Catheter Ablation for Atrial Fibrillation: Update on Clinical Trials

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University of Virginia
AF/VT/VF Symposium
Chicago, IL 12/07/2019

Disclosures: Celgene – consultant; Milestone – consultant; Novartis – consultant; Daiichi-Sankyo – consultant.
# Clinical Trials in Atrial Fibrillation Ablation

## Table 7: Selected clinical trials of catheter ablation of atrial fibrillation and/or for FDA approval

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Type</th>
<th>N</th>
<th>AF type</th>
<th>Ablation strategy</th>
<th>Initial time frame</th>
<th>Effectiveness endpoint</th>
<th>Ablation success</th>
<th>Drug/Control success</th>
<th>P-value for success</th>
<th>Abolition complications</th>
<th>Drug/Control complications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Trials Performed for FDA Approval</strong></td>
<td></td>
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<tr>
<td>JAMA 2010; 313: 332-340 (ThermoCool AF)<strong>[1]</strong></td>
<td>2010</td>
<td>Randomized to RF ablation or AAD, multicenter</td>
<td>167</td>
<td>Paroxysmal</td>
<td>PVI, optional ECRAs and lines</td>
<td>12 months</td>
<td>Freedom from symptomatic paroxysmal atrial fibrillation, acute procedural failure, or changes in specified drug regimen</td>
<td>64%</td>
<td>36%</td>
<td>&lt;0.001</td>
<td>4.9%</td>
<td>8.8%</td>
<td>FDA approval received</td>
</tr>
<tr>
<td>JACC 2013; 61: 1713-1723 (STOP AF)<strong>[2]</strong></td>
<td>2013</td>
<td>Randomized to ablation or AAD, multicenter</td>
<td>245</td>
<td>Paroxysmal</td>
<td>PVI</td>
<td>12 months</td>
<td>Freedom from any detectable AF, use of non-AAD, or non-pharmacological intervention for AF</td>
<td>70%</td>
<td>7%</td>
<td>&lt;0.001</td>
<td>3.1%</td>
<td>NA</td>
<td>FDA approval received</td>
</tr>
<tr>
<td>Heart Rhythm 2014; 11: 202-209 (TIP)<strong>[3]</strong></td>
<td>2014</td>
<td>Randomized to phased RF ablation or AAD; cardiovascular, multicenter</td>
<td>210</td>
<td>Persistent</td>
<td>CFAEs</td>
<td>6 months</td>
<td>Acute procedural success, &gt;90% reduction in AF burden, off AAD</td>
<td>26%</td>
<td>&lt;0.001</td>
<td>12.3%</td>
<td>NA</td>
<td>Not FDA approved</td>
<td></td>
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<tr>
<td>JACC 2014; 64: 64-456 (SMART-AF)<strong>[4]</strong></td>
<td>2014</td>
<td>Randomized to ablation or AAD, cardiovascular, multicenter</td>
<td>172</td>
<td>Paroxysmal</td>
<td>PVI, optional ECRAs and lines</td>
<td>12 months</td>
<td>Freedom from symptomatic AF, flutter, tachycardia, acute procedural failure, or changes in AAD</td>
<td>72.5%</td>
<td>NA</td>
<td>&lt;0.0001</td>
<td>7.5%</td>
<td>NA</td>
<td>FDA approval received</td>
</tr>
<tr>
<td>Circulation 2015; 132: 907-915 (TOCASTAR)<strong>[5]</strong></td>
<td>2015</td>
<td>Randomized to ablation or AAD, cardiovascular, multicenter</td>
<td>300</td>
<td>Paroxysmal</td>
<td>PVI, optional triggers, CFAEs and lines in both arms</td>
<td>12 months</td>
<td>Freedom from Symptomatic AF, Flutter/Tachycardia or AAD</td>
<td>67.8%</td>
<td>60.4%</td>
<td>0.0073 for noninferiority</td>
<td>7.2%</td>
<td>9.1%</td>
<td>FDA approval received</td>
</tr>
<tr>
<td>JACC 2015; 66: 1350-1340 (HeartLight)<strong>[6]</strong></td>
<td>2015</td>
<td>Randomized to ablation or AAD, cardiovascular, multicenter</td>
<td>353</td>
<td>Paroxysmal</td>
<td>PVI or CTI ablation vs PVI, optional ECRAs, and lines</td>
<td>12 months</td>
<td>Freedom from Symptomatic AF, Flutter/Tachycardia, acute procedural failure, AAD, or non-pharmacological intervention</td>
<td>61.1%</td>
<td>61.7%</td>
<td>0.003 for noninferiority</td>
<td>5.3%</td>
<td>6.4%</td>
<td>FDA approval received</td>
</tr>
</tbody>
</table>

