Explaining the CABANA Trial

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Overview

• Ablation vs. drug therapy on cardiovascular outcomes
  – Explaining the CABANA design & issues
  – Examining the Intention-to-treat & per protocol analysis
  – Impact on Quality of Life

• Take home messages from CABANA
The Purpose of CABANA

• Compare catheter ablation to state-of-the-art drug therapy for patients with new onset or undertreated AF

• Primary endpoint
  » All cause mortality, disabling strokes, serious bleeding or cardiac arrest

• Secondary endpoints
  » All cause mortality
  » Death (all-cause) or CV hospitalization
  » Quality of Life
Trial Design Overview

2204 symptomatic pts w/ new onset or under-treated paroxysmal, persistent, or longstanding persistent AF

- ≥ 65 years of age or < 65 years of age with ≥ 1 CVA risk factor
- Eligible for ablation and ≥ 2 rhythm or rate control drugs

1:1 Randomization (open label)

Ablation Therapy
- Primary ablation (PVI, WACA)
- Ancillary ablation (Linear lesions, CFAE,GP)
- Guideline-based anticoagulation

Drug Therapy
- Rhythm control
- Rate control
- Guideline-based anticoagulation

Clinical composite 1° endpoint: death, disabling stroke, serious bleeding, or cardiac arrest
2° endpoints: inclusive of quality of life outcomes

Median study follow-up 48.5 months

Patient Randomization

Important to recognize:

• Some potential post-randomization bias

• 9.2% from catheter ablation arm refused an ablation

• 27.5% of drug therapy arm crossed over to ablation arm

Quality of Life Assessment
Domain assessed and Instruments used

<table>
<thead>
<tr>
<th>QOL Domains</th>
<th>QOL instruments</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF symptoms</td>
<td>MAFSI * prespecified co-primary endpoints</td>
</tr>
<tr>
<td>AF-related QOL</td>
<td>AFEQT * prespecified co-primary endpoints</td>
</tr>
<tr>
<td>General Health Perceptions</td>
<td>SF-36, EQ-5D</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>DASI, SF-36</td>
</tr>
<tr>
<td>Psychological well being</td>
<td>SF-36 scales</td>
</tr>
<tr>
<td>Role and social functioning</td>
<td>SF-36 scales</td>
</tr>
</tbody>
</table>

- QOL data collected for 92% of eligible patients at 12 months and 81% at 60 months
- Comparisons defined by ITT
- Mixed regression analysis performed

Mayo AF specific Symptom Inventory
MAFSI Overview

- Based on AF Symptom Check list (Bubien & Kay, revised by Jenkins in 1993)
- 10 symptoms assessed over past month for frequency
- Score: 0 (no AF symptoms) - 40 (worst)

### Baseline Demographics

**Comparable between 2 groups**

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>No. (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Catheter Ablation (n = 1108)</td>
<td>Drug Therapy (n = 1096)</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (Q1, Q3), y</td>
<td>68 (62, 72)</td>
<td>67 (62, 72)</td>
</tr>
<tr>
<td>&lt;65</td>
<td>375 (33.8)</td>
<td>391 (35.7)</td>
</tr>
<tr>
<td>65-&lt;75</td>
<td>577 (52.1)</td>
<td>553 (50.5)</td>
</tr>
<tr>
<td>≥75</td>
<td>156 (14.1)</td>
<td>152 (13.9)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>695 (62.7)</td>
<td>690 (63.0)</td>
</tr>
<tr>
<td>Female</td>
<td>413 (37.3)</td>
<td>406 (37.0)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1018 (92.0)</td>
<td>1007 (92.1)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>39 (3.5)</td>
<td>38 (3.5)</td>
</tr>
<tr>
<td>Other</td>
<td>50 (4.5)</td>
<td>48 (4.4)</td>
</tr>
</tbody>
</table>

