Antiarrhythmics for atrial fibrillation – focus on dronedarone

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AF facts

- Progressive disease
- Increases risk of death ~2-fold
- Increases risk of stroke ~5-fold
- Longer time in AF => progression to permanent AF
- Synus rhythm is „God given”
What can we do to minimize "bad" and maximize "good" facts?

Rate Control
- Pharmacologic
  - Ca²⁺ blockers
  - β-blockers
  - Digitalis
  - Amiodarone
- Nonpharmacologic
  - Ablate and pace

Rhythm control
- Pharmacologic
  - Class I
  - Class III
- Nonpharmacologic
  - Catheter ablation
  - Pacing
  - Surgery (MAZE, PVI)
  - Impl. atrial defibrillator

Stroke Prevention
- Pharmacologic
  - Warfarin
  - Thrombin inhib.
  - ASA
  - dabigatran, rivaroxaban
- Nonpharmacologic
  - LA appendage removal / isolation

Prevent remodeling
- CCB
- ACEinh
- ARB

Decide on most appropriate therapy based on patient’s profile

Chronology antiarrhythmics

1785 Digitalis
1918 Quinidine
1936 Procainamide
1948 Lidocaine
1950 Phenytoin
1954 Disopyramide
1958 Ajmaline
1962 β-blocker
1964 Propafenon
1982 Flecainide
1982 Amiodarone
1994 Adenosine
1995 Ibutilide
1999 Dofetilide
2009 Dronedarone
2010 Vernakalant
The purpose of antiarrhythmics

- EKG: SR, prevent Afib; SVT; VA
- Symptoms, hospitalization
- Mortality
The disappointment

Interventions with superior effect on mortality are treating the consequences of arrhythmia:

- anticoagulation
- ICDs
Side effects

I stopped taking the medicine because I prefer the original disease to the side effects
Amiodarone - effect of reducing AF recurrence fades in the long term

A comparative study of low dose amiodarone and low dose propafenone after restoration of sinus rhythm showed that the efficacy of amiodarone is offset by a higher discontinuation rate due to AEs in the long term:

- 17% of patients receiving low dose amiodarone vs 3% receiving low dose propafenone (within 2 years)


AEs: adverse events
Despite better maintenance of SR with amiodarone vs. sotalol, there was a trend towards increased mortality vs. placebo.

SAFE-T study: Primary endpoint

![Graph showing probability of remaining in sinus rhythm over time for Amiodarone, Sotalol, and Placebo groups.]

- Amiodarone vs. sotalol, *p* < 0.001
- Amiodarone vs. placebo, *p* < 0.001
- Sotalol vs. placebo, *p* < 0.001

Deaths (N) and Mortality ratio adjusted for duration of follow-up:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Deaths (N)</th>
<th>Mortality ratio</th>
<th>P value vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>13</td>
<td>1.3</td>
<td><em>p</em> = 0.19</td>
</tr>
<tr>
<td>Sotalol</td>
<td>15</td>
<td>1.8</td>
<td><em>p</em> = 0.11</td>
</tr>
<tr>
<td>Placebo</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

* Day 0 was considered as 28 days after randomisation.

Older AADs may increase the risk of mortality and CV hospitalisation

Risk of mortality*¹
OR (95% CI) vs. placebo

<table>
<thead>
<tr>
<th>Treatment</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>2.73</td>
<td>(1.00, 7.41)</td>
<td>0.049</td>
</tr>
<tr>
<td>Sotalol</td>
<td>4.32</td>
<td>(1.59, 11.70)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

* Mixed treatment comparison of seven large scale clinical trials   OR = odds ratio

CV hospitalisation²

Patients not hospitalised (%)

Rate control**

Amiodarone

p=0.0001

* Rate control may include digoxin, metoprolol, atenolol, propranolol, diltiazem, and verapamil

Adapted from:
Dronedarone?
The most extensively studied AAD in AF; > 10,000 patients phase 2/3 clinical trials programme

