Rome Cardiology Forum
Update on Atrial Fibrillation
Rome, January 29th-31st 2014

Pharmacological Prevention of Atrial Fibrillation

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St. George’s University of London, UK

Conflicts of Interest: Consultant/Advisor/Speaker
Advisor / Speaker : Astra Zeneca, ChanRX, Gilead, Merck, Menarini, Otsuka, Sanofi, Servier, Xention, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi, Pfizer, Boston Scientific, Biotronik, Medtronic, St. Jude Medical, Actelion, GlaxoSmithKline, InfoBionic, Incarda, Johnson and Johnson, Mitsubishi, Novartis, Takeda
History of Antiarrhythmic Drugs

1914 – Quinidine

1920

1921 – Quinidine

1950 – Lidocaine
1951 – Procainamide
1956 – Ajmaline
1962 – Disopyramide

1967 – Amiodarone

1972 – Mexiletine
1973 – Aprindine, Tocainide
1975 – Flecaïnide
1976 – Propafenone
1985 – Sotalol

2000 – Dofetilide

2009 – Dronedarone
2010 – Vernakalant

AF Only

ICD, 1980

CAST, 1989

1962 – Verapamil
1964 – Propranolol
1965 – Bretylium
1969 – Diltiazem

1962 – Disopyramide

1967 – Amiodarone

2009 – Dronedarone
2010 – Vernakalant

AF Only
Antiarrhythmic Medical Therapies

Class Ia: Disopyramide, Quinidine, and Procainamide
- Class 1b: mexiletine, tocainide

Amiodarone
Sotalol
Nexterone and Budio-darone

Class III
Antiarrhythmic Agents
New and Old

Beta blocker

Propafenone
Flecainide

New Class III Agents

Beta blocker

Novel Drugs
- SAC Blockers
- Na+/H+ Inhibitor
- Na+/Ca2+ Inhibitor
- Rotigaptide Dangaptide
- Ranolazine
- NTC-801
- Chloroquine
- Xen 0103
- Colchicine

Upstream therapies

USA only
ICD/VT only
Abandoned
Abandoned

Multi-channel blockers

Modified from Savelieva I and Camm AJ. Europace 2008:10:647–65
SAFE-T Sotalol Amiodarone AF Efficacy Trial

- VA Cooperative Study
- N=665, 20% AF >1 year:
- Amio 267, Sot 261, Placebo 137

Follow-up 1 year with TTM weekly

1° EP: time to 1st AF recn after CV

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AADs for Mortality Reduction after DCC
Systematic Review of RCTs

Rates of Mortality and Hospitalizations

AFFIRM Study by Treatment Group

### Main Ion Channel/Receptor Effects

<table>
<thead>
<tr>
<th>Outward currents</th>
<th>Dronedarone</th>
<th>Amiodarone</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_{Kr}$ (ventricle) Guinea pig (IC$_{50}$; µM)</td>
<td>2–3</td>
<td>10</td>
</tr>
<tr>
<td>$I_{Ks}$ (ventricle) Guinea pig (IC$_{50}$; µM)</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>$I_{K1}$ (ventricle) Guinea pig (IC$_{50}$; µM)</td>
<td>&gt;30</td>
<td>&lt;30</td>
</tr>
<tr>
<td>$I_{K(Ach)}$ (atrium) Guinea pig (IC$_{50}$; µM)</td>
<td>0.01</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inward currents</th>
<th>Dronedarone</th>
<th>Amiodarone</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_{Na}$ (human; 3 µM)</td>
<td>97% block</td>
<td>41% block</td>
</tr>
<tr>
<td>$I_{Ca(L)}$ (Guinea pig; 10 µM)</td>
<td>76% block</td>
<td>85% block</td>
</tr>
<tr>
<td>Beta blockade (IC$_{50}$; µM)</td>
<td>1.8</td>
<td>8.7</td>
</tr>
</tbody>
</table>
ATHENA: Primary Outcome

Time to first cardiovascular hospitalization or death

Mean follow-up 21 ± 5 months.

Patients at risk

Placebo  | 2327 | 1858 | 1625 | 1072 | 385 | 3
Dronedarone  | 2301 | 1963 | 1776 | 1177 | 403 | 2

HR = 0.76
P < 0.001

Dronedarone as an Antiarrhythmic
Examples from ATHENA

Time to 1st DCV
Cumulative incidence, %

- Placebo
- Dronedarone

HR = 0.69
p < 0.001

Time to 1st AF/AFL
Cumulative incidence of AF/AFL, %

- Placebo
- Dronedarone

HR = 0.75
p < 0.001

No. in Permanent AF

- Placebo
- Dronedarone

p < 0.001

All AF related hospitalization:
HR = 0.626, 95% CI = [0.54; 0.73]
First AF related hospitalization:
HR = 0.63, 95% CI = [0.55; 0.72]

Was Antiarrhythmic Effect Important?

