Challenging Cases in Diagnosis and Management of Atrial Fibrillation 2018

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Disclosures

• Boston Scientific, Medtronic, St. Jude Medical: Consulting and Honoraria
• Boston Scientific, Medtronic: Research support
• Biotronik: Honoraria
• Biosense Webster: Honoraria, Research support
Lesson #1: New AF Guidelines
Case #1:

- 74 year old man with PAF and hypertension for 5 years
- No specific triggers, no other medical problems, and normal EF
- Episodes last 6-12 hours, associated with shortness of breath and lightheadedness
- Tried on beta blockers and diltiazem without much improvement
- Here today to discuss options:
  - A. Catheter ablation of AF
  - B. AAD drug therapy with IC (Propafenone)
  - C. AAD drug therapy with Class III (Sotalol)
  - D. AAD drug therapy with Multaq (Dronedarone)
  - E. Heart rate control with increasing dose of metoprolol
2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: Executive summary

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Heart Rhythm Volume 14,10; e445-494 (October 2017) DOI: 10.1016/j.hrthm.2017.07.009
Indications for Catheter Ablation of Symptomatic Atrial Fibrillation

Symptomatic AF

Paroxysmal AF

Persistent AF

Long-standing Persistent AF

AA Drugs

Catheter Ablation

AA Drugs

Catheter Ablation

AA Drugs

Catheter Ablation

<table>
<thead>
<tr>
<th>Indication</th>
<th>Reason</th>
<th>Grade</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>It is reasonable to use similar indications for AF ablation in selected patients with heart failure as in patients without heart failure.</td>
<td>IIa</td>
<td>B-R</td>
</tr>
<tr>
<td>Older patients (≥75 years of age)</td>
<td>It is reasonable to use similar indications for AF ablation in selected older patients with AF as in younger patients.</td>
<td>IIa</td>
<td>B-NR</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>It is reasonable to use similar indications for AF ablation in selected patients with HCM as in patients without HCM.</td>
<td>IIa</td>
<td>B-NR</td>
</tr>
<tr>
<td>Young patients (&lt;45 years of age)</td>
<td>It is reasonable to use similar indications for AF ablation in young patients with AF (&lt;45 years of age) as in older patients.</td>
<td>IIa</td>
<td>B-NR</td>
</tr>
<tr>
<td>Tachy-brady syndrome</td>
<td>It is reasonable to offer AF ablation as an alternative to pacemaker implantation in patients with tachy-brady syndrome.</td>
<td>IIa</td>
<td>B-NR</td>
</tr>
<tr>
<td>Athletes with AF</td>
<td>It is reasonable to offer high-level athletes AF as first-line therapy due to the negative effects of medications on athletic performance.</td>
<td>IIa</td>
<td>C-LD</td>
</tr>
<tr>
<td>Asymptomatic AF**</td>
<td>Paroxysmal: Catheter ablation may be considered in select patients.**</td>
<td>IIb</td>
<td>C-EO</td>
</tr>
<tr>
<td></td>
<td>Persistent: Catheter ablation may be considered in select patients.</td>
<td>IIb</td>
<td>C-EO</td>
</tr>
</tbody>
</table>
Case # 2:

- 72 year old man with PAF and NYHA Class II heart failure for 5 years
- Echo shows an ejection fraction of 35% and LA enlargement
- Episodes last 6-12 hours, associated with shortness of breath and lightheadedness
- Now taking carvedilol and ACE inhibitors and remains symptomatic with AF
- Here today to discuss options:
  - A. Catheter ablation of AF
  - B. Antiarrhythmic drug therapy with Amiodarone
  - C. Increasing carvedilol to maximal dose
Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device:
Results From the AATAC Multicenter Randomized Trial