<table>
<thead>
<tr>
<th>Studies</th>
<th>N</th>
<th>Population</th>
<th>Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rhythm and Rate Control</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAFNE</td>
<td>270</td>
<td>Persistent AF</td>
<td>Dose ranging - cardioversion and maintenance of sinus rhythm</td>
</tr>
<tr>
<td>EURIDIS</td>
<td>612</td>
<td>Paroxysmal/Persistent AF/AFL</td>
<td>Maintenance of sinus rhythm</td>
</tr>
<tr>
<td>ADONIS</td>
<td>625</td>
<td>Paroxysmal/Persistent AF/AFL</td>
<td>Maintenance of sinus rhythm</td>
</tr>
<tr>
<td>ERATO</td>
<td>174</td>
<td>Permanent AF</td>
<td>Ventricular rate control</td>
</tr>
<tr>
<td>DIONYSOS</td>
<td>504</td>
<td>Persistent AF</td>
<td>Comparative trial vs amiodarone</td>
</tr>
<tr>
<td><strong>Recently Decompensated CHF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANDROMEDA</td>
<td>627 / 1000</td>
<td>Unstable CHF and LV dysfunction (25% AF)</td>
<td>Morbidity-mortality study</td>
</tr>
<tr>
<td><strong>Clinical Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATHENA</td>
<td>4628</td>
<td>Paroxysmal/Persistent AF/AFL</td>
<td>Prevention of cardiovascular hospitalisation or death from any cause</td>
</tr>
<tr>
<td>PALLAS</td>
<td>3149 / 10800</td>
<td>Permanent AF</td>
<td>Prevention of major CV events and CV hospitalisation or death from any cause</td>
</tr>
</tbody>
</table>
For the first time in AF, ATHENA adopted an "outcomes focused" approach

The largest single antiarrhythmic drug trial ever conducted in AF
- >4,600 patients with a history of atrial fibrillation or atrial flutter
- More than 550 investigational sites in 37 countries

ATHENA’s objective:
- Evaluate the efficacy and safety of dronedarone vs. placebo on top of standard therapy* in the prevention of CV hospitalisation or death from any cause in patients with paroxysmal or persistent AF/AFL

* Standard therapy may have included rate control agents (beta-blockers, and/or Ca-antagonist and/or digoxin) and/or anti-thrombotic therapy (Vit. K antagonists and/or aspirin and other antiplatelets therapy) and/or other CV agents such as ACEIs/ARBs and statins

Was dronedarone an effective AAD in ATHENA?

All AF related hospitalisation:  
HR = 0.626; 95% CI = [0.54; .73]

First AF related hospitalisation:  
HR = 0.63; 95% CI = [0.55; .72]

DCV=Direct cardioversion

Adapted from:
Dronedarone significantly decreased risk of unplanned CV hospitalisation or death from any cause by 24%.

Placebo on top of standard therapy vs. DR 400mg bid on top of standard therapy:

- **Primary endpoint**: Cumulative incidence of hospitalisation or death from any cause.
- **HR** = 0.76, *p* < 0.001
- **24% reduction in relative risk**

The number needed to treat (NNT) to prevent one first CV hospitalisation or death is 16.

**Patients at risk:**
- Placebo: 2327, 1858, 1625, 1072, 385, 3
- DR 400mg bid: 2301, 1963, 1776, 1177, 403, 2

Adapted from:

Any unplanned hospitalisation (i.e., admission with an overnight stay in the hospital) was classified by the investigator as a hospitalisation due to either CV or non-CV causes.
Dronedarone non-significantly reduced risk of all-cause death by 16%.

The number needed to treat (NNT) to prevent one death from any cause is 105.

HR=0.84
NS (p=0.18)

Mean follow-up 21 ±5 months.
Dronedarone significantly reduced the risk of CV-related mortality in AF patients

<table>
<thead>
<tr>
<th>Secondary endpoints</th>
<th>Reduction in the relative risk of death (Dronedarone vs. placebo*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>-16% ( p=0.18 )</td>
</tr>
<tr>
<td>CV-related mortality**</td>
<td>-29% ( p=0.03 )</td>
</tr>
<tr>
<td>Cardiac arrhythmic death**</td>
<td>-45% ( p=0.01 )</td>
</tr>
</tbody>
</table>

* Dronedarone and placebo treatments were additional to standard therapy
** CV and arrhythmic deaths were secondary endpoints

Dronedarone significantly reduced the relative risk of stroke by 34%.