Baseline History
Comparable between 2 groups

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Catheter Ablation (n = 1108)</th>
<th>Drug Therapy (n = 1096)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension or LVH</td>
<td>924 (83.4)</td>
<td>927 (84.7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>876 (79.1)</td>
<td>900 (82.2)</td>
</tr>
<tr>
<td>LVH</td>
<td>334 (38.7)</td>
<td>328 (42.1)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>280 (25.3)</td>
<td>281 (25.7)</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>262 (23.6)</td>
<td>246 (22.5)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>208 (18.8)</td>
<td>216 (19.7)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>174 (15.7)</td>
<td>163 (14.9)</td>
</tr>
<tr>
<td>Family history of AF</td>
<td>130 (11.8)</td>
<td>122 (11.2)</td>
</tr>
<tr>
<td>Prior CVA or TIA</td>
<td>117 (10.6)</td>
<td>103 (9.4)</td>
</tr>
<tr>
<td>Prior CVA</td>
<td>68 (6.1)</td>
<td>58 (5.3)</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>41 (3.7)</td>
<td>49 (4.5)</td>
</tr>
<tr>
<td>Ejection fraction ≤35%</td>
<td>38/790 (4.8)</td>
<td>31/740 (4.2)</td>
</tr>
</tbody>
</table>

Packer DL, et al.
*JAMA*
2019;321:1261-1274.
# Primary & Secondary Outcomes

## Intention-to-Treat Analysis

<table>
<thead>
<tr>
<th>Events, No. (%)</th>
<th>Kaplan-Meier 4-Year Event Rate, %</th>
<th>Hazard Ratio (95% CI)(^a)</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>Absolute Reduction</td>
</tr>
<tr>
<td>Primary end point (death, disabling stroke, serious bleeding, or cardiac arrest)(^b)</td>
<td>89 (8.0)</td>
<td>101 (9.2)</td>
<td>7.2</td>
</tr>
<tr>
<td>Components of primary end point</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>58 (5.2)</td>
<td>67 (6.1)</td>
<td>4.7</td>
</tr>
<tr>
<td>Disabling stroke</td>
<td>3 (0.3)</td>
<td>7 (0.6)</td>
<td>0.1</td>
</tr>
<tr>
<td>Serious bleeding</td>
<td>36 (3.2)</td>
<td>36 (3.3)</td>
<td>3.0</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>7 (0.6)</td>
<td>11 (1.0)</td>
<td>0.7</td>
</tr>
<tr>
<td>Secondary end point</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death or cardiovascular hospitalization</td>
<td>573 (51.7)</td>
<td>637 (58.1)</td>
<td>54.9</td>
</tr>
</tbody>
</table>

Primary End Point by Intention-to-Treat

- No statistically significant difference between the two arms
- 4-year event rates
  - 7.2% for CA
  - 8.9% for drug therapy
- 14% relative risk reduction in the primary composite endpoint
Mortality & Cardiovascular Hospitalization
Intention-to-Treat Analysis

• Median follow up time 4 years in both groups

Primary Endpoint at 6 and 12 months by Per-Protocol Analysis

A At 6 mo

Hazard ratio, 0.74 (95% CI, 0.54-1.01); P = .056

B At 12 mo

Hazard ratio, 0.73 (95% CI, 0.54-0.99); P = .046

Recurrent Atrial Fibrillation
Intention-to-Treat Analysis

- Lower AF recurrence in ablation vs. drug arm
  - 50% vs. 69% at 3-years FU, post-blanking
- 17% required a repeat ablation

- Adverse events
  - Cardiac tamponade: 0.8%
  - Hematomas (2.3%)
  - pseudoaneurysms (1.1%)
  - No atrial esophageal fistula

Primary End Point Subgroup Analysis

Intention to Treat

- Multiple testing (so needs careful interpretation)
- Ablation may be more useful in younger patients, HF, minorities, lower BMI and presence of sleep apnea

AF Effect on Quality of Life (AFEQT)

Summary Scores

Mayo AF Specific Symptom Inventory Frequency Summary Scores

AF-Related Symptoms at Baseline & 12 months: AFEQT (Post-hoc) Summary Score

- Benefit of catheter ablation /drug therapy as a function of baseline AFEQT score; higher in more symptomatic group
- Extent of benefit of ablation also highest in the most symptomatic (7.7 points higher than drug therapy group)

• Catheter ablation compared with medical therapy did not produce a reduction in the primary endpoint or all cause mortality
  – Results impacted by cross-overs and lower than expected event rates

• Ablation significantly reduced mortality or cardiovascular hospitalization by 17%
Take Home Message

• Ablation produced incremental and clinically meaningful and significant (sustained) improvements in AF-related symptoms and QOL compared to medical therapy

• A significant and 47% reduction in recurrent AF with catheter ablation

• A 33% reduction in primary endpoint & 40% mortality risk reduction when patient actually underwent catheter ablation

• Ablation is safe with low adverse events