State-of-the-Art AF Management:

A Labor of Love

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Atrial Fibrillation
Mechanisms: Pulmonary veins

Treatment Goals

• #1: Symptom suppression

• #2: Improve outcomes:
  – Prevent strokes
  – Prevent tachycardia-induced cardiomyopathy
  – Prevent dementia?
  – Reduce mortality?

• Approaches:
  – Rhythm control
  – Rate control/anticoagulation
Goal #1: Improve symptoms
Rhythm Control: Drugs

No Structural Heart Disease

- Dofetilide
- Dronedarone
- Flecaïnide
- Propafenone
- Sotalol

- Catheter ablation

- Amiodarone

Structural Heart Disease

- CAD
- HF

- Dofetilide
- Dronedarone
- Sotalol

- Catheter ablation

- Amiodarone

- Dofetilide

- Amiodarone
Atrial Fibrillation
Mechanisms: Beyond PV ectopy
Atrial Fibrillation Ablation Strategies

Calkins et al Heart Rhythm 2017
Symptom control

PV isolation: More effective than drugs

Paroxysmal AF-Failed Drug


Paroxysmal AF-Cryo-ablation


Paroxysmal AF-Contact-force

Natale et al. J Am Coll Cardiol. 2014;64(7):647-656

Paroxysmal AF-Laser-ablation

Ablation as first-line?

Wazni et al JAMA 2005;293:2634

Nielsen et al NEJM 2012;367:1587

Morillo et al JAMA 2014;311:692

Primary endpoint: Symptomatic AF

Primary endpoint: AF burden

Primary endpoint: Time to documented atrial tachyarrhythmia
PV isolation: Unsatisfactory for Persistent AF

Chao et al Circ Arrhythm Electrophysiol. 2012;5:514520

Table 3 Recommendations regarding ablation technique
- Ablation strategies that target the PVs and/or PV antrum are the cornerstone for most AF ablation procedures.
- If the PVs are targeted, electrical isolation should be the goal.
- Achievement of electrical isolation requires, at a minimum, assessment and demonstration of entrance block into the PV.
- Monitoring for PV reconnection for 20 minutes following initial PV isolation should be considered.
- For surgical PV isolation, entrance and/or exit block should be demonstrated.
- Careful identification of the PV ostia is mandatory to avoid ablation within the PVs.
- If a focal trigger is identified outside a PV at the time of an AF ablation procedure, ablation of that focal trigger should be considered.
- If additional linear lesions are applied, operators should consider using mapping and pacing maneuvers to assess for line completeness.
- Ablation of the cavitricuspid isthmus is recommended in patients with a history of typical atrial flutter or inducible cavitricuspid isthmus dependent atrial flutter.
- If patients with longstanding persistent AF are approached, operators should consider more extensive ablation based on linear lesions or complex fractionated electrograms.
- It is recommended that RF power be reduced when creating lesions along the posterior wall near the esophagus.

Calkins et al et al Heart Rhythm 2012
Strategies and targets

- Pulmonary vein isolation
- Wide area circumferential ablation
- Antral isolation
- Complex and fractionated potential ablation
- Ganglionic vagal ablation
- Left atrial posterior linear ablation
- Mitral isthmus linear ablation

- Ectopic foci from the pulmonary veins
- Vagal innervation
- Triggers from the vein of Marshall
- Rotors in the posterior left atrium
- Elimination of iatrogenic flutter
- Rotor-anchoring and wavebreak sites
Persistent AF: Beyond the Pulmonary Veins?

Persistent AF: Beyond the Pulmonary Veins?

Persistent AF ablation
Additional lesions?

- Defragmentation - no impact. CHASE-AF
Persistent AF ablation
Additional lesions?

Extrapulmonary triggers
Longstanding Persistent AF: Left atrial appendage?