Mean follow-up 21 ± 5 months.
Adapted from Connolly et al; Circulation. 2009;120:1174-1180.
PALLAS: first co-primary outcome (stroke, MI, SE, CV death)


<table>
<thead>
<tr>
<th>First Co-primary Outcome</th>
<th>Dronedarone</th>
<th>Placebo</th>
<th>Dronedarone vs placebo HR and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>43 (2.7%)</td>
<td>19 (1.2%)</td>
<td>2.29 (1.34 – 3.94) p=0.002</td>
</tr>
</tbody>
</table>

Number at risk:

<table>
<thead>
<tr>
<th>Placebo</th>
<th>1,617</th>
<th>1,445</th>
<th>908</th>
<th>377</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR 400mg bid</td>
<td>1,619</td>
<td>1,421</td>
<td>930</td>
<td>353</td>
</tr>
</tbody>
</table>

Cumulative incidence (%)

Time (days)
Dronedarone: only AAD with monitoring regulations¹,²

**INDICATION**

Dronedarone is indicated for the maintenance of sinus rhythm after successful cardioversion in adult clinically stable patients with paroxysmal or persistent atrial fibrillation (AF). Due to its safety profile (see sections 4.3 and 4.4), dronedarone should only be prescribed after alternative treatment options have been considered. Dronedarone should not be given to patients with left ventricular systolic dysfunction or to patients with current or previous episodes of heart failure.

**CONTRA-INDICATIONS**

Permanent AF with an AF duration ≥ 6 months (or duration unknown) and attempts to restore sinus rhythm no longer considered by the physician.

Patients in unstable hemodynamic conditions

History of, or current heart failure or left ventricular systolic dysfunction

Co-administration with potent cytochrome P 450 (CYP) 3A4 inhibitors

Patients with liver and lung toxicity related to the previous use of amiodarone

Severe hepatic impairment

Severe renal impairment (CrCl <30 ml/min)

Co-administration with dabigatran

**MONITORING**

Patient should be monitored prior to and during dronedarone treatment

AF status: ECGs serially, at least every 6 months.

Heart failure, left ventricular function

Liver function tests should be performed prior and during treatment (after 1wk and 1mo following th. initiation; then repeated monthly for 6mo, at 9, and 12. month, and periodically thereafter). If ALT levels are confirmed to be ≥3 × ULN after re-measurement, treatment with dronedarone should be withdrawn

Pulmonary function status: dronedarone should be discontinued if pulmonary toxicity is confirmed

Plasma creatinine values should be measured prior to and 7 days after initiation of dronedarone. If creatinine continues to rise then consideration should be given to further investigation and discontinuing treatment.

INR values in case of vitamin K antagonist therapy as per clinical AF guidelines.

**COUNSELLING**

They should consult a physician if they develop signs or symptoms of heart failure;

They should immediately report to a physician any symptoms of potential liver injury;

They should consult a physician if they have breathlessness or non productive cough; dronedarone interacts with a number of medicines;

If they consult other doctors they should inform them that they are taking dronedarone;

They should not take St John’s Wort with dronedarone;

They should avoid grapefruit juice.

¹,² dronedarone SmPC xx, 2013., PIL xx, 2013.

Refer to dronedarone respective prescribing information for full list of contraindications and other prescribing information.
AADs: safety and efficacy comparison based on a mixed treatment analysis

**Efficacy (AF recurrence)**

- **Amiodarone**
  - n=978
  - 0.22 (0.16, 0.29, \(P < 0.0001\))

- **Propafenone**
  - n=1228
  - 0.36 (0.28, 0.48, \(P < 0.0001\))

- **Dronedarone**
  - n=1131
  - 0.53 (0.40, 0.72, \(P = 0.0002\))

- **Flecainide**
  - n=305
  - 0.31 (0.19, 0.49, \(P < 0.0001\))

- **Sotalol**
  - n=1404
  - 0.40 (0.31, 0.52, \(P < 0.0001\))

**All-cause mortality**

- **Amiodarone**
  - 2.41 (0.96, 6.06, \(P = 0.060\))

- **Dronedarone**
  - 2.02 (0.29, 13.81, \(P = 0.450\))

- **Flecainide**
  - 1.56 (0.49, 4.98, \(P = 0.429\))

- **Sotalol**
  - 1.28 (0.71, 2.31, \(P = 0.338\))

**Proarrhythmic events**

- **Amiodarone**
  - 1.45 (1.02, 2.08, \(P = 0.043\))

- **Dronedarone**
  - 4.06 (1.13, 14.52, \(P = 0.035\))

- **Flecainide**
  - 6.77 (0.85, 54.02, \(P = 0.067\))

- **Propafenone**
  - 5.45 (0.69, 42.93, \(P = 0.095\))

- **Sotalol**
  - 6.44 (1.03, 40.24, \(P = 0.047\))

**Serious adverse events**

- **Amiodarone**
  - 0.95 (0.73, 1.24, \(P = 0.699\))

- **Dronedarone**
  - 1.56 (0.49, 4.98, \(P = 0.429\))

- **Flecainide**
  - 2.02 (0.29, 13.81, \(P = 0.450\))

- **Propafenone**
  - 2.41 (0.96, 6.06, \(P = 0.060\))

- **Sotalol**
  - 1.28 (0.71, 2.31, \(P = 0.338\))

*versus placebo
†Proarrhythmic events includes bradyarrhythmia

Odds ratios and 95% confidence intervals
What changed in 2012?

