Current Trends in the Management of Atrial Fibrillation: Left Atrial Appendage Occlusion

Benjamin A. D’Souza, MD, FACC, FHRS
Assistant Professor of Clinical Medicine
Penn Presbyterian Medical Center
Cardiac Electrophysiology
Perelman School of Medicine at the University of Pennsylvania

Atrial fibrillation: Scope of the problem

- Higher stroke risk for older patients and those with prior stroke or TIA
- 15-20% of all strokes are Atrial fibrillation (AF)-related
- AF results in greater disability compared to non-AF-related stroke
- High mortality and stroke recurrence rate

AF-related hospitalizations almost tripled in 2000 compared with two decades ago

In 2001 the total annual costs for treatment of AF were estimated at $6.65 billion in the US

As a result of increasing age and improved survival rates in those with coronary artery disease, heart failure, and hypertension, an increase in the prevalence of atrial fibrillation is likely to be exponential and sustained in the foreseeable future.
**Sub-types of AF**

**Paroxysmal**
- Recurrent, ≥ 2 episodes
- Terminates spontaneously within 7 days

**Persistent**
- Episodes lasting > 7 days
- OR
- Episodes that require intervention to terminate (medication or electrical cardioversion)

**Long-Standing Persistent**
- Continuous AF of > 1 year

**Permanent**
- Mutual decision between patient and physician has been made to cease further attempts to restore/ maintain normal sinus rhythm by any means, including catheter ablation and surgery

---

**Progression of AF**

**Typical Progression**
- First episode of AF
- Recurrent AF
- Recurrent Persistent AF
- Permanent AF

- Median 2.5 months
- Median 10 months

20% of patients progress from Paroxysmal to Persistent AF within 1 year of diagnosis

---

**Risk Factors of AF**

- Over 60 Yrs of Age
- Diabetes
- Hypertension
- Prior Myocardial Infarctions
- Coronary Artery Disease
- Congestive Heart Failure
- Chronic Lung Disease
- Sleep Apnea
- Thyroid Disease
- Serious Infections
- Excessive Alcohol Use
- Prior Open Heart Surgery
- Untreated Atrial Flutter
- Structural Heart Disease
- Permanent AF
- Over 30 years

---
Mechanisms of AF

AF ablation

2014 AFib Management Consensus Guidelines

Class 1 
THE STRONGEST RECOMMENDATION

Level A 
THE HIGHEST LEVEL OF EVIDENCE

The 2014 AHA/ACC/HRS Guidelines for Afib Management provide the highest level recommendation (Class 1, Level of Evidence: A) for catheter ablation as treatment for drug-refractory, symptomatic paroxysmal Afib.

AF ablation versus medications

Kaplan-Meier curve of time to recurrence of symptomatic atrial arrhythmia following second line antiarrhythmic drug therapy (ADT)

Shows patients who had catheter ablation have fewer episodes of Afib than patients who take medications.
Evolution of AF ablation technology

- CARTO® System: Mapping of the heart to locate diagnosises of arrhythmias
- FDA Approval for Radio Frequency ablation for Atrial Fibrillation
- Medtronic Inc. introduces Artic Front® Catheter, a cryogenic technology to achieve pulmonary vein isolation
- First device approved in the U.S. to feature direct contact force technology

1st Generation Radio Frequency Ablation by Biosense Webster, Inc.
2nd Generation CryoAblation by Medical, Inc.
3rd Generation Contact Force Ablation by Biosense Webster, Inc.

Success rates with newer AF technology

- Success Rate After One Year
  - Traditional Catheter w/ No Direct Contact Force Technology: 63%
  - THERMOCOOL SMARTTOUCH Catheter: 74%
  - THERMOCOOL® SMARTTOUCH Catheter within stable force range: 88%
**Stroke prevention in AF**

<table>
<thead>
<tr>
<th>CHADS2/VASc STROKE RISK CRITERIA</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Congestive Heart Failure</td>
<td>1</td>
</tr>
<tr>
<td>H Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A Age ≥ 75</td>
<td>2</td>
</tr>
<tr>
<td>D Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S Stroke/TIA/Embolism</td>
<td>2</td>
</tr>
<tr>
<td>V Vascular Disease</td>
<td>1</td>
</tr>
<tr>
<td>A Age 65-74 Years</td>
<td>1</td>
</tr>
<tr>
<td>S Sex (female)</td>
<td>1</td>
</tr>
</tbody>
</table>

**Oral anticoagulation in AF**

**Warfarin**
- Bleeding risk
- Daily regimen
- High non-adherence rates
- Regular INR monitoring
- Food and drug interaction issues
- Complicates surgical procedures

**Novel Oral Anticoagulants**
- Bleeding risk
- Daily regimen
- High non-adherence rates
- Complicates surgical procedures
- Lack of reversal agents
- High cost