Permanent AF Patients

Mean follow-up 21 ± 5 months - on Study
# PALLAS

**Permanent Atrial fibrillation outcome Study**

- **Screen**
  - Permanent AF ≥ 6m + CV risk
  - No NYHA unstable III or IV NYHA CHF

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## 1<sup>st</sup> Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Dronedarone (n = 1619)</th>
<th>Placebo (n = 1617)</th>
<th>Dronedarone vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>%/yr</strong></td>
<td>8.2</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td><strong>HR</strong></td>
<td>2.29</td>
<td>1.34-3.94</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**1<sup>st</sup> Co-primary (Stroke/MI/SEE/CV Death)**

- Events: 43
- %/yr: 8.2
- Placebo: Events: 19
- %/yr: 3.6
- HR: 2.29
- 95% CI: 1.34-3.94
- P value: 0.002

**2<sup>nd</sup> Co-primary (All Death/Unplanned CV Hospitalization)**

- Events: 127
- %/yr: 25.3
- Placebo: Events: 67
- %/yr: 12.9
- HR: 1.95
- 95% CI: 1.45-2.62
- P value: <0.001

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## ATHENA (Overall) vs PALLAS Risk Factors

<table>
<thead>
<tr>
<th>PALLAS Risk Factors</th>
<th>ATHENA (Overall)</th>
<th>PALLAS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dronedarone n = 2301 %</td>
<td>Placebo n = 2327 %</td>
</tr>
<tr>
<td>CAD</td>
<td>28.7</td>
<td>31.3</td>
</tr>
<tr>
<td>Prior Stroke/TIA</td>
<td>7.3</td>
<td>7.1</td>
</tr>
<tr>
<td>Symptomatic HF</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LVEF ≤ 40%</td>
<td>4.2</td>
<td>4.7</td>
</tr>
<tr>
<td>Peripheral Arterial Disease</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age ≥ 75 with HTN &amp; Diabetes</td>
<td>2.1</td>
<td>2.7</td>
</tr>
</tbody>
</table>

## Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N</th>
<th>HR [95% CI] a</th>
<th>Hazard Ration (95% CI)</th>
<th>P value b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td>1.95 [1.45;2.62]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75</td>
<td>1562</td>
<td>2.24 [1.42;3.52]</td>
<td></td>
<td>0.423</td>
</tr>
<tr>
<td>≥75</td>
<td>1674</td>
<td>2.75 [1.19;2.59]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of perm. AF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months to 2 years</td>
<td>988</td>
<td>1.91 [1.20;3.04]</td>
<td></td>
<td>0.945</td>
</tr>
<tr>
<td>&gt;2 years</td>
<td>2243</td>
<td>1.94 [1.32;2.85]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline LVEF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF≤40%</td>
<td>680</td>
<td>2.17 [1.15;4.07]</td>
<td></td>
<td>0.717</td>
</tr>
<tr>
<td>LVEF&gt;40%</td>
<td>2556</td>
<td>1.89 [1.35;2.64]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No class II/III</td>
<td>1490</td>
<td>2.03 [1.23;3.36]</td>
<td></td>
<td>0.842</td>
</tr>
<tr>
<td>Class II/III</td>
<td>1746</td>
<td>1.91 [1.32;2.75]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHADS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHADS ≤2</td>
<td>1326</td>
<td>1.92 [1.16;3.19]</td>
<td></td>
<td>0.933</td>
</tr>
<tr>
<td>CHADS &gt;2</td>
<td>1908</td>
<td>1.96 [1.36;2.82]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke or TIA history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>2342</td>
<td>2.12 [1.49;3.01]</td>
<td></td>
<td>0.353</td>
</tr>
<tr>
<td>Y</td>
<td>894</td>
<td>1.55 [0.88;2.72]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>1908</td>
<td>1.87 [1.23;2.84]</td>
<td></td>
<td>0.834</td>
</tr>
<tr>
<td>Y</td>
<td>1327</td>
<td>1.98 [1.30;3.01]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline HR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR &lt;65 bpm</td>
<td>644</td>
<td>3.65 [1.75;7.59]</td>
<td></td>
<td>0.057</td>
</tr>
<tr>
<td>HR ≥65 bpm</td>
<td>2591</td>
<td>1.67 [1.20;2.32]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline SBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP &lt;130 mmHg</td>
<td>1468</td>
<td>1.84 [1.19;2.83]</td>
<td></td>
<td>0.805</td>
</tr>
<tr>
<td>SBP ≥130 mmHg</td>
<td>1708</td>
<td>1.97 [1.30;2.98]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>2166</td>
<td>2.07 [1.44;2.97]</td>
<td></td>
<td>0.554</td>
</tr>
<tr>
<td>Y</td>
<td>1070</td>
<td>1.70 [1.02;2.83]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blocking agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>834</td>
<td>1.62 [0.97;2.71]</td>
<td></td>
<td>0.377</td>
</tr>
<tr>
<td>Y</td>
<td>2402</td>
<td>2.13 [1.48;3.07]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin K antagonist or Dabigatran</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>447</td>
<td>1.31 [0.71;2.42]</td>
<td></td>
<td>0.099</td>
</tr>
<tr>
<td>Y</td>
<td>2789</td>
<td>2.23 [1.59;3.14]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America/Western Europe</td>
<td>1512</td>
<td>2.28 [1.48;3.51]</td>
<td></td>
<td>0.300</td>
</tr>
<tr>
<td>Other regions</td>
<td>1724</td>
<td>1.67 [1.11;2.51]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a: Determined from Cox regression model
b: P-value of interaction between baseline characteristics and treatment based on cox regression model

