Atrial Fibrillation

ESC Guidelines: Paroxysmal Atrial Fibrillation

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Declaration of Interest

Advisor / Speaker / Investigator:

Bristol Myers Squibb, Pfizer, Daiichi, Servier, Sanofi, Boehringer Ingleheim, Takeda, Bayer Pharma AG, MSD, Astellas, Menarini, Solvay Pharma, Mitsubishi Pharma, Richmond Pharmacology
“Paradoxes” of Paroxysmal Atrial Fibrillation

- Definitions
- Detection / “measurement”
- Anticoagulation - AHREs
- Progression
- Early intervention
- Ablation as first choice
“Paradox” of Paroxysmal Atrial Fibrillation: Definitions

- **ESC definition:** Paroxysmal AF is self-terminating, usually within 48 h, although AF paroxysms may continue for up to 7 days...

- **Definitions in clinical trials:** from 30 sec – 1 min to 7 days
"Paradox" of Paroxysmal Atrial Fibrillation: How to Measure PAF

The intensity and duration of monitoring should be determined by the clinical need to establish the diagnosis.

- Time to 1st event:
  - Any AF event
  - AF event > 1 hour
  - Symptomatic AF event

- Cumulative AF duration/burden:
  - Time to > \( \Sigma \) 24 h AF

- Persistent AF onset:
  - Time to last AF event, if > 24 h

- Cardiovascular outcomes (death, hospitalisation, stroke, HF, MI):
  - Sinus rhythm
  - Asymptomatic AF episode
  - Symptomatic AF episode
## How to Measure PAF: AF Burden Concept

<table>
<thead>
<tr>
<th>Study</th>
<th>No of pts</th>
<th>Drug</th>
<th>Design</th>
<th>Definition of AF burden</th>
<th>AF monitoring</th>
<th>Duration of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>J-RHYTHM II, 2011</td>
<td>318</td>
<td>Candesartan vs amlodipine</td>
<td>OL, no placebo</td>
<td>Number of days with AF per month (difference between baseline and the final month)</td>
<td>Daily TTM</td>
<td>12 months</td>
</tr>
<tr>
<td>ANTIPAF (NCT 00098137),</td>
<td>425</td>
<td>Olmesartan</td>
<td>DB, PC</td>
<td>% days with AF (number of days with AF / total days)</td>
<td>Daily TTM</td>
<td>12 months</td>
</tr>
<tr>
<td>reported 2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARYx, 2009</td>
<td>6</td>
<td>Budiodarone (ATI-2042)</td>
<td>OL, dose-escalating, no placebo</td>
<td>% time in AF (time in AF divided by the total time in each study period)</td>
<td>EGM data</td>
<td>12 weeks</td>
</tr>
<tr>
<td>PASCAL (NCT 00389792),</td>
<td>72</td>
<td>Budiodarone</td>
<td>DB, PC, dose-escalating</td>
<td>% time in AF (change from baseline over 12 weeks of treatment compared with placebo)</td>
<td>EGM data</td>
<td>20 weeks</td>
</tr>
<tr>
<td>reported 2009</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HESTIA (NCT 01135017),</td>
<td>430</td>
<td>Dronedarone</td>
<td>DB, PC, parallel group</td>
<td>% of time in AF</td>
<td>EGM data</td>
<td>12 months</td>
</tr>
<tr>
<td>ongoing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT 01356914, planned</td>
<td>20</td>
<td>BMS-914392</td>
<td>DB, PC, 4-way crossover</td>
<td>Not specified</td>
<td>EGM data</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

*Savelieva I, et al. Europace 2011*
PAF Assessed as AF Burden: PASCAL Study

(P)aroxysmal (A)trial fibrillation (S)tudy with (C)ontinuous (A)trial fibrillation (L)ogging

Reduction in AF burden from baseline at 1-3 months, %

Phase IIb PASCAL

n = 72
PAF and DDD PM
Dose ranging:
200, 400, 600 mg bid
Parallel Groups
Duration: 4 weeks baseline
12 weeks DB therapy

ATI-2042 dose, mg bid

<table>
<thead>
<tr>
<th>Placebo</th>
<th>200</th>
<th>400</th>
<th>600</th>
<th>600*</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>-10</td>
<td>-54</td>
<td>-75</td>
<td>-83</td>
</tr>
</tbody>
</table>

