Update on Atrial Fibrillation Clinical Trials

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Ohio ACC-Spring Summit
March 28th, 2018
Disclosures

• Honorarium
  - Bristol-Myers Squibb (Apixaban)
  - Janssen (Rivaroxaban)
Objectives

• A.Fib and Heart Failure clinical trials (CASTLE AF, PABA CHF)
• Watchman device approval (alternative to anticoagulation, PROTECT AF and PREVAIL)
• Persistent A.Fib ablation trials (Converge and AMAZE trials)
<table>
<thead>
<tr>
<th>Year</th>
<th>Projected number of persons with AF (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>5.1</td>
</tr>
<tr>
<td>2005</td>
<td>5.9</td>
</tr>
<tr>
<td>2010</td>
<td>6.7</td>
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<tr>
<td>2015</td>
<td>6.1</td>
</tr>
<tr>
<td>2020</td>
<td>6.8</td>
</tr>
<tr>
<td>2025</td>
<td>7.5</td>
</tr>
<tr>
<td>2030</td>
<td>8.4</td>
</tr>
<tr>
<td>2035</td>
<td>9.4</td>
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<tr>
<td>2040</td>
<td>10.3</td>
</tr>
<tr>
<td>2045</td>
<td>11.1</td>
</tr>
<tr>
<td>2050</td>
<td>12.1</td>
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</tbody>
</table>

Metabolic syndrome-Conundrum
Classification

• **Paroxysmal AF**
  – Self-terminating or with intervention < 7 days

• **Persistent AF**
  – Sustained >7 days

• **Long-standing persistent AF**
  – Continuous ≥1 year

• **Permanent AF**
  – Cease further attempts to restore and/or maintain sinus rhythm by patient (and physician)

• **NonValvular AF**
  • absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair
The Consequences of AF

**Thromboembolism**
- Stroke: 4.5× ↑risk
- Microemboli: ↓cognitive function

**Impaired hemodynamics**
- Loss of atrial kick
- Irregular ventricular contractions
- Heart failure
- Tachycardia-induced cardiomyopathy

**Hospitalizations**
- Most common arrhythmia requiring hospitalization
- 2-3× ↑risk for hospitalization

**Quality of life**
- ↓Palpitations, dyspnea, fatigue, ↓exercise tolerance

**Health care burden**
- Estimated US cost burden: 15.7 billion

Strategies for Rhythm Control in Patients with Paroxysmal and persistent AF
A.fib ablation Indications

- Failed / intolerant to AA class Ic / III drug (s)
- Symptomatic paroxysmal A.fib (class IA, “useful”)
- Symptomatic persistent A.fib (class IIA, “reasonable”)
- Symptomatic longstanding persistent (>1 year) (class IIB, may be)
A.fib ablation Indications

- Symptomatic paroxysmal / persistent AF, cannot tolerate or failed AA drug(s)
- Reasonable initial strategy in some patients
- Need to assess procedural risks and outcomes
- Does not obviate the need for anticoagulation
CASTLE-AF trial
Catheter Ablation for Atrial Fibrillation with Heart Failure

Nassir F. Marrouche, M.D., Johannes Brachmann, M.D., Dietrich Andresen, M.D., Jürgen Siebels, M.D., Lucas Boersma, M.D., Luc Jordaens, M.D., Béla Merkely, M.D., Evgeny Pokushalov, M.D., Prashanthan Sanders, M.D., Jochen Proff, B.S., Heribert Schunkert, M.D., Hildegard Christ, M.D., Jürgen Vogt, M.D., and Dietmar Bänsch, M.D., for the CASTLE-AF Investigators*
CASTLE AF

- Multicenter, open-label, randomized, controlled trial
- Catheter ablation (N=179)
- Medical therapy (N=184)
- Median follow-up: 37.8 months
- **Primary Outcome**: Death or hospitalization for heart failure
CASTLE AF

- CHF: NYHA I 11%, NYHA II 58%, NYHA III 29%, NYHA IV 2%
- Ischemic 40%, non-ischemic 60%, LVEF 32.5%
- AF: paroxysmal 30%, persistent 70%, long-standing persistent 28%
- LA diameter 48mm
- Devices: CRT-D 27%, ICD 73%
- Medications: History of amiodarone use 57%
Primary Endpoint