## Post-market Experience: Magdeburg and Leipzig Registries

<table>
<thead>
<tr>
<th>Registry</th>
<th>Magdeburg (MADRE)</th>
<th>Leipzig</th>
</tr>
</thead>
<tbody>
<tr>
<td># patients</td>
<td>191</td>
<td>120</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>$63 \pm 10$</td>
<td>$67 \pm 9$</td>
</tr>
<tr>
<td>PAF, %</td>
<td>63</td>
<td>34</td>
</tr>
<tr>
<td>Duration, yrs</td>
<td>$3.6 \pm 4.1$</td>
<td>$6.1 \pm 6.8$</td>
</tr>
<tr>
<td>HTN, %</td>
<td>66</td>
<td>93</td>
</tr>
<tr>
<td>CAD, %</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>Prior AAD, %</td>
<td>63</td>
<td>19</td>
</tr>
<tr>
<td>Prior PVI</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>Follow-up, mos</td>
<td>$14.3 \pm 4.9$</td>
<td>6-9</td>
</tr>
</tbody>
</table>

### Event rate, %

<table>
<thead>
<tr>
<th>Event Type</th>
<th>MADRE</th>
<th>Leipzig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>67</td>
<td>80</td>
</tr>
<tr>
<td>Stopped</td>
<td>72</td>
<td>73</td>
</tr>
<tr>
<td>For inefficacy</td>
<td>50</td>
<td>42</td>
</tr>
<tr>
<td>For side effects</td>
<td>22</td>
<td>32</td>
</tr>
</tbody>
</table>

More effective in non-lone AF (62% vs 84%), U-shape relationship with LA size


*Said SM, et al. JCP 2013;53:841-5*
A placebo-controlled, double-blind, randomized, multi-center study to assess the effects of Dronedarone 400 mg BID for 12 weeks on atrial fibrillation (AF) burden in subjects with permanent pacemakers.

- **Patients with PAF and DDD PM**
- **Planned n = 290, Enrolled n = 112**
- **AF burden at baseline Placebo vs Dronedarone: 16% vs 21%**
- **Duration: 4 weeks baseline, 12 weeks therapy**

**1° EP: changes in AF burden from baseline at 12 weeks, %**

- Placebo: -12.8%
- Dronedarone: -54.4%
- Placebo-extracted change: -59.1%

At 12 weeks: 23 vs 18%

- 76.3 to -29.4%
  p=0.0015
Overall Results

<table>
<thead>
<tr>
<th></th>
<th>Dronedarone N=2079</th>
<th>Other AADs N=4158</th>
<th>Digoxin N=4158</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of event</td>
<td>7</td>
<td>30</td>
<td>36</td>
</tr>
<tr>
<td>Percentages p-value(1)</td>
<td>0.34% Ref</td>
<td>0.73% 0.079</td>
<td>0.87% 0.022</td>
</tr>
<tr>
<td>Event-Rate / 10,000 PM p-value</td>
<td>5.16 Ref</td>
<td>12.11 0.044</td>
<td>13.48 0.014</td>
</tr>
<tr>
<td>HR (95%CI) P-value</td>
<td>Ref</td>
<td>2.28 (1.00 – 5.20)</td>
<td>2.64 (1.18 – 5.94)</td>
</tr>
</tbody>
</table>

Propensity-score matching of 2079 patients on dronedarone and 4158 patients on “other AADs”, and 4158 on digoxin

- All-cause mortality was significantly higher in the “other AADs (p= 0.049) and digoxin (p= 0.019)

Goehring E, et al. 2013 ACC San Francisco

Hazard ratio [HR] (Other AADs vs Dronedarone = 2.28; CI:1.00 to 5.20; P <.05)
Ranolazine

