There are future perspectives in the pharmacological treatment of arrhythmias

George Andrikopoulos, MD, PhD, FESC, Cardiologist, Director, 1st Department of Cardiology/Department of Electrophysiology & Pacing, “Henry Dunant” Hospital Center, Athens, Greece
Presenter Disclosure Information

The presenter has received honoraria for participation in lectures and advisory boards from the following pharmaceutical and biotechnology companies:

- AstraZeneca,
- Bard,
- Bayer Healthcare,
- Boehringer Ingelheim,
- Boston Scientific,
- Bristol-Myers Squibb,
- ELPEN,
- Galenica,
- Lilly,
- Medtronic,
- Menarini,
- MSD,
- Pfizer,
- Sanofi,
- Servier,
- StJude,
- Unifarma,
- Vianex.
- **Class I**: sodium inhibitors
  - Ia: Quinidine, Disopyramide
  - Ib: Lidocaïne, Mexiletine
  - Ic: Flecaïnide, Propafenone, Cibenzoline

- **Class II**: beta-blockers

- **Class III**: potassium blockers: Amiodarone, Sotalol

- **Class IV**: calcium inhibitors: Verapamil, Diltiazem
### Evidence for increased mortality in patients treated with antiarrhythmic drugs

<table>
<thead>
<tr>
<th>Study</th>
<th>Population/design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAST [1]</td>
<td>Randomized prospective comparison of placebo, flecainide and encainide in post-MI patients with PVCs.</td>
<td>Increased total and sudden death mortality with flecainide and encainide.</td>
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<tr>
<td>IMPACT [3]</td>
<td>Randomized prospective trial of mexiletine vs. placebo in post-MI patients with PVCs.</td>
<td>Increased mortality with mexiletine.</td>
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<tr>
<td>Flaker et al. [6]</td>
<td>Retrospective analysis of data from SPAF trial.</td>
<td>Excess mortality for AF patients with heart failure receiving antiarrhythmic drugs. No difference in absence of heart failure.</td>
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<tr>
<td>Nattel et al. [7]</td>
<td>Analysis of data from controlled trials of drug therapy of AF.</td>
<td>Increased mortality with quinidine, disopyramide, flecainide, and sotalol.</td>
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<tr>
<td>Moosvi et al. [8]</td>
<td>Retrospective analysis of empiric therapy for cardiac arrest patients.</td>
<td>Increased rate of recurrent cardiac arrest in patients receiving empiric quinidine or procainamide.</td>
</tr>
</tbody>
</table>

*Nattel S., et al. Cardiovascular Research 1998*
Arrhythmias

Environment

Genetic Susceptibility

Bradycardia
Gender
Hypokalemia
Autonomic control
Drugs, e.t.c.
Even in susceptible substrate arrhythmias occur very rare and in an unpredictable fashion.
Proarrhythmia

AF

Quinidine restored SR

Proarrhythmia
Brugada Syndrome
Reduction in the median number of ICD shocks before and after Quinididine administration

The total number of shocks (n= 203) was reduced with quinidine (n=41)

Anguera I. et al, JACC 2016
Sotalol-Induced QTc prolongation

Adapted from Salem et al. PLoS ONE 2017:12(8):e0181875
Case Report

Proarrhythmia Induced by Propafenone: What is the Mechanism?

Flutter with 1:1 AV conduction

Figure 1: 12-lead electrocardiogram A: Wide QRS complex tachycardia. Heart rate at 150 bpm, with right bundle branch block morphology, left axis deviation and visible atrial activity in V1 V2 (arrow). B: Typical atrial flutter with variable AV conduction.
Exercise-induced QRS prolongation in a 58-year old patient (physician) who was using propafenone to prevent AF

Before ET

Recovery (2 min)
The Role of Flecainide in the Management of Catecholaminergic Polymorphic Ventricular Tachycardia

Krystien VV Lieve, Arthur A Wilde, Christian van der Werf

Figure 1: ECGs at Maximum Heart Rate During Exercise Testing Before and After Drug Treatments in a Female Patient with Catecholaminergic Polymorphic Ventricular Tachycardia

A. At baseline before medication, polymorphic NSVT and VES were observed. B: After bisoprolol (5 mg/day); VES, bigeminy and a couplet. C: With metoprolol 50 mg/day and flecainide 150 mg/day ventricular arrhythmias were completely suppressed. CPVT = catecholaminergic polymorphic ventricular tachycardia; NSVT = non-sustained ventricular tachycardia; VES = ventricular extrasystoles.