A Death or Hospitalization for Worsening Heart Failure

- Probability of Survival Free of Hospital Admission
- Hazard ratio: 0.62 (95% CI: 0.43–0.87)
- P = 0.007 by Cox regression
- P = 0.006 by log-rank test

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Ablation</th>
<th>Medical therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 months</td>
<td>179</td>
<td>184</td>
</tr>
<tr>
<td>12 months</td>
<td>141</td>
<td>145</td>
</tr>
<tr>
<td>24 months</td>
<td>114</td>
<td>111</td>
</tr>
<tr>
<td>36 months</td>
<td>76</td>
<td>70</td>
</tr>
<tr>
<td>48 months</td>
<td>58</td>
<td>48</td>
</tr>
<tr>
<td>60 months</td>
<td>22</td>
<td>12</td>
</tr>
</tbody>
</table>

Ablation vs. Medical therapy
Primary Endpoint

B Death from Any Cause

Hazard ratio, 0.53 (95% CI, 0.32–0.86)
P=0.01 by Cox regression
P=0.009 by log-rank test

No. at Risk
Ablation 179 154 130 94 71 27
Medical therapy 184 168 138 97 63 19
Primary Endpoint

C Hospitalization for Worsening Heart Failure

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months of Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Ablation</td>
<td>179</td>
</tr>
<tr>
<td>Medical therapy</td>
<td>184</td>
</tr>
</tbody>
</table>

- Hazard ratio, 0.56 (95% CI, 0.37–0.83)
- P=0.004 by Cox regression
- P=0.004 by log-rank test
CASTLE AF

- **Primary Outcomes**
  - Death or hospitalization for heart failure
    - 51 (28.5%) vs. 82 (44.6%); HR 0.62 (95% CI 0.43-0.87); p = 0.007

- **Secondary Outcomes**
  - Death
    - 24 (13.4%) vs. 46 (25.0%); HR 0.53 (95% CI 0.32-0.86) p = 0.01

- Heart failure hospitalization
  - 37 (20.7%) vs. 66 (35.9%); HR 0.56 (95% CI 0.37-0.83); p = 0.004

- Cardiovascular death
  - 20 (11.2%) vs. 41 (22.3%); HR 0.49 (95% CI 0.29-0.84); p = 0.009
PABA-CHF: Study Design

Prospective, randomized, controlled trial

N = 81 with symptomatic, drug-resistant AF; LVEF ≤40%; NYHA Class II or III HF

Pulmonary-vein isolation (n = 41)  Atrioventricular-node ablation with biventricular pacing (n = 40)

Primary outcome: Composite of ejection fraction, 6-minute walk distance, and Minnesota Living with Heart Failure score at 6 months

Pulmonary Vein Antrum Isolation versus AV Node Ablation with Bi-Ventricular Pacing
PABA-CHF: Composite Primary Endpoints at 6 Months

Randomized trial of NYHA Class II or III CHF & EF <40% to PVI or AVN + BiV

- **6-Minute walk**
  - Distance (m)
  - PVI vs. AVN + BiV

- **Ejection fraction**
  - %
  - PVI vs. AVN + BiV

- **MLHF score**
  - Score
  - P < 0.001

20*↓ Score = ↑QoL

WATCHMAN device data
Adherence to Anticoagulation Remains a Challenge

~30% of NOAC patients stop taking any drug at 2 years

**WATCHMAN™ LAAC Closure Device**

**Nitinol Frame**
- Conforms to LAA anatomy to reduce embolization risk
- 10 active fixation anchors - designed to engage tissue for stability

**Proximal Face**
- Minimizes surface area facing the left atrium to reduce post-implant thrombus formation
- 160 micron membrane PET cap designed to block emboli and promote healing
Optimal Device Position

Fixation anchors engage LAA wall
WATCHMAN™ - Most Studied LAAC Device
Only one proven with long-term data from randomized trials and multi-center registries

<table>
<thead>
<tr>
<th>Key Trials</th>
<th>N</th>
<th>Highlights</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTECT AF¹ (2005-2008)</td>
<td>707</td>
<td>Prospective, randomized 2:1, non-inferiority trial of LAA closure vs. warfarin.</td>
</tr>
<tr>
<td>CAP² (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>PREVAIL³ (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>
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<tr>
<td>EWOLUTION (2013-2015)⁴</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>
<tr>
<td>Total patients</td>
<td>&gt;3,000</td>
<td>~9,000 Patient-Years of Follow-up</td>
</tr>
</tbody>
</table>