Choice of antiarrhythmic drug according to underlying pathology

- Minimal or no structural heart disease
  - Treatment of underlying condition and prevention of remodelling – ACEI/ARB/statin
    - Significant structural heart disease
      - HF
        - Sotalol
      - CHD
        - Dronedarone
      - HHD
        - No LVH
          - Dronedarone/flecainide/propafenone/sotalol
          - Amiodarone
        - LVH
          - Dronedarone
          - Amiodarone

**Notes:**
- MULTAQ® should not be given to patients with left ventricular systolic dysfunction or to patients with current or previous episodes of heart failure. Patients should be followed for the development of left ventricular systolic dysfunction during treatment. If left ventricular systolic dysfunction develops, treatment with MULTAQ® should be discontinued.
- MULTAQ® should be used with caution in patients with coronary heart disease.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CHD, coronary heart disease; HF, heart failure; HHD, hypertensive heart disease; LVH, left ventricular hypertrophy.
Progressive disease

- RRR of all-cause death - 16% (NS), but...
- RRR of stroke - 34%
- significantly lower vs. placebo
- favorable maintenance of sinus rhythm

....back to the facts and dronedarone
Dronedarone is indicated for ~40% of total AF Population\textsuperscript{1,2}

\begin{itemize}
  \item \textbf{FIRST DIAGNOSED EPISODE OF ATRIAL FIBRILLATION}
  \item Without history of, or current heart failure or left ventricular systolic dysfunction
  \item \textbf{PAROXYSMAL}
    \item Usually ≤ 48 hours
  \item \textbf{PERSISTENT}
    \item (>7 days or requires CV)
  \item \textbf{LONG-STANDING}
    \item Persistent (> 1 year)
  \item \textbf{PERMANENT}
    \item Accepted
\end{itemize}

AADs and/or left atrial ablation for rhythm control in AF

No or minimal structural heart disease

Paroxysmal

Patient choice

Dronedarone, flecainide, propafenone, sotalol

Catheter ablation

Amiodarone

Persistent

Patient choice

Relevant structural heart disease

Yes

HF

No

Yes

Due to AF

Amiodarone

No

Patient choice

Dronedarone, sotalol

Catheter ablation

Amiodarone

a = Usually pulmonary vein isolation is appropriate
b = More extensive left atrial ablation may be needed
c = Caution with coronary heart disease
d = Not recommended with LVH
Heart failure due to AF = tachycardiomyopathy.
Typical indications for dronedarone:

- lone AF patients
- younger patients
- patients with hypertension
- patients with CHD, without HF
- atrial ablation
What’s new in 2013?

- New data from clinical studies
- Real-life data with dronedarone
- Translating guidelines into clinical practice
Dronedarone in patients with lone AF

Pooled analysis from ATHENA/EURIDIS/ADONIS on first CV hospitalization (secondary)

The enrolled AF population in the ATHENA study is broader than the indicated population for dronedarone.

CV, cardiovascular.

Aim: to evaluate the effects of dronedarone on AF burden in patients with dual-chamber pacemakers
Changes (%) in AF burden induced by dronedarone

Poster presented at AHA 2012.
Effectiveness of dronedarone among US patients with AF/AFL in a real-world setting

* p < 0.0001, intra-group comparison of baseline versus follow-up periods.

~1,052,366 patients have received treatment with dronedarone worldwide since July 2009

1. Cumulative number of patients. Estimated. IMS/MIDAS Worldwide Monthly Database, Standard Units Sold up until 30 April 2013. For some countries, latest data available is from October and has been used for the calculation of the total.
Sinus rhythm is „God given”...

...I WAS BORN IN SINUS RHYTHM - AND I DON'T WANT TO DIE IN ATRIAL FIBRILLATION

Ronald Campbell, John Camm