Flecainide: Current status and perspectives in arrhythmia management

Andrikopoulos GK et al. Flecainide role in arrhythmia management

Figure 2 Mechanism of flecainide action during atrial fibrillation by inhibition of Na⁺ channels which reduces intracellular Ca²⁺ accumulation and reduces oxidative stress and mitochondrial dysfunction. AF: Atrial fibrillation; INa: Fast inward Na⁺ current; ROS: Reactive oxygen species; NFκB: Nuclear factor kappa β; ATP: Adenosine triphosphate.
The Present Value of Antiarrhythmic Therapy
Guidelines for the management of atrial fibrillation

The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA)†
Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS)

Amiodarone prevents recurrent AF better than propafenone and sotalol. The number of patients needed to treat is 3 with amiodarone, 4 with flecainide, 5 with dofetilide and propafenone, and 8 with sotalol. (111. Lafuente-Lafuente C, et al. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. Cochrane Database Syst Rev 2007;4:CD005049)

European Heart Journal 2010 (doi:10.1093/eurheartj/ehq278)
Cardiovascular Outcomes in the AFFIRM Trial: An Assessment of Individual Antiarrhythmic Drug Therapies compared to Rate Control Using Propensity Score Matched Analyses

Results—729 amiodarone patients, 606 sotalol patients & 268 class 1C patients were matched. The composite outcome of mortality or CV hospitalizations (CVH) showed better outcomes with Rate compared to amiodarone (Hazard Ratio [HR] 1.18, 95% confidence intervals {CI}: 1.03–1.36, p=0.02), sotalol (HR=1.32, CI: 1.13–1.54, p<0.001) and class 1C (HR=1.22, CI: 0.97–1.56, p=0.10). There was a non-significant increase in mortality with amiodarone (HR=1.20, CI: 0.94–1.53, p=0.15) with the risk of non-CV death, being significantly higher with amiodarone versus Rate. (HR=1.11, CI: 1.01–1.24, p=0.04). First CVH event rates at 3 years were 47% for amiodarone, 50% for sotalol and 44% for class 1C versus 40%, 40% and 36% respectively for Rate (amiodarone HR=1.20,CI:1.03–1.40,p=0.02, sotalol HR=1.364, CI:1.16–1.611, p<0.001, class 1C HR=1.24,CI:0.96–1.60,p=0.09). Time to CVH with intensive care unit stay (ICUH) or death was shorter with amiodarone (HR=1.22, CI: 1.02–1.46, p=0.03).

Potential benefit of rhythm control offset by antiarrhythmic drug toxicity

Conclusions—

1. In AFFIRM, composite mortality and CVH outcomes differed for Rate and AADs due to differences in CVH; CVH event rates during follow-up were high for all cohorts, but they were higher for all groups on AADs.

2. Death, ICUH and non-CV death were more frequent with amiodarone.
Projected U.S. Prevalence of AF

An Expanding Epidemic

Antiarrhythmic therapy and risk of death in patients with atrial fibrillation: a nationwide study
Methods

All 174,995 patients with a diagnosis of AF during 2010 to 2012 were identified in the Swedish Patient Register. Of these, 4,856 patients had received dronedarone according to the Swedish Drug Register, and 170,139 patients who had not were used as a control population. Mean follow-up was 1.6 years, with a minimal follow-up of 6 months.
Interpretation—Our data suggest that observed trends of increased incidence of atrial fibrillation in the community were partially due to enhanced surveillance. Stroke occurrence and mortality following atrial fibrillation onset declined over the decades, and prevalence increased approximately fourfold. The hazards for atrial fibrillation risk factors remained fairly constant. Our data indicate a need for measures to enhance early detection of atrial fibrillation through increased awareness coupled with targeted screening programs, and risk factor-specific prevention.

Figure 1: The trend in anti-arrhythmic drug dispensations in England 1998-2014
Classical Concepts: Role of Refractory Period and Wavelength Changes

A

Wavelength (WL) = refractory period x conduction velocity
- minimal path length for reentry
- size of functional reentry circuits

B

Normal atrial size
Normal WL
- AF not sustained

Normal atrial size
Short WL
- AF sustained

To stop AF:
↑WL (↑APD)
Classical Concepts: Role of Refractory Period and Wavelength Changes

What should we do in pts with Enlarged atrial size and Normal WL?
Novel $K^+$ Channels: Two-Pore Potassium Channels: Effects on action potentials

Blocking K2P channels prolongs APD selectively in AF
SUPRAVENTRICULAR TACHYARRHYTHMIAS* IN THE MERLIN - TIMI 36 TRIAL

A. Supraventricular Tachycardia

- Placebo: 1752 (53.5%)
- Ranolazine: 1413 (43.2%)

\( \Delta = 339, \text{ RR } 0.81, p < 0.001 \)

B. New-Onset Atrial Fibrillation

- Placebo: 75 (2.3%)
- Ranolazine: 55 (1.7%)

\( \Delta = 20, \text{ RR } 0.74, p = 0.08 \)

*Detected during 6 days of cECG monitoring

RISK OF SUDDEN CARDIAC DEATH ASSOCIATED WITH VENTRICULAR TACHYCARDIA LASTING ≥ 8 BEATS

**NO VT**
- Patients with No VT ≥ 8 beats
  - HR 0.96 (95% CI 0.66, 1.42); p=0.85

**VT**
- Patients with VT ≥ 8 beats
  - HR 0.36 (95% CI 0.10, 1.27); p=0.097

Modified from Scirica B et al, *Circulation* 122:455, 2010
Types of ionic currents significantly inhibited by therapeutic concentrations of ranolazine in atrial and ventricular cells, and implication of late sodium channel activation in arrhythmogenesis.