Luigi Di Biase, Prasant Mohanty, Sanghamitra Mohanty, Pasquale Santangeli, Chintan Trivedi, Dhanunjaya Lakkireddy, Madhu Reddy, Pierre Jais, Sakis Themistoclakis, Antonio Dello Russo, Michela Casella, Gemma Pelargonio, Maria Lucia Narducci, Robert Schweikert, Petr Neuzil, Javier Sanchez, Rodney Horton, Salwa Beheiry, Richard Hongo, Steven Hao, Antonio Rossillo, Giovanni Forleo, Claudio Tondo, J. David Burkhardt, Michel Haissaguerre, Andrea Natale

https://doi.org/10.1161/CIRCULATIONAHA.115.019406
Circulation. 2016;133:1637-1644
Originally published March 30, 2016
203 Patients Enrolled
(≥18 years, persistent AF, dual chamber ICD or CRT-D, NYHA II-III, LV EF ≤40%)

Randomized 1:1

Catheter Ablation (Group 1): n=102
Amiodarone (group 2): n=101

DAY 0
Treatment Period
Baseline: LVEF, 6MWD, MLHFQ

Month 3
Trial Period

Month 24
End of Trial: LVEF, 6MWD, MLHFQ
Group 1 (catheter ablation, n=102)

Group 2 (amiodarone, n=101)

Log-rank p < 0.0001

Proportion AF/AT Free

Number of Subjects at Risk

Group 1

Group 2

Time to Recurrence (month)
Primary Endpoint: Change in LVEF at Baseline and 6 Months by Treatment Arm

- Catheter Ablation: +18.3%
- Medical Rate Control: +4.4%

Mean difference = +14.0%, 95% CI: 8.5% to 19.5%

Catheter Ablation Lesion Set in Left Atrium: Pulmonary Vein and Posterior Wall Isolation

Catheter Ablation for Atrial Fibrillation with Heart Failure

Nassir F. Marrouche, M.D., and the CASTLE-AF Investigators*

February 1, 2018
DOI: 10.1056/NEJMoa1707855
<table>
<thead>
<tr>
<th>End Point</th>
<th>Ablation (N=179)</th>
<th>Medical Therapy (N=184)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>Log-Rank Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number (percent)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary†</td>
<td>51 (28.5)</td>
<td>82 (44.6)</td>
<td>0.62 (0.43–0.87)</td>
<td>0.007</td>
<td>0.006</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>24 (13.4)</td>
<td>46 (25.0)</td>
<td>0.53 (0.32–0.86)</td>
<td>0.01</td>
<td>0.009</td>
</tr>
<tr>
<td>Heart-failure hospitalization</td>
<td>37 (20.7)</td>
<td>66 (35.9)</td>
<td>0.56 (0.37–0.83)</td>
<td>0.004</td>
<td>0.004</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>20 (11.2)</td>
<td>41 (22.3)</td>
<td>0.49 (0.29–0.84)</td>
<td>0.009</td>
<td>0.008</td>
</tr>
<tr>
<td>Cardiovascular hospitalization</td>
<td>64 (35.8)</td>
<td>89 (48.4)</td>
<td>0.72 (0.52–0.99)</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>Hospitalization for any cause</td>
<td>114 (63.7)</td>
<td>122 (66.3)</td>
<td>0.99 (0.77–1.28)</td>
<td>0.96</td>
<td>0.96</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>5 (2.8)</td>
<td>11 (6.0)</td>
<td>0.46 (0.16–1.33)</td>
<td>0.15</td>
<td>0.14</td>
</tr>
</tbody>
</table>

* All numbers and percentages represent the total numbers of events and raw event rates after a median follow-up of 37.8 months. Deaths and cerebrovascular accidents were evaluated at baseline and 12 weeks after baseline for hospitalizations in the two groups (the “blanking period”). For Kaplan–Meier estimates at 12, 36, and 60 months, see Table S6 in the Supplementary Appendix.
† The primary end point is a composite of death from any cause or hospitalization for worsening heart failure.
Which of the following risk factor modification steps reduce the risk of recurrent AF?

