Personalized Medicine: AF

Peter R. Kowey, MD, FACC, FAHA, FHRS
Lankenau Heart Institute
Jefferson Medical College
DISCLOSURES

• Dr. Kowey has provided consultation to several dozen pharmaceutical and device companies that are developing new treatment for cardiac arrhythmia

• Dr. Kowey chairs the NCDR National AF Ablation Registry steering committee

• Dr. Kowey holds no equity interest in any pharmaceutical company and has never received compensation for any patient-directed research activity
WHY IS AF MANAGEMENT SO HARD?

• Ubiquitous disease
• Diverse pathogenesis/etiologies
• Potentially lethal
• No universally effective treatment
• Algorithms work poorly
• Multi-component therapy
• Some treatments are worse than disease
• Stroke lurks

∴ Each new patient is a new experience
Frank A. Clark

“If you find a path with no obstacles, it probably doesn’t lead anywhere.”
AF Prevalence Is Increasing Rapidly

# MANAGEMENT STRATEGIES FOR ATRIAL FIBRILLATION

## Benefits

- Rx to Prevent AF
  - Symptom Relief

## Risks

- Ventricular Proarrhythmia
- Bradyarrhythmia
- Other A.A. Drug Toxicity
- Negative Inotropy
- Bradyarrhythmia
- Anticoagulation

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#### Rx to Control Ventricular Rate

- ↓ Ventricular Proarrhythmia
- ↓ Other A.A. Drug Toxicity
RHYTHM OR RATE CONTROL IN ATRIAL FIBRILLATION

Evidence Based

5 Prospective, Controlled, Randomized Trials Comparing 2 Different Strategies

- **PIAF**  Pharmacological Intervention in Atrial Fibrillation
- **STAF**  Strategies in Atrial Fibrillation (pilot)
- **AFFIRM**  Atrial Fibrillation Follow-up Investigation of Rhythm Management
- **RACE**  Rate Control versus Electrical Cardioversion for Atrial Fibrillation
- **SAFE-T**  Sotalol and Amiodarone For Effectiveness Trial
“The optimist proclaims that we live in the best of all possible worlds; and the pessimist fears this is true.”
ThermoCool® Catheter vs AAD: Time to Chronic Failures

Freedom From AF Recurrence vs Days Into Effectiveness Follow-up

- **Ablation** (n=103) with 64% freedom from AF recurrence at 360 days.
- **AAD** (n=56) with 16% freedom from AF recurrence at 360 days.

Statistical Significance: $P<.001$

Number of subjects at risk:

<table>
<thead>
<tr>
<th></th>
<th>Ablation</th>
<th></th>
<th></th>
<th></th>
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<th></th>
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<td>103</td>
<td>69</td>
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<td>61</td>
<td>54</td>
<td>52</td>
<td>37</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>AAD</td>
<td>56</td>
<td>39</td>
<td>29</td>
<td>19</td>
<td>16</td>
<td>13</td>
<td>11</td>
<td>10</td>
<td>7</td>
<td>2</td>
<td>0</td>
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</tbody>
</table>

Wilber D. Presented at: American Heart Association 2008 Scientific Sessions; November 11, 2008; New Orleans, LA.
Cardiovascular Business

strategies in economics, practice & technology

Ablation & Afib
Zapping Barriers to Success

In This Issue:
Renal Denervation: A New Beginning or the End?
Heart Team Approach: Still a Work in Progress
Adding Total Vein Care: Good for Patients & Business
Sponsored by Covidien
Q&A: Cath Lab Boot Camp
Stress-only SPECT: Putting the Rest to Rest?
Structured Reporting: Improving Care, Refining Billing
Sponsored by Wolters Kluwer

May/June 2014 Vol. 8 No. 3
Seriously?