### Patient Level Meta-Analysis

**PROTECT AF, PREVAIL 5 Years**

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
</tr>
<tr>
<td>All stroke or SE</td>
<td>0.96 (0.9)</td>
</tr>
<tr>
<td>Ischemic stroke or SE</td>
<td>1.7 (0.08)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.2 (0.0022)</td>
</tr>
<tr>
<td>Ischemic stroke or SE &gt;7 days</td>
<td>1.4 (0.3)</td>
</tr>
<tr>
<td>Disabling/Fatal Stroke (MRS change of ≥2)</td>
<td>0.45 (0.03)</td>
</tr>
<tr>
<td><strong>Non-Disabling Stroke</strong></td>
<td></td>
</tr>
<tr>
<td>Non-Disabling Stroke</td>
<td>1.38 (0.35)</td>
</tr>
<tr>
<td>CV/unexplained death</td>
<td>0.59 (0.03)</td>
</tr>
<tr>
<td><strong>All-cause death</strong></td>
<td></td>
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<td>0.73 (0.04)</td>
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<tr>
<td>Major bleed, all</td>
<td>0.91 (0.6)</td>
</tr>
<tr>
<td>Major bleeding, non procedure-related</td>
<td>0.48 (0.0003)</td>
</tr>
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</table>

Source: Reddy VY, Doshi SK, Car S, et al. 5-Year Outcomes After Left Atrial Appendage Closure: From the PREVAIL and PROTECT AF Trials. J. Am Coll Cardiol. 2017; In Press.
Patient Level Meta-Analysis
PROTECT AF, PREVAIL 5 Years

<table>
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<tr>
<th>Event Type</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
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<tr>
<td><strong>Efficacy</strong></td>
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<td></td>
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<tr>
<td>All stroke or SE</td>
<td>0.96 (0.9, 0.9)</td>
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WATCHMAN Enables Patients to Discontinue Long-term OAC

92% of patients were able to discontinue warfarin after 45 days, with 99% able to discontinue after 1 year. 

<table>
<thead>
<tr>
<th>Study*</th>
<th>45-day</th>
<th>12-month</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTECT AF¹</td>
<td>87%</td>
<td>&gt;93%</td>
</tr>
<tr>
<td>CAP²</td>
<td>96%</td>
<td>&gt;96%</td>
</tr>
<tr>
<td>PREVAIL³</td>
<td>92%</td>
<td>&gt;99%</td>
</tr>
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</table>

**WATCHMAN is the most studied LAAC Device with Long-term Clinical Data**

<table>
<thead>
<tr>
<th></th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Safety</strong></td>
<td>WATCHMAN procedure is <strong>safe</strong></td>
</tr>
<tr>
<td></td>
<td>95% implant success; ~4% complication rates(^1)</td>
</tr>
<tr>
<td><strong>Primary Efficacy</strong></td>
<td>WATCHMAN <strong>comparable</strong> to warfarin</td>
</tr>
<tr>
<td></td>
<td>18% reduction in events (p=0.27)(^2)</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>WATCHMAN <strong>comparable</strong> to warfarin</td>
</tr>
<tr>
<td></td>
<td>55% reduction in disabling/fatal stroke (p=0.03)*, largely driven by</td>
</tr>
<tr>
<td></td>
<td>80% reduction in hemorrhagic stroke (p=0.003)(^2)</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>WATCHMAN <strong>statistically significant</strong> to warfarin</td>
</tr>
<tr>
<td></td>
<td>27% reduction in all-cause mortality (p=0.04)(^2)</td>
</tr>
<tr>
<td></td>
<td>41% reduction in CV/unexplained mortality (p=0.03)(^2)</td>
</tr>
<tr>
<td><strong>Major Bleeding</strong></td>
<td>WATCHMAN <strong>statistically significant</strong> to warfarin post-procedure</td>
</tr>
<tr>
<td></td>
<td>72% reduction after 6-months (p=0.001)(^3)</td>
</tr>
<tr>
<td><strong>Warfarin Cessation</strong></td>
<td>WATCHMAN allows the <strong>majority</strong> of patients to <strong>discontinue</strong> warfarin</td>
</tr>
<tr>
<td></td>
<td>92% of patients discontinue after 45-days; 99% of patients discontinue after 1 year(^4)</td>
</tr>
</tbody>
</table>

Very long-term outcome after initially successful catheter ablation of atrial fibrillation