- A. Ingestion of OMEGA-3 fish oils
- B. Aggressive blood pressure management
- C. Treatment of obstructive sleep apnea
- D. Weight loss
- E. Increased physical activity
Product-Limit Survival Estimates with Number of Subjects at Risk

HR = 1.10 (0.84 - 1.45) P = 0.48

Journal of the American College of Cardiology
Volume 64, Issue 14, October 2014 DOI: 10.1016/j.jacc.2014.07.956
Recurrent Symptomatic AF/AT/AFI 3 Months post Ablation

Cumulative Incidence (%)

Hazard Ratio 0.94, 95% confidence interval (0.65, 1.38) p=0.763

No. at Risk
Standard BP Treatment 85 84 57 45 38 32 25
Aggressive BP Treatment 88 88 61 52 37 33 28

Months of Follow-up
Unadjusted HR = 0.71 (95% CI, 0.60-0.83)
p <0.001
Ablation Drug AF Freedom

Follow-up (Days)

- Group
- WL ≥10%
- WL 3-9%
- WL < 3% or Gain

Time (Days) | 0 | 365 | 730 | 1095 | 1460 | 1825
---|---|---|---|---|---|---
≥10 WL | 135 | 101 | 72 | 42 | 31 | 18
3-9% WL | 103 | 62 | 36 | 22 | 13 | 7
<3% WL or gain | 117 | 66 | 44 | 22 | 11 | 9

Total AF Freedom

Follow-up (Days)

- Group
- WL ≥10%
- WL 3-9%
- WL < 3% or Gain

<table>
<thead>
<tr>
<th>0</th>
<th>365</th>
<th>730</th>
<th>1095</th>
<th>1460</th>
<th>1825</th>
</tr>
</thead>
<tbody>
<tr>
<td>135</td>
<td>130</td>
<td>114</td>
<td>86</td>
<td>67</td>
<td>36</td>
</tr>
<tr>
<td>103</td>
<td>93</td>
<td>83</td>
<td>57</td>
<td>35</td>
<td>22</td>
</tr>
<tr>
<td>117</td>
<td>105</td>
<td>85</td>
<td>53</td>
<td>32</td>
<td>22</td>
</tr>
</tbody>
</table>
**CENTRAL ILLUSTRATION**  
Cardiorespiratory Fitness and AF Recurrence: CARDIO-FIT trial

- **Structured**: Age and Ability Matched
- **Frequency**: 3 Days to 5 Days
- **Intensity**: Low to Moderate
- **Time**: 60 to 200 Minutes/Week
- **Type**: Aerobic and Strength Training
- **Heart Rate**: Monitor, 85% of 220 - Age

**Structured Exercise Program**  
- Weight Loss
- Improved Glycemic Control
- Optimal BP Control
- Better Lipid Profile
- Reduced Inflammation

**Improved Cardiorespiratory Fitness**

**Incremental Effect of CRF gain With <10% Weight Loss on 5-Year AF Freedom Without Rhythm Control**

- <2MET Gain: 13%
- ≥2MET Gain: 37%

**Atrial Fibrillation Burden**

- Incremental Effect of CRF gain With ≥10% Weight Loss on 5-Year AF Freedom Without Rhythm Control Strategies

- <2MET Gain: 44%
- ≥2MET Gain: 76%

Which of the following risk factor modification steps reduce the risk of recurrent AF?

- A. Ingestion of OMEGA-3 fish oils
- B. Aggressive blood pressure management
- C. Treatment of obstructive sleep apnea
- D. Weight loss
- E. Increased physical activity
Case # 3:

• 75 year old man/woman with PAF and hypertension and had the ablation.

• The patient comes back and asks you why he has to continue the apixaban. The patient says that he has had no palpitations since his ablation and a 30 day event monitor shows no episodes of AF longer than 1 minute.

• He wants to stop his NOACs. What are you going to tell your patient? What would you do when he tells you he wants to go skiing?

• A. Implant an ILR to better monitor his AF

• B. Stop the apixaban

• C. Continue the apixaban

• D. Offer him a WATCHMAN if he really wants to stop his NOAC.