**CHADS2 Score**

Anticoagulation Use Declines with Increased Stroke Risk

<table>
<thead>
<tr>
<th>CHADS2 Score</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulation Use</td>
<td>100%</td>
<td>90%</td>
<td>80%</td>
<td>70%</td>
<td>60%</td>
<td>50%</td>
</tr>
</tbody>
</table>

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

- Score 1: Annual stroke risk 1%, oral anticoagulants or aspirin may be considered
- Score 2: Annual stroke risk 2%-15%, oral anticoagulants are recommended

<table>
<thead>
<tr>
<th>CHADS2/VASc Score</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No anticoagulant</td>
</tr>
<tr>
<td>1</td>
<td>Aspirin 100-325 mg daily or warfarin (INR 2-3)</td>
</tr>
<tr>
<td>22</td>
<td>Oral anticoagulants are recommended (warfarin [INR 2-3]), dabigatran, rivaroxaban or apixaban</td>
</tr>
</tbody>
</table>
AF and bleeding risk

**HAS-BLED score**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
<th>HAS-BLED score</th>
<th>Bleeds per 100 participant-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>H: Hypertension</td>
<td>1</td>
<td>0</td>
<td>1.13</td>
</tr>
<tr>
<td>A: Abnormal renal or liver function (1 point each)</td>
<td>1 or 2</td>
<td>1</td>
<td>3.02</td>
</tr>
<tr>
<td>S: Stroke</td>
<td>1</td>
<td>2</td>
<td>1.88</td>
</tr>
<tr>
<td>B: Bleeding</td>
<td>1</td>
<td>3</td>
<td>3.74</td>
</tr>
<tr>
<td>L: Labile Hb</td>
<td>1</td>
<td>4</td>
<td>8.70</td>
</tr>
<tr>
<td>E: Elderly (&gt;65 years)</td>
<td>1</td>
<td>5</td>
<td>12.5</td>
</tr>
<tr>
<td>D: Drug or alcohol (1 point each)</td>
<td>1 or 2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: HAS-BLED has been validated for warfarin, but not for the new anticoagulants.

**Use of NOAC at 2 years**

![Graph showing the percentage of patients on NOAC and VKA over years since start of treatment.]

**AF and Stroke risk**

- AF is the most common cardiac arrhythmia
- AF increases risk of stroke
- Blood clots form in the left atrial appendage
- 5x greater risk of stroke with AF
- > 90% of stroke-causing clots that come from the left atrium in non-valvular AF are formed in the LAA
- < 90% of clots originate from the left atrial appendage
- 90% treated with Warfarin
- Contraindicated for intolerance
- ~45% of patients eligible for treatment are untreated (tolerance/adherence)

> 33M people with AF Worldwide

~45% of patients eligible for treatment are untreated (tolerance/adherence)
AF and Stroke

- Stasis-related LA thrombus is a predictor of TIA and ischemic stroke
- In non-valvular AF, >90% of stroke-causing clots that come from the left atrium are formed in the LAA

Left atrial appendage closure

- For atrial fibrillation patients not undergoing cardiac surgery who should be treated with long-term oral anticoagulation to prevent embolization but for whom such therapy poses an unacceptably high risk of bleeding
  - Thrombocytopenia or known coagulation defect associated with bleeding
  - Recurrent gastrointestinal bleeding
  - Prior severe bleeding, including intracranial hemorrhage

LAA anatomy

- Wind Sock: An anatomy in which one dominant lobe of sufficient length is the primary structure
- Chicken Wing: An anatomy whose main feature is a sharp bend in the dominant lobe of the LAA at some distance from the LAA ostium
- Broccoli: An anatomy in which the main feature is an LAA that has limited overall length with more complex internal characteristics
Transseptal puncture

Delivery system

TEE and anatomy of LAA

*Device should be at or just distal to the LAA ostium*
Endothelization of device

Canine Model – 30 Day

Canine Model – 45 Day

Human Pathology – 9 Months Post-implant
(Non-device related death)

LAA closure video

Time line for LAA closure
Clinical trials for LAA closure

<table>
<thead>
<tr>
<th>Key Trials</th>
<th>N</th>
<th>Highlights</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTECT AF</td>
<td>707</td>
<td>Prospective, randomized 2:1, non-inferiority trial of LAA closure vs. warfarin.</td>
</tr>
<tr>
<td>CAP (2008-2010)</td>
<td>566</td>
<td>Prospective registry allowing continued access to the WATCHMAN Device and gain further information prior to PMA approval.</td>
</tr>
<tr>
<td>PREVAIL (2010-2012)</td>
<td>407</td>
<td>Prospective, randomized 2:1, non-inferiority trial to collect additional information on the WATCHMAN Device.</td>
</tr>
<tr>
<td>CAP2 (2012-2014)</td>
<td>579</td>
<td>Prospective registry allowing continued access to the WATCHMAN Device prior to PMA approval.</td>
</tr>
<tr>
<td>EVOLUTION (2013-2015)*</td>
<td>1025</td>
<td>Prospective registry allowing all patients receiving a WATCHMAN Device at participating centers in Europe, Middle East and Russia</td>
</tr>
</tbody>
</table>