Overall p=0.0001

http://ClinicalTrials.gov
AHRE and Risk of Stroke or Death: *Post hoc* Analysis from the MOST Study

- Ancillary MOST Study
- 312 patients
- Event logged if AR > 220 bpm for 10 beats


AHR predicts
- Total mortality 2.48 [1.25-4.91], p = 0.0091
- Death or non-fatal stroke 2.79 [1.51-5.15], p = 0.0011
- AF 5.93 [2.88-12.2], p = 0.0001
**ASSERT Study:**  
Ischemic Stroke or Systemic Embolism

**Cumulative Hazard Rates**

<table>
<thead>
<tr>
<th>Year</th>
<th># at Risk</th>
<th>0.00</th>
<th>0.02</th>
<th>0.04</th>
<th>0.06</th>
<th>0.08</th>
<th>0.10</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>+ 261</td>
<td>249</td>
<td>238</td>
<td>218</td>
<td>178</td>
<td>122</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- 2319</td>
<td>2145</td>
<td>2070</td>
<td>1922</td>
<td>1556</td>
<td>1197</td>
<td></td>
</tr>
</tbody>
</table>

RR=2.49  
95% CI 1.28-4.85  
p=0.007

**Device-Detected AHREs**

- detected 0-3 months

**No AHREs**

- detected 0-3 months

# Monitoring of AF by Implantable Devices and Outcome: Clinical Trials and Registries

<table>
<thead>
<tr>
<th>Study</th>
<th>TRENDS NCT00279981</th>
<th>ASSERT NCT00256152</th>
<th>IMPACT NCT00559988</th>
<th>RATE Registry NCT00837798</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Medtronic</td>
<td>St Jude</td>
<td>Biotronik</td>
<td>St. Jude</td>
</tr>
<tr>
<td># patients</td>
<td>2486</td>
<td>2580</td>
<td>2718</td>
<td>5000</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Class I/II indication for DDD PM, ICD or CRT; CHADS₂ ≥1 (age ≥65)</td>
<td>Class I/II indications for pacing; no previous AF; age ≥ 65 with hypertension</td>
<td>Class I/II ICD or CRT-D indications; CHADS₂ ≥1</td>
<td>Conventional indications for PM or ICD</td>
</tr>
<tr>
<td>Device and monitoring</td>
<td>Device interrogation every 3 mos; AHRE ≥20 s detected; AF burden in 30-day rolling window</td>
<td>Identity ADx DR or similar; device interrogation every 6 mos; AHRE &gt; 190 bpm, &gt; 6-min detected</td>
<td>Lumax HF-T or DR-T with home monitoring for AF &gt; 48 h and active OAC upon detection</td>
<td>Victory, Atlas II, Frontier II, etc., with advanced AT/AF diagnostics</td>
</tr>
<tr>
<td>1ˢᵗ endpoint</td>
<td>Ischemic stroke, TIA, SE</td>
<td>Composite: ischemic stroke and SE</td>
<td>Composite: stroke, SE, major bleed</td>
<td>AT/AF burden and frequency; patterns of AF onset; CHF; stroke or SE; QoL; therapy; hospitalizations for AF and CHF; inappropriate shocks; mortality</td>
</tr>
<tr>
<td>2ⁿᵈ endpoints</td>
<td>QoL; costs; VR; AF progression; impact of new onset AF</td>
<td>ECG-documented AF; composite of MI, vascular death, SE, CHF admission; AF burden; major bleed</td>
<td>ACM, stroke (any); major bleed; AF burden; QoL; HR</td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>Mean, 1.4 years Published in full 2010</td>
<td>Mean 2.8 years Results November 2010</td>
<td>Completion expected 2014</td>
<td>Completion expected 2014</td>
</tr>
</tbody>
</table>
CHA\textsubscript{2}DS\textsubscript{2}-VASc-guided Anticoagulation

Assess Thromboembolic Risk (CHA\textsubscript{2}DS\textsubscript{2} VASc) and Bleeding Risk (HAS-BLED)

- **CHADS\textsubscript{2} < 2**
  - CHA\textsubscript{2}DS\textsubscript{2} VASc=0
    - No antithrombotic over Aspirin
  - CHA\textsubscript{2}DS\textsubscript{2} VASc ≥ 1
    - OAC preferred over Aspirin