## First-Line Therapy Trials

| JAMA 2005; 293: 2634-2640 (RAMAT)**[7]** | 2005 | Randomized to drug, multicenter | 70 | Paroxysmal | PVI | 12 months | Freedom from detectable AF | 84% | 37% | <0.01 | 9% | 11% |
| NEJM 2012; 367:1578-1595 (WANDA-PAT)**[8]** | 2012 | Randomized to drug, multicenter | 294 | Paroxysmal | PVI, roof line, and tricuspid line | 24 months | Cumulative AF burden | 28% | 18% | 17% | 17% | 15% |
| JAMA 2015; 313: 692-700 (SMART-C)**[9]** | 2014 | Randomized to drug, multicenter | 127 | Paroxysmal | PVI plus optional non-PVI targets | 24 months | Freedom from detectable AF, flutter, tachycardia | 45% | 26% | 0.02 | 9% | 4.9% |

## Other Paroxysmal AF Ablation Trials

| JACC 2006; 48: 2348-2347 (AFPR)**[10]** | 2006 | Randomized to drug, single center | 198 | Paroxysmal | PVI, roof line and tricuspid line | 12 months | Freedom from detectable AF, flutter, tachycardia | 88% | 22% | <0.001 | 1% | 23% |
| Circulation 2008; 118: 2446-2009 (VISTA-AF)**[11]** | 2008 | Randomized to drug, multicenter | 110 | Paroxysmal | PVI (optional LA lines, CTI, focal) | 12 months | Freedom from detectable AF, flutter, tachycardia | 89% | 23% | <0.0001 | 5.7% | 1.7% |
| JACC 2018; 71: 2239-2245 (SMILE AND 23)**[12]** | 2018 | Randomized to drug, multicenter | 762 | Paroxysmal | PVI | 12 months | Freedom from detectable AF, flutter, tachycardia | 64.1% (RF) | 65.4% (cryo) | NA | 12.8% | 10.2% |

(Continued)
Clinical Trials in Atrial Fibrillation Ablation - 2

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Type</th>
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<th>Ablation complications</th>
<th>Drug/Control complications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>JACC 2010; 66: 2747-2757</td>
<td>2010</td>
<td>Randomized to hot balloon or drug, multicenter</td>
<td>100</td>
<td>Paroxysmal AF</td>
<td>PVI</td>
<td>12 months</td>
<td>Freedom from AF</td>
<td>59%</td>
<td>5%</td>
<td>&lt;0.001</td>
<td>10.4%</td>
<td>4.7%</td>
<td></td>
</tr>
<tr>
<td>Other Persistent AF Ablation Trials</td>
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<tr>
<td>NDM 2006; 354: 934-941</td>
<td>2006</td>
<td>Randomized to RF ablation or to Ca and short term amio</td>
<td>146</td>
<td>Persistent</td>
<td>PVI, roof, m/valve line</td>
<td>12 months</td>
<td>No AF or flutter month 12</td>
<td>74%</td>
<td>58%</td>
<td>0.05</td>
<td>1.3%</td>
<td>1.4%</td>
<td></td>
</tr>
<tr>
<td>HJ 2014; 35: 505-507 (JAMA)</td>
<td>2014</td>
<td>Randomized to drug (2:11</td>
<td>Persistent</td>
<td>PVI (optional LA lines, (FAEs)</td>
<td>32 months</td>
<td>Freedom from AF/Flutter lasting &gt;360h</td>
<td>70%</td>
<td>44%</td>
<td>0.002</td>
<td>6.1%</td>
<td>2.0%</td>
<td></td>
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</tr>
</tbody>
</table>

ClinicalTrials.gov

- 619 interventional trials
- 262 completed
- 87 with results
- 149 recruiting

www.clinicaltrials.gov 10/16/2019
Interpreting Clinical Trials in AF Ablation

Comparisons – Ablation Technologies, Mapping/Ablation Strategies, Clinical Strategy, Sham Procedures (?), etc.

AF pattern - Paroxysmal, Persistent, Long-standing Persistent

Demographics – Heart disease, gender, age, CHF, prior therapy, geography, etc.

Endpoints – AF recurrence (? definitions and measurements), mortality, hospitalizations, complications, other clinical endpoints, QOL, subtraction anxiety

Overall Clinical Management - e.g. sleep apnea, HTN, obesity, antiarrhythmic drugs, ICD/CRTD, unspecified medical therapy, etc.