• E. Refer for LAA clip
## The Real-World: State of Play

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients (Aetna, Humana, Harvard Pilgrim)</td>
<td>16.2 million</td>
</tr>
<tr>
<td>Patients with AF</td>
<td>231,696 (1.4% of all pts)</td>
</tr>
<tr>
<td>AF pts with CHA\textsubscript{2}DS\textsubscript{2}-VASc ≥ 2</td>
<td>201,882 (87% of AF pts)</td>
</tr>
<tr>
<td>Patients with at least one oral anti-coagulation fill</td>
<td>105,256 (52% of AF pts)</td>
</tr>
<tr>
<td>Proportion of days covered by anti-coagulation in AF patients</td>
<td>32%</td>
</tr>
</tbody>
</table>

Despite NOAC Adoption and Ability to switch to NOACs, Adherence to Anticoagulation Remains a Challenge

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

# NOAC Trials: Adherence and Bleeding Issues

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study Drug Discontinuation Rate</th>
<th>Major Bleeding (rate/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban&lt;sup&gt;1&lt;/sup&gt;</td>
<td>24%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Apixaban&lt;sup&gt;2&lt;/sup&gt;</td>
<td>25%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Dabigatran&lt;sup&gt;3&lt;/sup&gt; (150 mg)</td>
<td>21%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Edoxaban&lt;sup&gt;4&lt;/sup&gt; (60 mg / 30 mg)</td>
<td>33% / 34%</td>
<td>2.8% / 1.6%</td>
</tr>
<tr>
<td>Warfarin&lt;sup&gt;1-4&lt;/sup&gt;</td>
<td>17 – 28%</td>
<td>3.1 – 3.6%</td>
</tr>
</tbody>
</table>

1 Connolly, S. NEJM 2009; 361:1139-1151 – 2 yrs follow-up (Corrected)
2 Patel, M. NEJM 2011; 365:883-891 – 1.9 yrs follow-up, ITT
3 Granger, C NEJM 2011; 365:981-992 – 1.8 yrs follow-up,
Real-world Comparison of Bleeding in NVAF
Apixaban, Dabigatran, Rivaroxaban

Data source: MarketScan Earlyview insurance claims database,
Eligible patients: NVAF patients ≥18 years who received NOAC or switched from
warfarin to NOAC from 01/01/2013-31/10/2014 NOAC were excluded.
   Apixaban: 8,785
   Dabigatran: 20,963
   Rivaroxaban: 30,529

Follow-up: Patients were followed up to 6 months until bleeding, discontinuation/switch of
therapy, disenrollment, or end of the study.

<table>
<thead>
<tr>
<th></th>
<th>Apixaban (N=8,785)</th>
<th>Dabigatran (N=20,963)</th>
<th>Rivaroxaban (N=30,529)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n/N (%)</td>
<td>Unadjusted Incidence (%/year)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>355</td>
<td>4.0</td>
<td>14.5</td>
</tr>
<tr>
<td>ICH</td>
<td>41</td>
<td>0.5</td>
<td>1.7</td>
</tr>
<tr>
<td>GI</td>
<td>98</td>
<td>1.1</td>
<td>4.0</td>
</tr>
<tr>
<td>Other</td>
<td>238</td>
<td>2.7</td>
<td>9.7</td>
</tr>
<tr>
<td>CRNM</td>
<td>747</td>
<td>8.5</td>
<td>30.5</td>
</tr>
<tr>
<td>GI</td>
<td>243</td>
<td>2.8</td>
<td>9.9</td>
</tr>
<tr>
<td>Other</td>
<td>536</td>
<td>6.1</td>
<td>21.9</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>975</td>
<td>11.1</td>
<td>39.9</td>
</tr>
</tbody>
</table>

Tepper P, et al. ESC abstract 2015
**GI Bleeding: 86% of all Major Bleeds**

**US DoD Database Analysis**

- 51,842 NVAF patients taking rivaroxaban were included

<table>
<thead>
<tr>
<th>MB Incidence Rate per 100 person-years (95% CI)*</th>
<th>MB Cases N=1613</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>2.71 (2.58–2.84)</td>
</tr>
<tr>
<td><strong>Intracranial</strong></td>
<td>1386 (85.9)</td>
</tr>
<tr>
<td><strong>Genitourinary</strong></td>
<td>133 (8.2)</td>
</tr>
<tr>
<td><strong>Other/Unspecified</strong></td>
<td>14 (0.9)</td>
</tr>
<tr>
<td><strong>Fatal MB Incidence Rate per 100 person-years (95% CI)#</strong></td>
<td>0.08 (0.06–0.11)</td>
</tr>
</tbody>
</table>