- **CHADS\textsubscript{2} ≥ 2**
  - OAC

CHA\textsubscript{2}DS\textsubscript{2}-VASc to be used for initial risk stratification
### CHA₂DS₂-VASc

<table>
<thead>
<tr>
<th>Score</th>
<th>Annual stroke rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>2</td>
<td>2.2</td>
</tr>
<tr>
<td>3</td>
<td>3.2</td>
</tr>
<tr>
<td>4</td>
<td>4.0</td>
</tr>
<tr>
<td>5</td>
<td>6.7</td>
</tr>
<tr>
<td>6</td>
<td>9.8</td>
</tr>
<tr>
<td>7</td>
<td>9.6</td>
</tr>
<tr>
<td>8</td>
<td>6.7</td>
</tr>
<tr>
<td>9</td>
<td>15.2</td>
</tr>
</tbody>
</table>

- **Congestive heart failure/ LV dysfunction**
- **Hypertension**
- **Age ≥ 75**
- **Diabetes mellitus**
- **Stroke/TIA/TE**
- **Vascular disease** (CAD, CArD, PAD)
- **Age 65-74**
- **Sex category (female)**

Score 0 – 9

Validated in 1084 NVAF pts not on OAC with known TE status at 1 year in Euro Heart Survey.

OR for stroke if:
- Female: 2.53 (1.08 – 5.92), p=0.029
- Vascular disease: 2.27 (0.94 – 5.46), p=0.063
Are AHREs Risk Factors or Markers?

Substudies from ASSERT

- AHREs of any duration (ranging from ≥ 6 min to ≥ 24-48 h) had similar risk of stroke.
- There was no clear temporal relationship between AHREs and imminent stroke; risk remained increased after the occurrence of AHRE for the duration of follow-up.
- Only 6 of 59 strokes were associated with AHRE > 6 min within 1 month of the episode.
- Need to be incorporated in CHA₂DS₂-VASc?
Natural History and Progression from Paroxysmal to Permanent AF

Study | No. of pts | Follow-up, years | Progression to permanent AF
--- | --- | --- | ---
Euro Heart Survey, 2010 | 1219 | 1 | 15%
Tokyo study, 1995 | 137 | 1 | 22%
UK general practice, 2005 | 525 | 2.7 | 17%
CARAF, 2001 | 899 | 4.14 | 19%
Italian study (Pappone), 2008 | 106 | 5 | 28.8%
CARAF, 2005 | 757 | 8 | 25%
Danish study, 1986 | 426 | 9 | 33%
Parkinson, 1930 | 200 | 10 | 25%
Tokyo study, 2004 | 171 | 14 | 77%
Olmsted County (lone AF), 2007 | 71 | 25.2 | 31%

Progression of AF: HATCH

- Euro Heart Survey on AF
- 1219 patients with PAF
- Follow-up: 1 year
- Progression: 178 (15%)

- Hypertension x 1, Age > 75 yrs x 1, Stroke/TIA x 2, COPD x 1, Heart failure x 2

De Vos CB, et al. JACC 2010;55:725-31
Progression of AF: RECORD-AF

- Enrolled AF within 1 year of diagnosis
- 2,137 patients with PAF
- Follow-up: 1 year
- Progression: 318 (15%)

Progression to persistent AF

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1.5 (1.1 - 2.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>CHF</td>
<td>2.2 (1.7 - 9.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rate vs rhythm control</td>
<td>3.2 (2.5 - 4.1)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Early Intervention Impacts Progression?

- Age 58 ± 12 years
- LAD dimension < 40 mm: 87% pts
- “Lone” AF: 51% pts
- Comorbidities predicted progression

Consent not provided (n = 52)
Inclusion criteria not met (n = 244)

Enrolled patients with first paroxysmal AF (n = 106)

Paroxysmal recurrent AF (n = 56)

ADT (n = 56)

Ablation (n = 11)

Persistent AF (n = 24)

No treatment
No recurrence
No progression
(n = 50)

No recurrence
(n = 11)

Progression to permanent AF (n = 16)

Remaining persistent AF (n = 8)

Paroxysmal recurrent AF (n = 21)

