Lessons Learned from Negative Trials:
Antiarrhythmic Agents in AF

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Disclosures

Relationships with industry:

- **Medtronic Inc**
  - Speaker Honoraria
  - Investigator – Industry sponsored clinical trials

- **AHA**
  - Associate Editor Circulation Arrhythmia and Electrophysiology
Projected Prevalence of AF to 2050

AF Epidemic Fuelled by:
- Aging
- Life style (Sedentary Obesity) →
- Hypertension
- Diabetes
- OSA

JAMA 2001;285:2370
AFFIRM

- N = 4060
- Elderly: Mean age 70 yr
- Male: 60%
- Persistent AF: 65%
- Few with CHF and low LVEF (8%)
- 90% symptomatic
- 38% → 63% Amiodarone
- Digoxin > 50%

Arch Intern Med 2005;165:1185
RACE

- N = 522
- Mean age 68 yr
- Male: 63%
- Persistent AF: 100%
- Hx CHF 50%
- Digoxin 53%

Primary Outcome
CV Death, Heart Failure, Thromboembolism, Bleeding, Pacemaker, Adverse Effects AAD

Van Gelder I et al
AF-CHF

- N = 1376
- Elderly: mean age 67 yr
- Male: > 80%
- Persistent AF: 69%
- All with CHF and LVEF ≤0.35
- 100% Symptomatic
- 82% amiodarone
- Digoxin 64%

Roy et al New Engl J Med 2008;358;2667
### AFFIRM: Covariates Significantly Associated With Survival

<table>
<thead>
<tr>
<th>Covariate</th>
<th>P</th>
<th>HR</th>
<th>99% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at enrollment*</td>
<td>&lt;0.0001</td>
<td>1.06</td>
<td>1.05 1.08</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>&lt;0.0001</td>
<td>1.56</td>
<td>1.20 2.04</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>&lt;0.0001</td>
<td>1.57</td>
<td>1.18 2.09</td>
</tr>
<tr>
<td>Diabetes</td>
<td>&lt;0.0001</td>
<td>1.56</td>
<td>1.17 2.07</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>&lt;0.0001</td>
<td>1.70</td>
<td>1.24 2.33</td>
</tr>
<tr>
<td>Smoking</td>
<td>&lt;0.0001</td>
<td>1.78</td>
<td>1.25 2.53</td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
<td>0.0065</td>
<td>1.36</td>
<td>1.02 1.81</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>0.0043</td>
<td>1.36</td>
<td>1.03 1.80</td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>&lt;0.0001</td>
<td>0.53</td>
<td>0.39 0.72</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>&lt;0.0001</td>
<td>0.50</td>
<td>0.37 0.69</td>
</tr>
<tr>
<td>Digoxin use</td>
<td>0.0007</td>
<td>1.42</td>
<td>1.09 1.86</td>
</tr>
<tr>
<td>Rhythm-control drug use</td>
<td>0.0005</td>
<td>1.49</td>
<td>1.11 2.01</td>
</tr>
</tbody>
</table>

AFFIRM
Cause-specific Mortality, Under-emphasized

Efficacy Analysis

Sinus rhythm was not associated with:

- Cardiovascular mortality [HR: 1.22, 95% CI: 0.80 to 1.87; p = 0.35]
- Total mortality [HR: 1.11, 95% CI: 0.78 to 1.58; p = 0.57]
- Worsening HF [HR: 0.62, 95% CI: 0.37 to 1.02; p = 0.059].
CV Outcomes in AFFIRM
Rate vs Individual AADs

A

Rhythm (versus Rate)
HR: 1.336 (1.226, 1.456)

Amio (versus Rate)
HR: 1.183 (1.026, 1.364)

Sotalol (versus Rate)
HR: 1.318 (1.127, 1.541)

Class IC (versus Rate)
HR: 1.222 (0.961, 1.555)

HR & 95% CI 0.5 1 1.5 2

B

Mortality
CV Hospitalizations

Rate vs Amio

% without CVH or Death

LR statistic = 5.33
p = 0.02

Time (Years)

C

Rate vs Sotalol

% without CVH or Death

LR statistic = 12.08
p < 0.001

Time (Years)

D

Rate vs Class IC

% without CVH or Death

LR statistic = 2.68
p = 0.1

Time (Years)

Saksena et al J Am Coll Cardiol 2011;58:1975-85
Initial Lessons Learned

- Rate control is an initial option.
- Arrhythmia treatment strategies change over time.
- Digoxin not to be used as monotherapy and with caution.
- Antithrombotic therapy must be continued.
SAFE-T
Persistent AF
Randomized amiodarone, sotalol, placebo
Cardioverted at 4 weeks

Singh et al J Am Coll Cardiol 2006;48:721-30
Validation of a New Simple Scale to Measure Symptoms in Atrial Fibrillation
The Canadian Cardiovascular Society Severity in Atrial Fibrillation Scale


<table>
<thead>
<tr>
<th>CCS SAF Score</th>
<th>Impact on QOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>1</td>
<td>Minimal Effect</td>
</tr>
<tr>
<td>2</td>
<td>Minor Effect</td>
</tr>
<tr>
<td>3</td>
<td>Moderate Effect</td>
</tr>
<tr>
<td>4</td>
<td>Severe Effect</td>
</tr>
</tbody>
</table>

Dorian et al Circ Arrhythm Electrophysiol 2009;2:218-24
AF Symptoms and Health Care Utilization

- Specialist Visits
- ED Visits
- Hospitalizations

Mean Events per Year

CCS SAF Score

Dorian et al Circ Arrhythm Electrophysiol 2009;2:218-24
We recommend that the goals of rhythm control therapy should be to improve patient symptoms and clinical outcomes, and that these do not necessarily imply the elimination of all AF.