*The MB incidence rate was calculated using person-time for the denominator value (exposure time at risk) for all first major bleeding events within the study period; #Occurred during hospitalization for the MB event

*Tamayo S et al, Circulation 2016:134:A15047*
Major Bleeding with NOACs

- Truven MarketScan® US claims database
- NVAF patients
- Aged ≥18 years
- Newly prescribed oral anticoagulant
- 01Jan2013–31Dec2014
- 1-year baseline period
- Major bleeding: bleeding requiring hospitalization
- Propensity score matching
- No efficacy data

Bleeding in Renal Disease

<table>
<thead>
<tr>
<th>Event</th>
<th>No. of Person-yr</th>
<th>No. of Events</th>
<th>Event Rate per 100 Person-yr (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or thromboembolism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No renal disease</td>
<td>461,134</td>
<td>16,648</td>
<td>3.61 (3.55–3.66)</td>
</tr>
<tr>
<td>Non–end-stage CKD</td>
<td>13,078</td>
<td>842</td>
<td>6.44 (6.02–6.89)</td>
</tr>
<tr>
<td>Disease requiring renal-replacement therapy</td>
<td>2,922</td>
<td>164</td>
<td>5.61 (4.82–6.54)</td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No renal disease</td>
<td>457,605</td>
<td>16,195</td>
<td>3.54 (3.48–3.59)</td>
</tr>
<tr>
<td>Non–end-stage CKD</td>
<td>12,515</td>
<td>1,097</td>
<td>8.77 (8.26–9.30)</td>
</tr>
<tr>
<td>Disease requiring renal-replacement therapy</td>
<td>2,734</td>
<td>243</td>
<td>8.89 (7.84–10.08)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No renal disease</td>
<td>480,745</td>
<td>9,037</td>
<td>1.88 (1.84–1.92)</td>
</tr>
<tr>
<td>Non–end-stage CKD</td>
<td>13,500</td>
<td>784</td>
<td>5.81 (5.41–6.23)</td>
</tr>
<tr>
<td>Disease requiring renal-replacement therapy</td>
<td>2,925</td>
<td>175</td>
<td>5.98 (5.16–6.94)</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No renal disease</td>
<td>493,305</td>
<td>55,297</td>
<td>11.21 (11.12–11.30)</td>
</tr>
<tr>
<td>Non–end-stage CKD</td>
<td>14,052</td>
<td>5,431</td>
<td>38.65 (37.63–39.69)</td>
</tr>
<tr>
<td>Disease requiring renal-replacement therapy</td>
<td>3,114</td>
<td>914</td>
<td>29.35 (27.51–31.32)</td>
</tr>
</tbody>
</table>

**NOACs: Meta-Analysis of the Four “Registration” Trials**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic Stroke</td>
<td>0.92 (0.83-1.02)</td>
</tr>
<tr>
<td>ICH</td>
<td>0.48 (0.39-0.59)</td>
</tr>
<tr>
<td>GI bleed</td>
<td>1.26 (1.01-1.55)</td>
</tr>
<tr>
<td>Major bleed</td>
<td>0.86 (0.73-1.00)</td>
</tr>
<tr>
<td>All cause death</td>
<td>0.90 (0.85-0.95)</td>
</tr>
</tbody>
</table>
Are there still contraindicated patients?

- Intolerant to OAC
- Refuse to take anticoagulant
- Elderly Patients/Fragile patients
- Concomitant Aspirin/Clopidogrel/Ticagrelor
- Pts who are active lifestyle/sports
- Pts with high HAS-BLED scores
- Pts who bleed on NOACs or Warfarin
- INR’s NOT in therapeutic range more than 66%
- Taking inappropriate doses of NOACs due to concern about bleeding
Left Atrial Appendage with WATCHMAN Implant
## WATCHMAN™ - Most Studied LAAC Device