Total patients: >3,000 ~9,000 Patient-Years of Follow-up

Clinical Trial data

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Study Design</th>
<th>Primary Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTECT AF</td>
<td>Demonstrate safety and effectiveness of the WATCHMAN implant compared to long-term warfarin</td>
<td>1. Effectiveness: Stroke, systemic embolism and cardiovascular/unexplained death 2. Safety: Life-threatening events, which include device embolization requiring retrieval and bleeding events</td>
</tr>
<tr>
<td>CAP Registry</td>
<td>Non-randomized 2:1 Randomized, non-inferiority</td>
<td>1. Effectiveness: Stroke, systemic embolism and cardiovascular/unexplained death 2. Effectiveness: Ischemic stroke or systemic embolism occurring after 7 days post-randomization or WATCHMAN implant procedure</td>
</tr>
<tr>
<td>PREVAIL</td>
<td>Demonstrate safety and effectiveness of the WATCHMAN implant compared to long-term warfarin</td>
<td>3. Safety: Death, ischemic stroke, systemic embolism and procedure/device-related complications within 7 days of implantation procedure</td>
</tr>
<tr>
<td>CAP2 Registry</td>
<td>Non-randomized 2:1 Randomized, non-inferiority</td>
<td>1. Effectiveness: Stroke, systemic embolism and cardiovascular/unexplained death 2. Effectiveness: Ischemic stroke or systemic embolism occurring after 7 days post-randomization or WATCHMAN implant procedure</td>
</tr>
</tbody>
</table>

CHADS scores in trials

- Anticoagulation Eligible
- CHADS2-VASc Score ≥ 2
- High Risk
- PROTECT AF: 53%
- CAP: 96%
- PREVAIL: 100%
- CAP2: 100%

Patients (%)
HAS BLED scores in the trials

Implant success rates

| Implant Success Rates in Clinical Studies and Initial US Commercial Experience |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                 | 90.9%             | 94.4%           | 95.1%            | 94.8%           | 95.6%           |

Complication rates

| Procedural Complication Rates in Clinical Studies and Initial US Commercial Experience |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                 |                  |                 |                 |                 |                 |
| Number of Patients              | N=466            | N=560           | N=500           | N=378           | N=1322          |
| Partial Thrombosis             | 20 (4.3%)         | 8 (1.4%)         | 5 (1.0%)         | 11 (1.9%)        | 36 (1.02%)       |
| Percutaneous Effusion (no ablation) | 4 (0.9%)        | 5 (0.9%)         | 0               | 3 (0.3%)         | 11 (0.33%)       |
| Procedure/Related Stroke       | 5 (1.1%)          | 0               | 1 (0.2%)         | 2 (0.3%)         | 3 (0.09%)        |
| Device Extravasation           | 3 (0.6%)          | 1 (0.2%)         | 2 (0.4%)         | 0               | 0 (0.01%)        |
| Procedure/Related Deaths       | 1 (0.2%)          | 0               | 0               | 0               | 2 (0.06%)        |
Registry data for LAA closure devices

- JAAC patient-level meta-analysis of 5 year data from two randomized clinical trials: PROTECT AF and PREVAIL.
- 5-Year Outcomes After Left Atrial Appendage Closure: From the PREVAIL and PROTECT AF Trials
  - 55% reduction in disabling and fatal stroke
  - 80% reduction in hemorrhagic stroke
  - 52% reduction in non-procedure related major bleeding
  - 27% reduction in all-cause mortality
  - 41% reduction in cardiovascular/unexplained death

New ACC/AHA guidelines

4.4. Nonpharmacological Stroke Prevention
4.4.1. Percutaneous Approaches to Oclude the LAA

| Recommendation for Percutaneous Approaches to Occlude the LAA |
|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| COR | LOE | Statement 4 |
| tns | s-net | 1. Percutaneous LAA occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation (4.4.1.5-4.4.1.5-4.4.1.5). New: Clinical trial data and FDA approval of the Watchman device necessitate this recommendation. |

Prominent cardiologist calls for a halt to Watchman implants

A prominent cardiologist is calling for a stop to left atrial appendage closure procedures using Boston Scientific’s (BOSTON: BSC) Watchman device, claiming the procedures, which seek to reduce stroke in patients with nonvalvular atrial fibrillation, result in the opposite.

Dr. John Mundare argues that randomized, controlled trials of the Watchman, designed for LAA closure, showed the device failed to reduce ischemic stroke, despite being designed for that purpose.

"Yet we look away, as we tell advocates distinct with complicated statistics," Dr. Mundare writes in an op-ed for the Boston Globe. "You've avoided calling for a halt to LAA closure for as long as possible, but I suspect events have changed my mind."

Mundare said that the 1st event to show non-apparent LAA comes from the "testing process" of colleagues to organize a left atrial appendage closure program at his hospital, due to other hospitals in the area developing similar programs.