Emergent techniques and technologies

- More on PV isolation:
  - Pulsed electrical fields
  - Lattice radiofrequency (Affera)
  - Radiofrequency balloon (Apama)
  - Cyberheart
  - Cardiofocus HeartLight X3
  - Vytronus® robotic ablation
- Ablative technology
  - Diamond tip
- Propagation Mapping
  - Acutus®
  - ICAN
- Techniques:
  - LAA isolation
  - VOM ethanol infusion
Pulsed-Field ablation

**CENTRAL ILLUSTRATION:** Pulmonary Vein Isolation for Atrial Fibrillation by Pulsed Field Ablation

Radiofrequency Ablation
- Damage to Esophagus
- Damage to Pulmonary Vein
- Damage to Phrenic Nerve

Cryoballoon Ablation
- Normal Esophagus
- Normal Pulmonary Vein
- Normal Phrenic Nerve

Pulsed Field Ablation
- Normal Esophagus
- Normal Pulmonary Vein
- Normal Phrenic Nerve

Frequency of Patients With ALL PVs Durably Isolated

Affera® Lattice electrode ablation catheter

Ultra-rapid ablation

CTI 13 sec

Reddy et al. S-AB08-02. Heart Rhythm Sessions. 2019

Ikeda et al. S-AB07-01. Heart Rhythm Sessions. 2019

Nakagawa et al. S-PO01-046. Heart Rhythm Sessions 2019
Radiofrequency balloons for PVI

- HelioStar® RF balloon.
- In IDE clinical trial in the US.

- Apama® RF balloon
- In IDE clinical trial in the US.
Temperature-controlled RF (EPIX®)

- Diamond tip dissipates heat
- Thermocouples effectively reflect tissue temperature
- RF titrated to tissue temperature
- Contact force sensing not needed

J Am Coll Cardiol 2017;70:542–53
AcQMap® High Resolution Imaging and Mapping System

- Non-contact 3D electro-anatomic Visualization System capable of mapping all types of complex atrial arrhythmias
- Ultrasound anatomy reconstruction in as little as 2-3 minutes
- Full-chamber mapping, clear view of cardiac activation
- Charge source mapping reveals conduction patterns in the substrate
- Rapid re-mapping to assess effect of ablation
- CE Mark - April 2014
- FDA clearance - October 16, 2017

Brief Summary: Please review the Instructions for Use prior to using these devices for a complete listing of indications, contraindications, warnings, precautions, potential adverse events and directions for use. The following presentation may contain information that is considered off-label in the U.S.
Current *Procedural* limitations in AF ablation

- Technical limitations of the PV isolation procedure:
  - Inability to achieve durable PV isolation
  - Procedure time and complexity
  - Procedure risks

- Mechanistic limitations of the PV isolation procedure:
  - Are all mechanisms of AF ablated with PV isolation?
  - How much PV antrum/posterior wall should be included in a PVI

- What other targets besides PV isolation should be ablated?
  - Rotors?
  - Focal triggers?
  - Innervation?
  - Scar?
  - LAA?

- What ablation strategy should be used in each individual patient?
  - Paroxysmal vs persistent
  - Lone vs “accompanied’ AF
  - LA scar vs healthy
  - Young vs old.
Current *Clinical* limitations in AF ablation

- **Patient selection**
  - Paroxysmal vs persistent vs longstanding persistent
  - Impact of structural heart disease
    - Atrial scar
    - Ventricular dysfunction

- **Timing of the procedure**
  - Guided by symptoms?

- **Prognostic implications:**
  - Do we prevent stroke, dementia, reduce mortality?
  - Can we stop oral anticoagulants in high-risk patients?
Case Study

- 73 year-old woman
- Paroxysmal AF since age 62. Sporadic AF episodes managed with pill-in-the-pocket propafenone until age 65.
- CHADS-Vasc: age, female, HTN, vascular
- TIA at age 71: CHADS-Vasc: 6
- Rivaroxaban led to GU bleeding: spontaneous ureteral bleeding, leading to urinary obstruction and transient AKI, requiring transfusion
- AF becomes persistent at age 71, rate control in the 100s at rest, with progressive DOE and functional decline
Challenges and possible approaches

- Needs stroke protection in the face of OAC-induced bleeding
- Needs rhythm control
- Ablation challenges:
  - Longstanding persistent AF
  - Enlarged LA
    - LA diameter 6 cm
    - LA volume 189 cc.
- A strategy of aggressive ablation – including LAA isolation- combined with LAA occlusion was planned
  - 2-stage procedure
First procedure
One week post ablation EKG
One month later: bipolar voltage map
One month later: propagation
One month later: propagation
Ablation at septal site
Reinforcing septal line

