<td>- Randomized data for use in persistent AF ablation (AMAZE)</td>
</tr>
<tr>
<td></td>
<td>- LAA Electrical isolation</td>
<td>- Technically challenging procedure</td>
<td></td>
<td>- Improving procedural safety</td>
</tr>
<tr>
<td></td>
<td>- Limited by LAA anatomy &amp; prior surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Anti-thrombotic therapy after left atrial appendage occlusion

<table>
<thead>
<tr>
<th>Device/patient</th>
<th>Aspirin</th>
<th>OAC</th>
<th>Clopidogrel</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watchman/low bleeding</td>
<td>75 - 325 mg/day</td>
<td>Start warfarin after procedure (target INR 2 - 3) until 45 days or continue until adequate LAA sealing is confirmed&lt;sup&gt;a&lt;/sup&gt; by TOE. NOAC is a possible alternative</td>
<td>Start 75 mg/day when OAC stopped, continue until 6 months after the procedure</td>
<td>Some centres do not withhold OAC at the time of procedure (no data to support/deny this approach)</td>
</tr>
<tr>
<td>Watchman/high bleeding</td>
<td>75 - 325 mg/day</td>
<td>None</td>
<td>75 mg/day for 1 - 6 months while ensuring adequate LAA sealing&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Clopidogrel often given for shorter time in very high-risk situations</td>
</tr>
<tr>
<td>ACP/Amulet</td>
<td>75 - 325 mg/day</td>
<td>None</td>
<td>75 mg/day for 1 - 6 months while ensuring adequate LAA sealing&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Clopidogrel may replace long-term aspirin if better tolerated</td>
</tr>
</tbody>
</table>

<sup>a</sup> With an INR < 2.0, if procedure is performed within 3 months of implantation.
PROTECT AF

- **707** NVAF patients (n=463 to WATCHMAN and n=244 to Warfarin)
- **Efficacy** – Primary composite endpoint of stroke, cardiovascular death, and systemic embolism
- **88%** had successful implant; 86% successfully discontinued warfarin at 45 days
- **At 1065 Pt-years follow-up:**
  - **Efficacy** - 3% vs. 4.3% for warfarin; RR 0.62, 95% CI 0.35-1.25
  - **Safety** - 7.4% vs. 4.4% for warfarin; RR 1.69; 95% ci 1.01-3.19
- Pericardial Effusion **4.8%;** Major bleeding **3.5%**
- Met non-inferiority for primary efficacy endpoint
PREVAIL

- 407 patients in a 2:1 randomization to Watchman vs. Warfarin
- 25% of patients treated by new operators
- Implant Success: 95% had successful implant
- Watchman did not meet primary efficacy endpoint (0.063 vs 0.064%; RR1.07; 95% CrI: 0.57-1.89)
- 2.2% early safety events (non-inferior to warfarin)

**TABLE 3** Coprimary Efficacy Endpoint Observed Events by Type: PREVAIL Subjects Only (Intention-to-Treat)*

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Device Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Events</td>
<td>% of Events</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>5</td>
<td>1.9</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Death (cardiovascular/unexplained)</td>
<td>7</td>
<td>2.6</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>1</td>
<td>0.4</td>
</tr>
</tbody>
</table>

ARISTOTLE
ROCKET AF
RE-LY
PREVAIL

Rate Per Patient-years
Watchman – Contraindications

- LAA thrombus
- Unfavorable LAA anatomy
  - Shallow, wide LAA
  - LA ostial size > 31 mm
- Absolute contraindication for OAC: Cannot take warfarin or ASA/Clopidogrel
Novel Oral Anticoagulants

**Better than Warfarin:**
1. Dabigatran 150 mg twice daily
2. Rivaroxaban 20 mg PO daily
3. Apixaban 5 mg PO twice daily

**Less major bleeding than Warfarin:**
1. Dabigatran 110 mg twice daily
2. Apixaban 5 mg PO twice daily

**Use in ESRD/Dialysis:**
Apixaban 5 mg PO twice daily

**Survival Benefit:**
Apixaban 5 mg PO twice daily

**Dialyzable:**
Dabigatran
AF is Responsible for 15-20% of all Strokes

- Non-valvular AFib is responsible for a 5-fold increase in the risk of ischemic stroke