Single Procedure vs. Eventual Outcome

Blanking Period Events

Responder Analyses; Drop outs; Crossovers

Pre-Randomization Biases – Investigator and Patient
CABANA Trial

2204 Randomized

1108 Randomized to catheter ablation
1006 Received catheter ablation
102 Did not receive catheter ablation
84 Patient or family refusal
14 Physician discretion
4 Insurance issues
215 Received repeat ablation(s)

1096 Randomized to drug therapy
1092 Received drug therapy
853 Received rhythm and rate control
123 Received rate control only
116 Received rhythm control only
4 Did not receive drug therapy
3 Withdrew consent
1 Physician decided not to prescribe
301 Received catheter ablation

1002 Completed the study
79 Withdrew consent <3 y
27 Lost to follow-up

1108 Included in the primary analysis

966 Completed the study
112 Withdrew consent <3 y
18 Lost to follow-up

1096 Included in the primary analysis

CABANA Trial
Death, Disabling Stroke, Serious Bleeding, Cardiac Arrest

Hazard ratio, 0.86 (95% CI, 0.65-1.15); Log-rank $P = .30$

Event Rate, %
0 3 6 9 12 15
0 6 12 18 24 30 36 42 48 54 60
Time Since Randomization, mo

No. at risk
Drug therapy
1096 1036 1006 970 880 763 652 578 499 418 312
Catheter ablation
1108 1045 1021 996 915 793 700 614 535 432 309

CABANA Trial
ITT analysis

**A** All-cause mortality

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

**B** Mortality or cardiovascular hospitalization

- Hazard ratio, 0.83 (95% CI, 0.74-0.93); Log-rank P = .001

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No. at risk
- Catheter ablation: 1108, 1058, 1035, 1013, 933, 814, 724, 632, 555, 455, 332