Approximately 80% of AF ablation procedures in the US are carried out in laboratories that perform less than 25 procedures per year (data free zone).
AF ABLATION: Reality

- We make it hard on ourselves and our patients by insisting on perfection
- AF is a chronic progressive disease that has no cure but has multiple palliative treatments, including rate control
- Registries and RWD are helpful but without a sham control study, ablation efficacy is difficult to estimate
- CABANA will help if we can wait until it finishes (now expected at HRS, 2018)
CABANA Trial: Primary endpoint was total mortality—altered to accommodate low enrollment

- Recent-onset AF
- Eligible for ablation or drug therapy
  - ≥65 years old or <65 years with ≥1 risk factor for CAD or stroke

- Drug Therapy
  (Rate or rhythm control [at operator discretion] with anticoagulation)

- Primary Ablation
  (Technique at operator discretion)
DRUGS FOR AF

• Termination
• Prevention of recurrence
• Adjuvative
• Preventative
2011 ACCF/AHA/HRS Guidelines:
Antiarrhythmic Approaches to Maintain SR in Patients with Recurrent Paroxysmal AF or Persistent AF*

Maintenance of SR

No (or minimal) heart disease
- Dronedarone
- Flecainide
- Propafenone
- Sotalol
- Amiodarone
- Dofetilide
- Catheter ablation

HTN
- Substantial LVH
- Dofetilide
- Dronedarone
- Sotalol
- Amiodarone

CAD
- Dofetilide
- Dronedarone
- Sotalol
- Amiodarone
- Catheter ablation

HF
- Amiodarone
- Dofetilide
- Catheter ablation

A Safety-Driven Approach
Dronedarone

• Amiodarone-like compound lacking the iodine moiety
• Similar electrophysiologic properties
• No evidence of thyroid or pulmonary toxicity
• 24-hour half-life
• Food-fast effect
• Extensive first-pass metabolism (CYP450 3A4)

ATHENA: SIGNIFICANT REDUCTION IN TIME TO 1ST CV HOSPITALIZATION OR DEATH

Cumulative incidence of primary outcome (%)

- Placebo (n = 2327)
- Dronedarone (n = 2301)

24% Relative risk reduction
Primarily related to ↓CV hospitalization

HR = 0.76
P < 0.001

## PALLAS TRIAL: SAFETY AND EFFICACY OF DRONEDARONE IN PERMANENT AF: PRELIMINARY DATA ANALYSIS*

Is There a Pleotropic Effect of Dronedarone Unrelated to Maintenance of Sinus Rhythm?

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (N=1577)</th>
<th>Dronedarone (N=1572)</th>
<th>Hazard Ratio</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death, MI, CVA, Embolus</td>
<td>14 (0.9%)</td>
<td>32 (2.0%)</td>
<td>2.3</td>
<td>0.009</td>
</tr>
<tr>
<td>CV Death; Unplanned CV Hospitalization</td>
<td>81 (5.1%)</td>
<td>118 (7.5%)</td>
<td>1.5</td>
<td>0.006</td>
</tr>
<tr>
<td>Death</td>
<td>7 (0.4%)</td>
<td>16 (1.0%)</td>
<td>2.3</td>
<td>0.065</td>
</tr>
<tr>
<td>MI</td>
<td>3 (0.2%)</td>
<td>3 (0.2%)</td>
<td>1.0</td>
<td>1.000</td>
</tr>
<tr>
<td>Stroke</td>
<td>7 (0.4%)</td>
<td>17 (1.1%)</td>
<td>2.4</td>
<td>0.047</td>
</tr>
<tr>
<td>HF Hospitalization</td>
<td>15 (1.0%)</td>
<td>34 (2.2%)</td>
<td>2.3</td>
<td>0.008</td>
</tr>
</tbody>
</table>

*PALLAS events as of 06.30.2011.

Dronedarone is not approved for treatment of permanent AF.
HARMONY

• Randomized, double-blind, placebo-controlled, parallel arm pacemaker based trial to examine the efficacy and safety of a dronedarone/ranolazine combination on AF burden
• 150 patients with AFib >3% and <50% to be recruited at 45 sites in North America and Europe
• R 750 combined with dronedarone 225 and 150 mg
PRIMARY ENDPOINT: % CHANGE FROM BASELINE IN AFB OVER 12 WEEKS

- PL
- D225
- R750
- R750/D150
- R750/D225

Synergy

AFB (% Change from Baseline)

- p = 0.78
- p = 0.49
- p = 0.072
- p = 0.008

∑(R750 + D225)
Will Rogers

“Things will get better—despite our efforts to improve them.”
Upstream Approaches