*Heart Rhythm*
Volume 11, Issue 5, Pages 771-776 (May 2014)
445 patients, 66 +/- 34 months f/up

16% at 5 years, 30% at 10 years
VLR: Very late recurrence

Heart Rhythm 2014 11, 771-776 DOI: (10.1016/j.hrthm.2014.02.003)
445 patients, 66 +/- 34 months f/up
AtriCure Randomized Pivotal Study
VAL-1200
Control Arm
Standalone Endocardial Ablation Procedure
Study Procedure
Convergent Procedure

- Treatment Arm
  Convergent Procedure
Study Design

❖ Randomized 2:1 (convergent procedure versus standard ablation) multi-center, prospective, open label pivotal study

❖ 27 US Sites, 3 OUS sites

❖ 153 patients

❖ Initial Post procedure follow-up: 12 months
  ❖ 3 month Blanking Period

❖ Long-term follow-up 18 months with annual phone follow-up for 5 years
Study Primary Efficacy Endpoint

Primary Efficacy Endpoint

Recurrent atrial fibrillation / flutter
Study Safety Endpoints

Primary Safety Endpoint
30 day procedure related adverse events
Left Atrial Appendage Ligation with the LARIAT® Suture Delivery System as Adjunctive Therapy to Pulmonary Vein Isolation for Persistent or Longstanding Persistent Atrial Fibrillation
LARIAT Procedure
## Protocol Overview

<table>
<thead>
<tr>
<th>Principal Purpose</th>
<th>Evaluate freedom from AF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Population</strong></td>
<td>Persistent or longstanding persistent AF (&lt; 3 yrs continuous AF) planned for catheter ablation</td>
</tr>
<tr>
<td><strong>Investigational Tx</strong></td>
<td>LARIAT LAA ligation followed by PVI catheter ablation (4 weeks)</td>
</tr>
<tr>
<td><strong>Control Tx</strong></td>
<td>PVI catheter ablation without LAA ligation</td>
</tr>
</tbody>
</table>
**ASAP-TOO (NCT02928497): Overview**

<table>
<thead>
<tr>
<th>Study Objective</th>
<th>Evaluate LAA Closure with WATCHMAN in NVAF patients deemed not suitable for oral anti-coagulation therapy</th>
</tr>
</thead>
</table>
| Study Design    | Prospective, multi-center  
|                 | Randomized 2:1 (Watchman vs Control)  
|                 | Considering Group Sequential Design |
| Primary Endpoint| Effectiveness Endpoint  
|                 | Time to first occurrence of ischemic stroke or systemic embolism |
|                 | Safety Endpoint  
|                 | 7-day rate of all-cause death, ischemic stroke, systemic embolism, or device- or procedure- related events requiring open cardiac surgery or major endovascular intervention |
| Patient Population | 888 |
| Number of Sites | 100 global sites |
| Follow-up* |  
|     | 45 Day with TEE  
|     | 6,18 month phone visit  
|     | 12 month with TEE  
|     | Bi-annually for years 2-5 |

*Brain imaging required at baseline if prior stroke or TIA*

Holmes et al. AHJ 2017; in press
Oral Anticoagulation is Standard of Care, but Not Ideal for All

NCDR Pinnacle Registry

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

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 or 2x/daily regimen
- High non-adherence rates
- Complicates surgical procedures
- Limited reversal agents
- High cost

1. Hsu, J et al. JAMA Cardiol. Published online March 16, 2016. doi:10.1001/jamacardio.2015.0374
Diagnosis

Symptoms / Incidental finding (exam/ECG)

Clinical examination + ECG

Profiling

Non-invasive

Genetic

Biomarkers

Imaging

Invasive

Electro-anatomical mapping

Classification

Genetic

Monogenic

Polygenic

Acquired

Electrophysiology ‘triggers’

Atrial cardiomyopathy ‘substrate’

Anticoagulation

Personalized management & clinical trial allocation*

Reversible cause or targeted therapy available

‘Biomarker guided’

Hypothesis driven

Classical RCT vs. standard of care

Exploratory study

Single arm

Staged approach (incremental benefit)

No recognized targeted therapy available

‘Biomarker discovery/validation’

Unselected ‘novel’ therapy

Staged approach/adaptive design

Standard of care

Serial ‘biomarker’ measurement
Ablation is salvation
All Arrhythmias Straighten Themselves Out in THE END