LAA activation sequence change
Vein of Marshall ethanol
Vein of Marshall ethanol
Vein of Marshall ethanol: VENUS trial
Treatment Goals

• #1: Symptom suppression

• #2: Improve outcomes:
  – Prevent strokes
  – Prevent tachycardia-induced cardiomyopathy
  – Prevent dementia?
  – Reduce mortality?
Ablation and Stroke prevention

- Observational studies:

![Graph showing cumulative proportion free from thromboembolic events over months.](image)

- Patients with AF & ≥1 risk factor (n=411)
- Patients with AF & no risk factor (n=344)
- Framingham cohort with no AF

Stroke prevention
AF ablation ~ no AF

AF ablation, n=4212
AF no ablation, n=16848
No AF, n=16848

Bunch TJ et al Heart Rhythm 2013;10:1272
Ablation and Mortality

Log Rank Test: P=0.005

Log Rank Test: P=0.002

Does AF ablation improve survival?

- **AATAC:** EF <40%. Lower death from all causes in ablation group (8% vs 18% in amiodarone), 53% reduction. Di Biase et al *Circulation*. 2016;133:1637–1644.

- **CASTLE AF:** Heart failure population, EF <35%.
CABANA Trial

CABANA analyses

• Primary analysis as “intention to treat”.
• “Per-protocol” comparisons were performed in which:
  – Drug group consisted of all patients randomized to drug therapy, with the follow-up of patients who received drug therapy and crossed over to catheter ablation censored at the time of ablation (n=301).
  – Catheter ablation group included patients randomized to catheter ablation who received an ablation within the 6-month time window following randomization. (censored 102 patients)
• ”Treatment received”: all catheter-ablation treated patients vs drug-treated patients
CABANA “Intention-to-Treat” Analysis

As Randomized (Intent-to-Treat) Analysis

<table>
<thead>
<tr>
<th>Randomized</th>
<th>Treatment Status</th>
<th>Follow-up Attributed to</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ablation 1108</td>
<td>Ablated 1006 (90.8%)</td>
<td>Ablation (entire study) 1006</td>
<td>Ablation 1108</td>
</tr>
<tr>
<td></td>
<td>Never Ablated 102 (9.2%)</td>
<td>Ablation (entire study) 102</td>
<td></td>
</tr>
<tr>
<td>Drug Therapy 1096</td>
<td>Remained in Drug Group 795 (72.5%)</td>
<td>Drug (entire study) 795</td>
<td>Drug 1096</td>
</tr>
<tr>
<td></td>
<td>Crossed over to Ablation during follow-up 301 (27.5%)</td>
<td>Drug (entire study) 301</td>
<td></td>
</tr>
</tbody>
</table>
CABANA “Per-protocol” Analysis

Per Protocol Analysis

Randomized: Ablation 1108
- Ablated ≤1yr: 987 (89.1%)
- Ablated >1yr: 19 (1.7%)
- Never Ablated: 102 (9.2%)

Treatment Status:
- Ablation 987
- Excluded 19
- Excluded 102

Follow-up Attributed to:
- Ablation 987

Analysis:
- Analyzed as:
  1. Ablated within 6 mo
  2. Ablated within 12 mo
CABANA “Treatment Received” Analysis

Treatment Received Analysis

- Randomized
  - Ablation 1108
    - Ablated 1006 (90.8%)
    - Never Ablated 102 (9.2%)
  - Drug Therapy 1096
    - Remained in Drug group 795 (72.5%)
    - Crossed over to ablation during follow-up 301 (27.5%)

- Treatment Status
  - Ablation
    - (entire study) 1006
  - Drug
    - (entire study) 102

- Follow-up Attributed to
  - Ablation
    - 1006
    - + 301 after crossover
  - Drug
    - 795
    - + 301 before crossover
  - Drug until censored and moved to ablation 301
  - Ablation after crossover 301
# Outcomes by Intention-to-treat