<table>
<thead>
<tr>
<th>Trial</th>
<th>Years</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilot</td>
<td>2003-2005</td>
<td>66</td>
</tr>
<tr>
<td>PROTECT AF</td>
<td>2005-2008</td>
<td>707</td>
</tr>
<tr>
<td>CAP</td>
<td>2008-2010</td>
<td>566</td>
</tr>
<tr>
<td>ASAP</td>
<td>2009-2011</td>
<td>150</td>
</tr>
<tr>
<td>PREVAIL</td>
<td>2010-2012</td>
<td>407</td>
</tr>
<tr>
<td>CAP2</td>
<td>2012-2014</td>
<td>579</td>
</tr>
<tr>
<td>EWOLUTION</td>
<td>2013-2015</td>
<td>1020</td>
</tr>
<tr>
<td>WASP</td>
<td>2014-2015</td>
<td>201</td>
</tr>
<tr>
<td>NESTed PAS</td>
<td>2017</td>
<td>2000</td>
</tr>
<tr>
<td>SALUTE</td>
<td>2017</td>
<td>42</td>
</tr>
<tr>
<td>ASAP-TOO</td>
<td>2016-2017</td>
<td>Up to 888</td>
</tr>
<tr>
<td><strong>Total patients</strong></td>
<td></td>
<td>&gt;6,000*</td>
</tr>
</tbody>
</table>

### Highlights

- **Pilot (2003-2005)**: Feasibility trial assessing the feasibility of implanting a device in the left atrial appendage (LAA).
- **PROTECT AF (2005-2008)**: Prospective, randomized 2:1, non-inferiority trial of LAA closure vs. warfarin.
- **CAP (2008-2010)**: Prospective registry allowing continued access to the WATCHMAN Device and gain further information prior to PMA approval.
- **ASAP (2009-2011)**: Prospective registry to evaluate appendage closure in a population contraindicated to warfarin therapy.
- **PREVAIL (2010-2012)**: Prospective, randomized 2:1, non-inferiority trial to collect additional information on the WATCHMAN Device.
- **CAP2 (2012-2014)**: Prospective registry allowing continued access to the WATCHMAN Device prior to PMA approval.
- **EWOLUTION (2013-2015)**: Prospective registry allowing all patients receiving a WATCHMAN Device at participating centers in Europe, Middle East and Russia.
- **WASP (2014-2015)**: Prospective registry allowing all patients receiving a WATCHMAN Device at participating centers in East Asian, Australia, and Saudi Arabia.
- **NESTed PAS (2017)**: Prospective registry designed to assess safety and effectiveness of the WATCHMAN Device in real world use (US only).
- **SALUTE (2017)**: Prospective non-randomized trial to evaluate the safety and effectiveness of WATCHMAN in Japanese Medical Environment.
- **ASAP-TOO (2016-2017)**: Prospective randomized 2:1, superiority trial of WATCHMAN in patients not suitable for oral anti-coagulation therapy.
- **Total patients**: >6,000* >10,000 Patient-Years of Follow-up.
Procedural Success

* The EWOLUTION Registry is a European prospective registry which reflects CE Mark indications for use which differ from the FDA indications for use. Boersma, L.et al. EHJ 2016; 37(31): 2465
Favorable Procedural Safety Profile: All Device & Procedure-related SAE within 7 Days

Majority of Patients Able to Stop Long Term Warfarin Therapy

<table>
<thead>
<tr>
<th>Study*</th>
<th>45-day</th>
<th>12-month</th>
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<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>
</tbody>
</table>

³ Holmes, DR et al. JACC 2014; 64(1):1-12.; CAP2 N/R
Pts with known medication: N = 997

Pts without FU information: N = 52

Pts with first medication discontinuation info: N = 945

Post-implant
- sAPT: 60%
- DAPT: 27%
- none: 7%
- OAC: 6%

After first discontinuation
- sAPT: 55%
- DAPT: 28%
- none: 9%
- OAC: 8%

OAC drop within 3 mo
DAPT drop within 6 mo
Conclusions

1. Ablation of AF has become a first line approach for many patients
2. Anticoagulation therapy is still not prescribed in many patients who qualify
3. LAA occlusion (WATCHMAN) is tried and true therapy and should be considered for most patients who cannot tolerate or do not want anticoagulation