Incidence of AFib in the General Population – Gender Differences

Olmsted County study

Observational period: 20 years

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>0.49 %</td>
</tr>
<tr>
<td>Women</td>
<td>0.28 %</td>
</tr>
</tbody>
</table>

Ratio men to women = 1.86

The lifetime risk of AF in men and women over 40 years of age: 1 in 4

Left Atrial Appendage closure for Stroke Prevention
Left Atrial Appendage closure for Stroke Prevention
Watchman FLX and Amulet
WATCHMAN™ Procedure

- One-time implant
- Performed in a cardiac EP Lab
- Performed by a heart team
  - EP or IC with transseptal and structural experience, 1 expert echocardiographer, general anesthesia, surgical back up, WATCHMAN Clinical Specialist
- Transfemoral Access: 14 F WATCHMAN Sheath advanced to the LAA via the femoral vein
- 1 hour procedure  1 day hospital stay
Watchman Clinical Studies

Over 2,000 patients with 4,800 patient years follow-up

- **Pilot**: Early feasibility with > 6 years of follow up
- **PROTECT-AF**: Superior to warfarin for primary efficacy, CV death, and all-cause mortality at 4 years
- **CAP Registry**: Significantly improved safety results
- **ASAP**: Expected rate of stroke reduced by 77% in patients contraindicated to warfarin
- **PREVAIL**: Improved success and procedural safety confirmed with new and experienced operators
- **CAP2**: Currently enrolling up to 1500 patients at ~60 sites
# Procedural Success and Risks: Commercial Experience

<table>
<thead>
<tr>
<th>Procedural Parameters</th>
<th>Aggregate Clinical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Procedures</td>
<td>6,720</td>
</tr>
<tr>
<td>Implantation Success, %</td>
<td>94.9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complication Rates</th>
<th>Aggregate Clinical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periodical Tamponade</td>
<td>1.28%</td>
</tr>
<tr>
<td>Procedure-Related Stroke</td>
<td>0.18%</td>
</tr>
<tr>
<td>Device Embolization</td>
<td>0.25%</td>
</tr>
<tr>
<td>Procedure-Related Death</td>
<td>0.06%</td>
</tr>
</tbody>
</table>

Reddy VY, Gibson DN, et al. JACC. 2016
Patient-Level Meta-analysis of PROTECT AF, PREVAIL, and CAP Registries

2,406 patients with 5,931 patient years of follow up. (Mean follow up 2.69 years)

<table>
<thead>
<tr>
<th>Event</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All stroke or SE</td>
<td>0.79</td>
<td>0.22</td>
</tr>
<tr>
<td>Ischemic stroke or SE</td>
<td>1.02</td>
<td>0.94</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>1.95</td>
<td>0.05</td>
</tr>
<tr>
<td>Ischemic stroke or SE &gt;7 days</td>
<td>0.22</td>
<td>0.004</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>

Hazard Ratio (95% CI)
Cost Effectiveness

- Both NOACs and LAAC with the Watchman device were cost-effective relative to warfarin.
- Only LAAC demonstrated cost savings by year 10 relative to warfarin, and by year 5 relative to NOACs.

LAAC – Market Capture & Growth Opportunities

• At present, LAAC with WATCHMAN captures only 1% of the market in which it is indicated
• Tremendous room to improve patient care in this population
• Several new devices in horizon
• Expansion of indications with more data
A significant proportion of NVAF patients who need OAC are either not on it or cannot take it long-term.

LAA is the primary source for NVAF-related thromboembolism.

Percutaneous LAAC is a promising alternative to anticoagulation in patients with NVAF at high risk for bleeding or having contraindications to OAC.

WATCHMAN: Only FDA-approved percutaneous LAAC device in the U.S. and has the most data.

Indication: Moderate to high risk of stroke with appropriate rationale to seek alternative to long-term anticoagulation.

Randomized trials have proved efficacy and safety of WATCHMANN compared to warfarin → Equivalent for total stroke; superior for hemorrhagic stroke and cardiovascular mortality.

Trials are underway to assess LAAC as first line therapy instead of OAC.