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<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Events/Patients (Person-Years)</th>
<th>Hazard Ratio (95% CI)</th>
<th>Favors</th>
<th>Interaction P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>14/375 (1483)</td>
<td>27/391 (1498)</td>
<td>0.52 (0.27-1.00)</td>
<td>.07</td>
</tr>
<tr>
<td>≥65 and &lt;75</td>
<td>50/577 (2159)</td>
<td>36/553 (2019)</td>
<td>0.84 (0.57-1.23)</td>
<td>.16</td>
</tr>
<tr>
<td>≥75</td>
<td>25/156 (514)</td>
<td>18/152 (529)</td>
<td>1.46 (0.86-2.67)</td>
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</tr>
<tr>
<td>Sex</td>
<td></td>
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<tr>
<td>Male</td>
<td>54/695 (2670)</td>
<td>71/690 (2591)</td>
<td>0.74 (0.52-1.06)</td>
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<tr>
<td>Female</td>
<td>35/413 (1485)</td>
<td>30/406 (1456)</td>
<td>1.14 (0.76-1.68)</td>
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</tr>
<tr>
<td>Minority status</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>White</td>
<td>80/995 (3721)</td>
<td>82/984 (3654)</td>
<td>0.96 (0.71-1.31)</td>
<td>.07</td>
</tr>
<tr>
<td>Minority§</td>
<td>9/113 (414)</td>
<td>19/112 (193)</td>
<td>0.43 (0.26-0.79)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation type§</td>
<td></td>
<td></td>
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<tr>
<td>Pafakysmial</td>
<td>31/470 (1756)</td>
<td>38/476 (1761)</td>
<td>0.82 (0.51-1.31)</td>
<td>.91</td>
</tr>
<tr>
<td>Persistent</td>
<td>49/524 (1922)</td>
<td>55/518 (1860)</td>
<td>0.87 (0.59-1.28)</td>
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<tr>
<td>Long-standing persistent</td>
<td>9/114 (477)</td>
<td>8/101 (426)</td>
<td>1.01 (0.39-2.63)</td>
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<tr>
<td>Time since onset of atrial fibrillation, y</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≤1</td>
<td>50/540 (1922)</td>
<td>58/523 (1835)</td>
<td>0.83 (0.57-1.21)</td>
<td>.72</td>
</tr>
<tr>
<td>&gt;1</td>
<td>39/560 (2207)</td>
<td>42/562 (2177)</td>
<td>0.92 (0.59-1.42)</td>
<td></td>
</tr>
<tr>
<td>Baseline NYHA class§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No heart failure or class I</td>
<td>55/710 (2735)</td>
<td>52/689 (2657)</td>
<td>1.04 (0.71-1.52)</td>
<td>.15</td>
</tr>
<tr>
<td>≥ Class II</td>
<td>34/378 (1396)</td>
<td>49/400 (1372)</td>
<td>0.68 (0.44-1.05)</td>
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<tr>
<td>History of congestive heart failure</td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>68/934 (3106)</td>
<td>72/931 (3500)</td>
<td>0.95 (0.68-1.32)</td>
<td>.20</td>
</tr>
<tr>
<td>Yes</td>
<td>21/174 (650)</td>
<td>29/163 (547)</td>
<td>0.61 (0.35-1.08)</td>
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<tr>
<td>Hypertension</td>
<td></td>
<td></td>
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<tr>
<td>Absent</td>
<td>15/232 (857)</td>
<td>14/195 (761)</td>
<td>0.97 (0.47-2.01)</td>
<td>.73</td>
</tr>
<tr>
<td>Present</td>
<td>74/876 (3298)</td>
<td>87/900 (3287)</td>
<td>0.85 (0.62-1.15)</td>
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<tr>
<td>Hypertension with LVH§</td>
<td></td>
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<tr>
<td>Absent</td>
<td>53/632 (2391)</td>
<td>51/544 (2022)</td>
<td>0.89 (0.61-1.21)</td>
<td>.84</td>
</tr>
<tr>
<td>Present</td>
<td>22/286 (1126)</td>
<td>27/301 (1152)</td>
<td>0.83 (0.47-1.60)</td>
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<tr>
<td>CHA2DS2-VASc score§</td>
<td></td>
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<tr>
<td>≤2 (Less risk)</td>
<td>26/481 (1861)</td>
<td>28/478 (1859)</td>
<td>0.93 (0.54-1.58)</td>
<td>.72</td>
</tr>
<tr>
<td>&gt;2 (More risk)</td>
<td>63/627 (2295)</td>
<td>73/618 (2188)</td>
<td>0.83 (0.39-1.66)</td>
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<tr>
<td>Sleep apnoea</td>
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</tr>
<tr>
<td>Absent</td>
<td>65/846 (3129)</td>
<td>69/849 (3106)</td>
<td>0.94 (0.67-1.32)</td>
<td>.34</td>
</tr>
<tr>
<td>Present</td>
<td>24/262 (1027)</td>
<td>32/246 (941)</td>
<td>0.69 (0.41-1.2)</td>
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<tr>
<td>Body mass index§</td>
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<tr>
<td>≤30 (Not obese)</td>
<td>43/541 (3012)</td>
<td>53/533 (1886)</td>
<td>0.74 (0.49-1.13)</td>
<td>.38</td>
</tr>
<tr>
<td>≥30 (Obese)</td>
<td>45/545 (2088)</td>
<td>48/561 (2122)</td>
<td>0.96 (0.64-1.44)</td>
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</tr>
<tr>
<td>All patients</td>
<td>89/1108 (4155)</td>
<td>101/1096 (4047)</td>
<td>0.86 (0.65-1.15)</td>
<td></td>
</tr>
</tbody>
</table>
CABANA Trial
Primary Endpoints in Ablation Recipients

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

Event Rate, %

Time Since Randomization, mo

No. at risk
- Drug therapy: 1096, 954, 860, 778, 680, 566, 464, 396, 330, 275, 204
- Catheter ablation: 970, 941, 920, 901, 835, 721, 636, 555, 483, 397, 287
Hazard ratio, 0.52 (95% CI, 0.45-0.60); P < .001

ITT analysis
Study monitor only

Percent AF Burden Holter Analysis by Baseline Pattern of AF in CABANA

Poole et al. presented at ESC 2018

*Cabana study recording system only
Quality of Life Measurements:

- Mayo AF Specific Symptom Inventory
- AF Effect on Quality of Life
- SF-36
- Duke Activity Status Index
- EuroQual-5D

Conclusions:

- “Ablation produced incremental, clinically relevant, significant improvements in AF-related symptoms and QoL relative to drug treatment”
- “In symptomatic AF patients, both treatment groups showed substantial improvement over initial 12 months that were sustained for 5 years”

CABANA Trial - Controversies

Milton Packer
Unbelievable! Electrophysiologists embrace “alternative facts”!

Douglas Packer
You can’t benefit from ablation unless you get ablated.

Rita Redberg
People say “It’s unethical to do a sham controlled trial.” I think it’s unethical not to.

John Mandrola
If we ablate AF to relieve subjective endpoints, …, then the only way not to fool ourselves is a placebo-controlled trial.