Time Course of Atrial Substrate Remodeling: When to Intervene

ECV and maintain SR to prevent remodelling

Secondary prevention

Primary prevention

Paroxysmal Persistent Permanent

Years +5 +10 +15 +20

## RCTs of Ablation vs AADs or No Treatment in AF

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Type of AF</th>
<th>Previous use of AAD</th>
<th>Crossed to ablation in the AAD group</th>
<th>AF free at 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krittayaphong, et al. 2003</td>
<td>30</td>
<td>Paroxysmal, persistent</td>
<td>≥1</td>
<td>Not stated</td>
<td>79% 40%</td>
</tr>
<tr>
<td>Wazni, et al. 2005, (RAAFT)</td>
<td>70</td>
<td>Mainly paroxysmal</td>
<td>No</td>
<td>49%</td>
<td>87% 37%</td>
</tr>
<tr>
<td>Stabile, et al. 2005 (CACAF)</td>
<td>137</td>
<td>Paroxysmal, persistent</td>
<td>≥2</td>
<td>57%</td>
<td>56% 9%</td>
</tr>
<tr>
<td>Oral, et al. 2006</td>
<td>146</td>
<td>Persistent</td>
<td>≥1 (mean 2.1±1.2)</td>
<td>77%</td>
<td>74% 4%</td>
</tr>
<tr>
<td>Pappone, et al. 2006 (APAAF)</td>
<td>198</td>
<td>Paroxysmal</td>
<td>≥2 (mean 2±1)</td>
<td>42%</td>
<td>86% 22%</td>
</tr>
<tr>
<td>Jais, et al. 2008, (A4 study)</td>
<td>112</td>
<td>Paroxysmal</td>
<td>≥1</td>
<td>63%</td>
<td>89% 23%</td>
</tr>
<tr>
<td>Forleo, et al. 2008</td>
<td>70</td>
<td>Paroxysmal, persistent</td>
<td>≥1</td>
<td>Not stated</td>
<td>80% 43%</td>
</tr>
<tr>
<td>Wilber, et al. 2009 (Thermocool)</td>
<td>167</td>
<td>Paroxysmal</td>
<td>≥1 (mean 1.3)</td>
<td>59%</td>
<td>66% 16%</td>
</tr>
<tr>
<td>Packer, et al. 2010, (STOP-AF)</td>
<td>245</td>
<td>Paroxysmal</td>
<td>≥1</td>
<td>79%</td>
<td>69.9% 7.3%</td>
</tr>
</tbody>
</table>

*Modified from Savelieva I and Camm J. Nat Rev Cardiol 2009;6:332-4*
Recommendation for Catheter Ablation: Patients with No Significant Structural Heart Disease

No or minimal heart disease (including HT without LVH)

Paroxysmal

Persistent

Catheter ablation

Dronedarone
Flecainide
Propafenone
Sotalol

ESC Recommendation

<table>
<thead>
<tr>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>A</td>
</tr>
</tbody>
</table>

Catheter ablation for paroxysmal AF should be considered in symptomatic patients who have previously failed a trial of antiarrhythmic medication.

Ablation of persistent symptomatic AF that is refractory to antiarrhythmic therapy should be considered a treatment option.

Catheter ablation of AF may be considered prior to antiarrhythmic drug therapy in patients with paroxysmal symptomatic AF despite adequate rate control and no significant underlying heart disease.

Amiodarone
Ablation as First-line Therapy: RAAFT II

Radiofrequency ablation versus Antiarrhythmic drugs in Atrial Fibrillation Trial

- N = 127, mean age 55 years, 87.5% PAF
- Mean # episodes: 48 in the ablation group vs 33 in the AAD group
- AADs: flecainide and propafenone
- TTM every 2 weeks and during symptoms
- 1º endpoint: symptomatic or asymptomatic recurrence at 2 years
- Cross-over: 10.6% vs 47.5%; re-ablation: 15.2%

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Ablation N = 66 (%)</th>
<th>AAD N = 61 (%)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AF, flutter, AT</td>
<td>55</td>
<td>72</td>
<td>0.56 (0.35 – 0.90)</td>
<td>0.02</td>
</tr>
<tr>
<td>Symptomatic AF, flutter, AT</td>
<td>47</td>
<td>59</td>
<td>0.56 (0.33 – 0.95)</td>
<td>0.03</td>
</tr>
<tr>
<td>Symptomatic AF</td>
<td>41</td>
<td>58</td>
<td>0.52 (0.30 – 0.89)</td>
<td>0.01</td>
</tr>
<tr>
<td>Clinical recurrence</td>
<td>24</td>
<td>31</td>
<td>0.86 (0.42 – 1.72)</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Complications: 7.7% versus 19.7%
Ablation as First-line Therapy: MANTRA-PAF