**Values and Preferences**
These recommendations place a high value on the decision of individual patients to balance relief of symptoms and improvement in QOL and other clinical outcomes with the potential greater adverse effects of Class I/III antiarrhythmic drugs compared to rate control therapy.

Gillis et al Can J Cardiol 2011;27:47-59
We recommend that the assessment of patient well-being, symptoms, and quality of life (QOL) be part of the evaluation of every patient with AF.  

**Strong Recommendation**  
Low Quality of Evidence

We suggest that QOL of the AF patient can be assessed in routine care using the CCS-SAF scale.  

**Conditional Recommendation**  
Low Quality of Evidence

**Values and Preferences:** These recommendations recognize that improvement in QOL is a high priority for therapeutic decision making.

Healey et al Can J Cardiol 2011;27:31-7
ATHENA
(Primary Outcome: First Hospitalization for CV Cause or Death)

4628 Patients
Dronedarone vs placebo
Age 72 yr
53% Male
Hypertension 86%
CAD 30%
LVEF < 45%:12%
In AF at randomization: 25%

ATHENA:CAD

Hospitalization for CV Cause or Death

CAD

No CAD

ANDROMEDA
All-Cause Mortality or Hospitalization for Worsening Heart Failure

627 pts with HF hospitalization, NYHA Class III/IV within mo prior to enrollment; LV ≤ 0.35

Median FU 2 mo

25 (8.1%) in dronedarone group vs 12 pts (3.8%) in placebo group died (HR 2.1) due to worsening heart failure

PALLAS
(Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy)

Risk of the First Coprimary Outcome
(Stroke, Myocardial Infarction, Systemic Embolism, or Death from Cardiovascular Causes).

Risk of the Second Coprimary Outcome
(Unplanned Hospitalization for Cardiovascular Causes or Death).

### Dronedarone: CCS Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of Recommendation</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>We recommend that dronedarone not be used in patients with permanent AF nor for the sole purpose of rate control.</td>
<td>Strong</td>
<td>High Quality Evidence</td>
</tr>
<tr>
<td>We recommend that dronedarone not be used in patients with a history of heart failure or a left ventricular ejection fraction ≤ 40%.</td>
<td>Strong</td>
<td>Moderate Quality Evidence</td>
</tr>
<tr>
<td>We suggest that dronedarone be used with caution in patients on digoxin.</td>
<td>Conditional</td>
<td>Moderate Quality Evidence</td>
</tr>
</tbody>
</table>

**Values and Preferences:** Although the mechanism(s) for the differences between the results of the ATHENA and the PALLAS trials have not yet been determined, these recommendations are based on the known differences between the two patient populations and are also informed by the results of the ANDROMEDA trial.
AF-CHF

Not all patients in Rhythm Control group in sinus rhythm at follow-up

Antiarrhythmic Drug Rx vs Ablation

Radiofrequency Ablation vs Antiarrhythmic Drugs as First-Line Treatment of Paroxysmal Atrial Fibrillation (RAAFT-2)
A Randomized Trial

Carlos A. Morillo, MD, FRCP; Atul Verma, MD, FRCP; Stuart J. Connolly, MD, FRCP; Karl H. Kuck, MD, FHR; Girish M. Nair, MBBS, FRCP; Jean Champagne, MD, FRCP; Laurence D. Sterns, MD, FRCP; Heather Beresh, MSc; Jeffrey S. Healey, MD, MSc, FRCP; Andrea Natale, MD; for the RAAFT-2 Investigators

127 Treatment Naïve Patients
Paroxysmal AF

Morillo et al JAMA 2014;311:692-700
Personalized AF Rhythm Control Therapy

No or Minimal Heart Disease
- Dronedarone*
- Flecainide
- Propafenone
- Sotalol
  - Catheter Ablation

Structural Heart Disease
- CAD
- HF or LVEF ≤ 35%
  - Dronedarone*
  - Sotalol
  - Catheter Ablation
  - Amiodarone
  - Dofetilide
  - Catheter Ablation
Personalized Rhythm Control

Clinical Presentation (risk factors, comorbidities, symptoms)

ECG (Focal AF, AF patterns/burden AF complexity)

Imaging Heart (LA size, strain, fibrosis)

Biomarkers Genomics
Lessons Learned

• Goals of therapy to be more focused on patients symptoms and clinical outcomes, not just major endpoints of death or stroke.

• Consider effectiveness of therapy not efficacy.

• Therapeutic approach individualized based on patient symptoms, values and preferences.

• Avoidance of use of antiarrhythmic drugs in high risk subgroups.

• Need to develop more effective, safe antiarrhythmic drugs.