Bradley Knight
The biggest disappointment from the CABANA trial is the comments from our non-EP colleagues who seem to have been poised to pounce.
Generalizability of CABANA Results
Propensity Score Matching in a Large Administrative Cohort

CASTLE-AF

Catheter Ablation vs Medical Therapy in HFrEF Meta-analysis

Stroke Risk After Left Atrial Appendage Electrical Isolation

Observational Study in 1,854 Patients in Sinus Rhythm 6 Months After AF Ablation With LAAEI
Circumferential PVI with/without Posterior Box Isolation

A Overall  B AAD Free Subjects

Log rank, P = 0.626

Log rank, P = 0.941


Single procedure AT/AF freedom with (A) and without antiarrhythmic drugs between CPVI-alone group and POBI group (B). AAD = antiarrhythmic drug; AF = atrial fibrillation; AT = atrial tachycardia; CPVI = circumferential pulmonary vein isolation; POBI = posterior box isolation.
Pulsed Field Ablation in AF

Catheter Ablation Can Delay Progression From Paroxysmal to Persistent Atrial Fibrillation

Karl-Heinz Kuck,¹ Dimitry Lebedev,² Evgeny Mikhaylov,² Alexander Romanov,³ László Gellér,⁴ Oskars Kalejs,⁵ Thomas Neumann,⁶ Karapet Davtyan,⁷ Young-Keun On,⁸ Sergey Popov,⁹ Feifan Ouyang¹

¹Asklepios Klinik St. Georg, Hamburg, Germany; ²Almazov National Medical Research Centre, Saint-Petersburg, Russia; ³E. Meshalkin National Medical Research Center of the Ministry of Health of the Russian Federation, Novosibirsk, Russia; ⁴Semmelweis University, Heart and Vascular Center, Budapest, Hungary; ⁵P. Stradins Clinical University Hospital, Riga, Latvia; ⁶Kerckhoff-Klinik, Bad Nauheim, Germany; ⁷National Medical Research Center for Preventive Medicine, Moscow, Russia; ⁸Sungkyunkwan University School of Medicine, Seoul, Korea; ⁹Federal State Budgetary Scientific Institution Research Institute for Cardiology, Tomsk, Russia
Patient Disposition

ITT population
- 128 assigned to RF ablation
- 102 received treatment
- 3 died
- 4 lost to follow up
- 14 withdrew consent
- 5 excluded
- 1 discontinued
- 2 AEs
- 51 sponsor closed study

Completed 3-year follow up
- 46 patients

AAD population
- 127 assigned to AAD
- 123 received treatment
- 123 started AAD, completed 2-wk dose-loading, did not undergo ablation, had no major protocol deviations, and were treated for PAF
- 15 received RF ablation
- 4 died
- 4 lost to follow up
- 9 withdrew consent
- 3 excluded
- 2 discontinued
- 1 AE
- 50 sponsor closed study
- 2 other

Safety population
- 95 treated with study catheter, had no major protocol deviations, and were treated for PAF

PP population
- 52 patients

†These subjects are counted toward RF Ablation group for PP population analyses
Significantly Lower Rate of Persistent AF/AT With Ablation Than With AAD

- Patients undergoing RF ablation were ~10× less likely than AAD patients to develop persistent AF (HR: 0.114)

![Graph showing ITT population with comparison of RF ablation vs AAD](image)
Data from National Readmissions Database – annual state based data

Catheter Ablation of Atrial Fibrillation, 2010-2015

- 60,203 admissions
- 0.46% early mortality, with over half occurring during 30-day readmission

Trends Associated With AF Ablation

<table>
<thead>
<tr>
<th>Trend in Early Mortality</th>
</tr>
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<tbody>
<tr>
<td>Percent Dead (%)</td>
</tr>
<tr>
<td>2010: 0.2%</td>
</tr>
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<table>
<thead>
<tr>
<th>Trend in Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index Complications (%)</td>
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<tr>
<td>2010: 2%</td>
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<thead>
<tr>
<th>Trend in Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbidity (%)</td>
</tr>
<tr>
<td>2010: 10%</td>
</tr>
</tbody>
</table>

Risk Factors for Early Mortality Post-AF Ablation

Procedural Complications

aOR 4.06; p < 0.001

Congestive Heart Failure

aOR 2.20; p = 0.011

Low AF Ablation Hospital Volume

aOR 2.35; p = 0.003

Evidence Based Personal Approach
Initial Therapy For Most AF Patients

Medical Rx ↔ Ablation
Evidence Based Personal Approach
Initial Therapy For AF Patients with HFrEF