• Preventative measures seem to make sense
• Multiple concepts have failed and some (like fish oil) have died hard
• Failures likely caused by incomplete knowledge of pathophysiology, dosing, timing of intervention, etc.
Caveats

• Primary versus secondary prevention
• Dose response rarely considered
• Most evaluable among high risk patients, e.g. POAF
• Detection bias
  – Highly influenced by the density of the arrhythmia and the sensitivity of the monitoring methods
• High level of interest because of CVA risk
• Hard to prove any outcome benefit past simple AF prevention
### Omega-3 Fatty Acids in AF Prevention: Conflicting Results in Clinical Trials

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Design</th>
<th>Patients</th>
<th>Intervention</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular Health Study (2004)</td>
<td>Population-based, prospective cohort 12-yr FU</td>
<td>N = 4815 Age ≥65 yr</td>
<td>Fish consumption</td>
<td>AF risk (vs Low) Med: ↓28% (P=0.005)</td>
</tr>
<tr>
<td></td>
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<td>Low (&lt;1x per mo) Med (1–4x per wk) High (≥5x per wk)</td>
<td>High: ↓31% (P=0.008)</td>
</tr>
<tr>
<td>Calo et al (2005)</td>
<td>Randomized Open-label</td>
<td>N = 160 CABG Mean age 65 yr</td>
<td>PUFAs ≥5 days pre-surgery</td>
<td>↓65% in postoperative AF risk (P = 0.013)</td>
</tr>
<tr>
<td>Nodari et al (2005)</td>
<td>Placebo-controlled</td>
<td>N = 70 Persistent AF Cardioversion Mean age 70 yr</td>
<td>PUFAs 1 g/day for 6 months</td>
<td>AF recurrence: 3.3% (PUFA) vs 40% (placebo) P &lt; 0.0001</td>
</tr>
<tr>
<td>Danish Diet, Cancer &amp; Health Study (2005)</td>
<td>Population-based, prospective cohort 5.7-yr mean FU</td>
<td>N = 47,949 Mean age 56 yr</td>
<td>Fish consumption</td>
<td>No effect</td>
</tr>
<tr>
<td>Rotterdam Study (2006)</td>
<td>Population-based, prospective cohort 6.4-yr mean FU</td>
<td>N = 5184 Mean age 67 yr</td>
<td>Fish / PUFA consumption</td>
<td>No effect</td>
</tr>
</tbody>
</table>

Primary Endpoint: Time to First Recurrence of Symptomatic AF/Flutter (PAF)

Event Free Survival (%)

PLA: 129/269 (48%)

P-OM3: 135/258 (52%)

Analysis based on Cox model: log (HR)=treatment+region+ACE/ARB+Statin

HR: 1.15
CI: (0.90, 1.46)
P value: 0.263
Monty Python and The Holy Grail

“I am not dead yet.”
Novel Methods of Administration

- Nasally administered L-type calcium channel blocker for acute SVT termination (Milestone)
- Inhaled flecainide for acute AF termination (InCarda)
- Intravenous AA drug release from implanted reservoir following arrhythmia detection
- Self-absorbing epicardial patch containing an antiarrhythmic drug for post-op AF
Canakinumab

• Human monoclonal antibody that selectively neutralizes IL-1beta
• Reduces C-reactive protein
• CONVERT-AF is determining its efficacy for prevention of post cardioversion recurrence in patients with persistent AF
Botox

• 60 AF patients undergoing cardiac surgery
  Botox injection in epicardia fat pad
  7 vs 27% AF recurrence at 11 months
  No adverse effects ascribed to BT

• Duke study at AHA
  Larger cohort
  36% vs 47% AF recurrence at 6 days
  No safety signal

Pokushalov et al HRS, 2015; AHA, 2017
GS-458967

- Selective late sodium current blocker
- Potential benefit for ventricular arrhythmia
- ICD study failed
- Niche indication for LQT3
- Potential for treating acquired LQTS and ischemia-related VT/VF
“The two most common elements in the universe are hydrogen and stupidity.”
Lifestyle Modification

• Abundant data (principally from Australia) that exercise and weight loss can reduce AF recurrence and burden
• Effect size not much different than drug or ablative therapy
• Not yet clear if the treatment effect is independent of expected risk factor modification
SO WHY IS AF Rx SO HARD?

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