Effect of ranolazine on atrial fibrillation in patients with non-ST elevation acute coronary syndromes: observations from the MERLIN-TIMI 36 trial

Methods: This prospective, multicenter, randomized, double-blind, placebo-control parallel group phase II dose-ranging trial randomized patients with persistent AF (7 days-6 months) 2 hours after successful ECV to placebo, ranolazine 375, 500 or 750 mg bid. Patients were monitored daily with trans-telephonic ECG. The primary endpoint was the time to first AF recurrence.

Results:
Of 241 patients randomized 238 took at least 1 drug dose. Ranolazine proved to be safe and tolerable. No dose of the drug significantly prolonged time to AF recurrence. AF recurred in 56.4%, 56.9%, 41.7% and 39.7% of the placebo, ranolazine 375 mg, ranolazine 500 mg and ranolazine 750 mg patients, respectively.

Figure 2: Kaplan-Meier recurrence-free survival curves comparing the 500+750 mg combined group with placebo (n= 173, A, left) and for the pre-specified population of patients who were still in sinus rhythm after 48 hours (n=157, B, right).
**Methods** Seventeen implantable cardioverter defibrillator (ICD) recipients, who had experienced a worsening of their ventricular arrhythmia burden, and 12 ICD recipients with angina were enrolled. Patients were followed up for 6 months after the addition of ranolazine (postranolazine). Data were compared with before its administration (preranolazine).

**Conclusion** In this small study, ranolazine proved to be effective, well tolerated, and safe in reducing ventricular arrhythmia episodes and ICD interventions in patients with recurrent antiarrhythmic drug-refractory events. In addition, none of the patients with chronic angina developed major ventricular arrhythmias.
C-LBCT02 Session: Late-Breaking Clinical Trials II

Friday, May 12, 2017
10:30 a.m. - 12 p.m.

CHAIRS:
Andrea M. Russo, MD, FHRS. Cooper University Hospital, Camden, NJ
Christine M. Albert, MD. Brigham and Women’s Hospital, Boston, MA

C-LBCT02-01

RANOLAZINE IN HIGH-RISK ICD PATIENTS (RAID) TRIAL

Effect of Ranolazine vs. Placebo on Arrhythmic Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VT/VF or Death</td>
<td>0.84</td>
<td>0.67-1.05</td>
<td>0.117</td>
</tr>
<tr>
<td>VT/VF requiring ATP or Schock</td>
<td>0.81</td>
<td>0.62-1.04</td>
<td>0.100</td>
</tr>
<tr>
<td>VT requiring ATP</td>
<td>0.73</td>
<td>0.55-0.98</td>
<td>0.038</td>
</tr>
<tr>
<td>VT/VF requiring Shock</td>
<td>1.01</td>
<td>0.73-1.41</td>
<td>0.947</td>
</tr>
<tr>
<td>VT/VF requiring Shock or Death</td>
<td>0.98</td>
<td>0.76-1.26</td>
<td>0.891</td>
</tr>
<tr>
<td>Inappropriate ICD Shock</td>
<td>0.75</td>
<td>0.38-1.47</td>
<td>0.398</td>
</tr>
<tr>
<td>Inappropriate ATP</td>
<td>0.72</td>
<td>0.41-1.28</td>
<td>0.262</td>
</tr>
<tr>
<td>Death</td>
<td>0.97</td>
<td>0.69-1.38</td>
<td>0.869</td>
</tr>
</tbody>
</table>

Methods: This was a randomized, double-blind, placebo controlled clinical trial in which high-risk ICD patients with ischemic or nonischemic cardiomyopathy were randomly assigned 1:1 to ranolazine 1,000 mg bid or placebo. High-

Application: RAID trial enrolled 1,012 patients with a mean age of 64±10 years, 18% females, 53% with ischemic cardiomyopathy, 42% with CRT-D, mean EF of 31±12%. During a mean 28±16 months of follow-up there were 372 (37%) VT/VF or death events, 270 (27%) VTVF events, and 148
Hard Work or Good luck?

- Amiodarone
- Quinidine
- Ranolazine
Biological Pace Makers

Gene-based biological pacemaker

or

Cell-based
Antibodies targeting cardiac ion channels

Autoantibodies to cardiac conducting tissue and their characterization by immunofluorescence

A. Fairfax & Deborah Doniach Department of Immunology, The Middlesex Hospital Medical School, London

Anti-SCN5A antibody

$I_{Na}$ in rat cardiomyocytes with serum from

ECG in rats

Control

SCN5A-immunized

![Graph showing ECG changes](image)

Megadata Analysis will boost the development of novel antiarrhythmic strategies