New-Onset Atrial Fibrillation

\[ \Delta = 20, \quad RR = 0.74, \quad p = 0.08 \]

75 (2.3%)

55 (1.7%)

Number of patients

Sodium Current

Peak \( I_{\text{Na}} \)

Late \( I_{\text{Na}} \)

Human Cardiac NaCh in HEK293 Cells

Peak \( IC_{50} = 428 \mu M \)

Late \( IC_{50} = 6.9 \mu M \)

\( \% \text{ inhibition} \)

Concentration of Ranolazine (mM)

Rajamani S., et al., Eur Heart J. 28(1) 2007

Ranolazine versus Amiodarone
AF Prophylaxis After CABG

• Retrospective cohort study
• 393 pts undergoing CABG
• Amiodarone (400 mg preoperative followed by 200 mg twice daily for 10–14 days) - N=211 (53.7%)
• Ranolazine (1,500 mg preoperative followed by 1,000 mg twice daily for 10–14 days) - N=182 (46.3%)
• Mean age 65 ± 10 years, 72% male

Ranolazine associated independently with a reduction of post-op AF

Murdock D, et al. ACC Abstracts 2011, New Orleans, LA, USA
Synergistic Effect on AF of Combination of Ranolazine and Dronedarone

- Canine isolated coronary-perfused RA, LA, PV, and LV preparations
- Ranolazine 5 μmol/L
- Dronedarone 10 μmol/L

Pulmonary vein preparations

Induction or termination of persistent AF, %

<table>
<thead>
<tr>
<th>Condition</th>
<th>AF induction</th>
<th>AF termination</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACh</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>ACh+Dronedarone</td>
<td>83</td>
<td>1/6</td>
</tr>
<tr>
<td>ACh+Ranolazine</td>
<td>71</td>
<td>5/7</td>
</tr>
<tr>
<td>ACh+R+D</td>
<td>60</td>
<td>1/10</td>
</tr>
</tbody>
</table>

V_{\text{max}} (% of control at 5000 ms CL)

- * p < 0.05 vs control
- † p <0.05 vs R or D alone

Pharmacological Cardioversion of AF
Combination of Amiodarone and Ranolazine

- Pilot RCT
- $N = 51$ with AF $< 48$ h
- Age $63 \pm 8$ years, 65% men
- HTN 68–77%, CAD 20–27%
- I.V. amio 5 mg/kg for 1 h followed by infusion of 50 mg/h for 24 h
- I.V. amio + ranolazine 1,500 mg p.o.
- 1º EP: conversion within 24 h

SR=sinus rhythm
Vanoxerine and Pharmacologic AF CV
The COR-ART Study

Percent Conversion to NSR

- Vanoxerine: potent blocker of IKr (hERG) channel and Na and L-type Ca channel blocker
- Extensive safety experience as anti Parkinson Syndrome drug

Subjects who have been in symptomatic AF/AFL for 3 hours to <7 days

Randomized, Double-Blind, Placebo-Controlled, Dose-Modifying

- Placebo - 30 patients
- 200 mg - 25 patients
- 300 mg - 25 patients
- 400 mg - 25 patients

- No VT adverse event
- 1 sinus pause (3s) at 200 mg
- 3 QT prolongation at 400 mg

Dittrich H, et al. AHA Poster Dallas 2013
Conclusions

- Amiodarone is the best AAD drug to suppress recurrences of AF, but does not reduce mortality or hospitalisation

- Dronedarone reduces CV hospitalisations and CV mortality in patients with recurrent forms of AF

- Dronedarone should not be used in patients with permanent AF, or moderate or severe heart failure/LV dysfunction

- There have been promising reports on the antiarrhythmic potential of ranolazine, but definitive studies are awaited

- The development of many potential antiarrhythmic agents has been suspended others continue to be developed
Thank you for your attention
When Use Dronedarone

Dronedarone

Atrial Fibrillation

No Heart Failure

Heart Failure

Recurrent

Permanent

Paroxysmal

Persistent

No Dronedarone

SR

Cardioversion

RAFFAELLO: Ranolazine in Atrial Fibrillation Following An Electrical cardioversion

- Phase IIb
- ~ 40 centres in Europe (Germany, Italy, Spain, UK)
- Planned DCC off AADs; SR maintained for 2 h
- Ranolazine: 375, 500, 750 mg bd or Placebo
- Treatment duration: 16 weeks or until documented AF recurrence in need of medical intervention
- Recruitment completed (n = 260), database locked
Clinical Trial RANO+DRONE Combination: HARMONY

- PAF with pacemakers
- N = 150, 45 centres
- Follow-up: 12 weeks
- Primary endpoint: reduction in AF burden
- Secondary endpoints: AF burden at each clinic visit at 4, 8, 12 weeks and the number of AF episodes
- Expected March 2014

NCT01522651