## Table 2. Primary and Secondary Outcomes by Intention-to-Treat Analysis

<table>
<thead>
<tr>
<th></th>
<th>Events, No. (%)</th>
<th>Kaplan-Meier 4-Year Event Rate, %</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Catheter Ablation Group (n = 1108)</td>
<td>Drug Therapy Group (n = 1096)</td>
<td>Catheter Ablation Group (n = 1108)</td>
<td>Drug Therapy Group (n = 1096)</td>
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<tr>
<td><strong>Primary end point</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(death, disabling stroke,</td>
<td>89 (8.0)</td>
<td>101 (9.2)</td>
<td>7.2</td>
<td>8.9</td>
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<tr>
<td>serious bleeding, or</td>
<td></td>
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<tr>
<td>cardiac arrest)**</td>
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<tr>
<td><strong>Components of primary end</strong></td>
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<tr>
<td>point**</td>
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<td></td>
</tr>
<tr>
<td>Death</td>
<td>58 (5.2)</td>
<td>67 (6.1)</td>
<td>4.7</td>
<td>5.3</td>
</tr>
<tr>
<td>Disabling stroke</td>
<td>3 (0.3)</td>
<td>7 (0.6)</td>
<td>0.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Serious bleeding</td>
<td>36 (3.2)</td>
<td>36 (3.3)</td>
<td>3.0</td>
<td>3.7</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>7 (0.6)</td>
<td>11 (1.0)</td>
<td>0.7</td>
<td>1.1</td>
</tr>
<tr>
<td><strong>Secondary end point</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death or cardiovascular</td>
<td>573 (51.7)</td>
<td>637 (58.1)</td>
<td>54.9</td>
<td>62.7</td>
</tr>
<tr>
<td>hospitalization</td>
<td></td>
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</tbody>
</table>
Outcomes by Intention-to-treat

**Primary Endpoint:**
dead, disabling stroke, serious bleeding, or cardiac arrest

**All-cause mortality**
Hazard ratio, 0.85 (95% CI, 0.60-1.21); Log-rank P = .38

**Death-Hospitalization**
Hazard ratio, 0.83 (95% CI, 0.74-0.93); Log-rank P = .001
Outcomes by Per-protocol analysis

Primary Endpoint:
death, disabling stroke, serious bleeding, or cardiac arrest

Kaplan-Meier estimates of the cumulative risk of death, disabling stroke, serious bleeding, or cardiac arrest (primary end point) by 6-month (A) and 12-month (B) per-protocol analysis. Figure includes patients randomized to catheter ablation who were ablated within 6 months (A) or 12 months (B) after randomization. It also includes all patients randomized to drug therapy, with follow-up censored at crossover to ablation. A. The median (25th, 75th percentiles) length of patient follow-up was 4.1 years (2.6, 5.2) in the catheter ablation group and 4.0 years (2.5, 5.2) in the drug therapy group. B. The median (25th, 75th percentiles) length of patient follow-up was 4.2 years (2.6, 5.2) in the catheter ablation group and 4.0 years (2.5, 5.2) in the drug therapy group.
Mortality by Per-protocol analysis

**eFigure 1A. Kaplan-Meier Estimates of Mortality (6 Month Per-Protocol)**
Kaplan-Meier estimates of all-cause mortality by *Per-Protocol* analysis.

**eFigure 1B. Kaplan-Meier Estimates of Mortality (12 Month Per-Protocol)**
Kaplan-Meier estimates of all-cause mortality by *Per-Protocol* analysis.

Conclusions

• AF ablation is a valuable tool in the management of AF:
  – Greatest impact on symptoms and quality of life
  – Can reduce death-hospitalization
• Valuable as first-line treatment but drug therapy may be more acceptable
• Does not worsen outcomes
• Most effective in paroxysmal AF
Conclusions

- Novel technologies promise to continue improving the safety, efficacy and speed of PV isolation
- The limitations of PV isolation largely remain unaltered by technology
- Rotor mapping remains in search of a role
- Techniques like LAA isolation and VOM ethanol need to refine:
  - Their indications
  - Optimal timing and procedural logistics
- Combination of LAA isolation plus LAA occlusion is particularly attractive from standpoint of rhythm control and stroke prevention