Medical ANtiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation

- N = 294 with PAF
- Follow-up: 2 years (n = 194)
- 7-day Holter at 3, 6, 12, 18, 24 months
- 1º endpoint: cumulative AF burden over 35 days and in follow-up
- 2º endpoints: any AF and symptomatic AF at 24 months, burden of symptomatic AF at each follow-up interval, flutter, QoL, SAEs

No difference in primary endpoint
Improvement in QoL

Cosedis Nielsen J, et al. NEJM 2012 [In press]
Recommendation for Catheter Ablation: Patients with Structural Heart Disease

ESC Recommendation

<table>
<thead>
<tr>
<th>Relevant structural heart disease</th>
<th>Clas</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension with LVH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA III/IV or unstable II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable NYHA I-II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dronedarone</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Dronedarone Sotalol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dronedarone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter ablation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Catheter ablation of AF in patients with heart failure may be considered when antiarrhythmic medication, including amiodarone, fails to control symptoms.

Catheter ablation of AF may be considered in patients with symptomatic long-standing persistent AF refractory to antiarrhythmic drugs.
## On-going Trials of Catheter Ablation

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Study Title</th>
<th>N</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARA</td>
<td>Study of Ablation versus anti-arrhythmic drugs in persistent Atrial fibrillation</td>
<td>208</td>
<td>Freedom from AF &gt; 24 hrs</td>
</tr>
<tr>
<td>AATAC</td>
<td>Ablation vs Amiodarone for Treatment of Atrial fibrillation in patients with CHF and an ICD</td>
<td>120</td>
<td>AF &gt; 15sec</td>
</tr>
<tr>
<td>CASTLE-AF</td>
<td>Catheter Ablation versus Standard conventional Treatment in patients with Left ventricular dysfunction and Atrial Fibrillation</td>
<td>400</td>
<td>All-cause mortality and HF hospitalisations</td>
</tr>
<tr>
<td>CABANA</td>
<td>Catheter Ablation versus Antiarrhythmic drug therapy for Atrial fibrillation</td>
<td>3000</td>
<td>All-cause mortality</td>
</tr>
<tr>
<td>EAST</td>
<td>Early Atrial fibrillation Stroke Prevention Trial</td>
<td>3000</td>
<td>All-cause mortality + CV hospitalisations</td>
</tr>
</tbody>
</table>
### Recommendations for Secondary Prevention of AF with Upstream Therapy

<table>
<thead>
<tr>
<th>ESC Recommendation</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment with ARBs or ACEIs may be considered in patients with recurrent AF undergoing electrical cardioversion and receiving antiarrhythmic drug therapy</td>
<td>IIB</td>
<td>B</td>
</tr>
<tr>
<td>ARBs or ACEIs may be useful for prevention of recurrent paroxysmal AF or in patients with persistent AF in the absence of significant structural heart disease if these agents are indicated for other reasons (e.g. hypertension)</td>
<td>IIB</td>
<td>B</td>
</tr>
</tbody>
</table>
ANTIPAF: Angiotensin II ANTAGonist In Paroxysmal Atrial Fibrillation

Primary endpoint:
Percentage of days with documented episodes of PAF (number of days with PAF divided by number of days with TTM recording) during 1-year follow-up

- 425 patients with documented PAF and SR (≤ 6 months)
- Placebo vs Olmesartan 40 mg
- Age ~ 61 years, men ~ 60%, HTN ~ 50%, LAE ~ 35%

No difference in AF burden, cumulative incidence of all AF (symptomatic and asymptomatic), or progression to persistent AF

Intervene Early to Prevent PAF

- PAF is a progressive disease due to remodeling associated with ageing, underlying heart disease, and AF itself
- Insufficient, unstructured and delayed therapy of AF is a likely contributor to the limited efficacy of rhythm control therapy
- Ablation is a viable first-line therapy for PAF in (still) selected patients
- Whether early and comprehensive rhythm control therapy including ablation is beneficial is currently being tested
Thank you!

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University of London