Ranolazine for Atrial Fibrillation: A New Indication?

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Pharmacotherapy Rounds
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Objectives:
1. Describe the background, pathophysiology, and general treatment of atrial fibrillation (AF)
2. Explain therapy limitations of currently available anti-arrhythmic drugs (AAD)
3. Evaluate available medical literature for ranolazine therapy in AF management
4. Discuss current clinical challenges and future directions of AF pharmacotherapy treatment
INTRODUCTION\textsuperscript{1-3}

- AF is the most common type of cardiac arrhythmia
- Prevalence increases with age (≥ 33% of AF patients are ≥80 years of age)
- Affects 2.7-6.2 million Americans; expected to double by 2050
- Higher prevalence in Caucasian race
- Greater occurrence in men compared to women
- Associated with up to 5-fold risk of ischemic stroke; 3-fold risk of HF; and 2-fold risk of dementia
- >467,000 hospitalizations yearly and >99,000 deaths annually in America
- Estimated incremental burden cost of $26 billion per year on US healthcare system

BACKGROUND

Definition: A supraventricular tachyarrhythmia with uncoordinated atrial activation, and consequently ineffective atrial contraction.\textsuperscript{1}

![Figure 1 Normal vs. AF EKG Comparison](image)

Presentation:
- Characterized by rapid atrial rate of 400–600 beats per minute.\textsuperscript{2}
- Variance of no symptoms to different degrees of fatigue, palpitations, dyspnea, hypotension, syncope, and development or exacerbation of HF.\textsuperscript{1}

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal AF</td>
<td>AF that terminates within 7 days of onset. May recur.</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>Continuous AF that is sustained for &gt;7 days</td>
</tr>
<tr>
<td><strong>Longstanding Persistent AF</strong></td>
<td>Continuous AF that is sustained for &gt; 12 months</td>
</tr>
<tr>
<td>Permanent AF</td>
<td>Joint decision by the patient and the clinician(s) to cease further attempts to restore and/or maintain sinus rhythm</td>
</tr>
<tr>
<td>Non-valvular AF</td>
<td>AF in the absence of rheumatic mitral stenosis, a mechanical or bio-prosthetic heart valve, or mitral valve repair</td>
</tr>
<tr>
<td>Lone AF</td>
<td>“Should not be used to guide therapeutic decisions\textsuperscript{1}”</td>
</tr>
<tr>
<td>Post-operative AF</td>
<td>20-50% of patients after cardiac surgery.\textsuperscript{5} Usually temporary.</td>
</tr>
</tbody>
</table>
PATHOPHYSIOLOGY

Each heart beat is a synchronous interaction between mechanical property and electrical property.\textsuperscript{6} The exact mechanism of AF remains unknown; however, cardiac structural abnormalities as well as electrophysiological irregularities are theorized to contribute to the manifestation of AF.

A. Structural Abnormalities\textsuperscript{1,6,8} – inflammation, fibrosis, hypertrophy of the atria, and underlying heart conditions (including HTN, CAD, HF, cardiomyopathies)

B. Electrophysiological Irregularities

- Impulse formation abnormalities due to rapid depolarization near or at pulmonary veins, superior vena cava, coronary sinus, and other non-venous triggers within the atria.\textsuperscript{1,6}
- Impulse conduction abnormalities resulting from either delayed or early afterdepolarization of cardiac action potential (following the spontaneous release of diastolic Ca\textsuperscript{2+} from sarcoplasmic reticulum). Or re-entry activity due to slowed signal conduction speed or shortened refractory period of cardiac action potential.\textsuperscript{8,11}

TREATMENT

- ‘Upstream’ therapy of concomitant conditions
- Anticoagulation
- Rate control
  - Antiarrhythmic drugs
  - Ablation
  - Cardioversion

Figure 2 Cardiac Model of Atrial Fibrillation\textsuperscript{7}

Figure 3 Overview of AF Management\textsuperscript{9}
Primary treatment goals:
- Prevent complications
- Alleviate symptoms

NON-PHARMACOTHERAPY
- Electrical cardioversion to shock the heart back to normal rhythm
- Catheter ablation to create lesions to stop the abnormal electrical impulses

PHARMACOTHERAPY
I. Anti-thrombotics to reduce the risk of strokes and thromboembolism - Refer to APPENDIX A

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Anti-Thrombotic Therapy Management Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHA/ACC/HRS 2014&lt;sup&gt;1&lt;/sup&gt;</td>
<td>ESC 2012&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td>Risk Scoring Basis</td>
<td>CHA2DS2-VASc</td>
</tr>
<tr>
<td>Low risk Score = 0</td>
<td>No antithrombotic therapy</td>
</tr>
<tr>
<td>Moderate risk Score = 1</td>
<td>No therapy</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
</tr>
<tr>
<td></td>
<td>Oral anticoagulant</td>
</tr>
<tr>
<td>High risk Score ≥ 2</td>
<td>Oral anticoagulant (warfarin or newer agents dabigatran, rivaroxaban, or apixaban)</td>
</tr>
</tbody>
</table>

II. Anti-arrhythmics to restore/maintain normal heart rhythm
A. Rate control - control the ventricular response, but leave patients in AF - Refer to APPENDIX B
   Lenient goal <110 beats per minute.<sup>1</sup> Strict goal <80 beats per minute.<sup>1</sup>
B. Rhythm control - restore and maintain sinus rhythm - Refer to APPENDIX C
   Therapy strategy for patients with significant symptoms despite adequate rate control.<sup>9</sup>

NOT ALL ANTIARRHYTHMIC DRUGS ARE CREATED EQUAL!

Similar long-term outcomes (thromboembolism and mortality) between rate vs. rhythm control strategy.<sup>11</sup>
Although AADs are able to reduce AF recurrences, therapies are limited by adverse side effects.
AAD therapy restrictions are numerous! Some major limitations are:

- Patient with structural heart diseases (specifically coronary heart disease) cannot use flecainide.
- CYP2D6 substrate poor metabolizers (~7-10% AF patients) require longer time to metabolize propafenone.
- Inpatient initiation/dose escalation required for dofetilide, followed by special outpatient dispensing protocol.
- Stringent renal monitoring with sotalol use.
- Dronedarone is contraindicated in NYHA Class IV patients or symptomatic HF patients with recent decompensation requiring hospitalization.
- Use of amiodarone in AF management without therapy indication.
- All AADs carry proarrhythmic risks – except propafenone, amiodarone, and dronedarone.

**AMIODARONE**

<table>
<thead>
<tr>
<th>BENEFITS</th>
<th>RISKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The most effective drug for sinus rhythm maintenance in paroxysmal or persistent AF.</td>
<td>• Cardiac: sinus bradycardia; women have higher risk of pacemaker requirement.</td>
</tr>
<tr>
<td>• Most commonly prescribed AAD in US.</td>
<td>• Non-cardiac: blue-gray skin discoloration with chronic high doses; pulmonary toxicities</td>
</tr>
<tr>
<td>• Low incidences of torsades de pointes.</td>
<td>• Long half-life and extended drug interactions</td>
</tr>
</tbody>
</table>

**Table 3  Pharmacokinetics and therapeutic profile of Amiodarone**

<table>
<thead>
<tr>
<th>MOA:</th>
<th>(1985) Exhibit actions of all antiarrhythmic classes (blocks Na⁺, Ca²⁺, and K⁺ channels).</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG:</td>
<td>Immediate: sinus and AV nodal function suppression</td>
</tr>
<tr>
<td></td>
<td>Delayed: antiarrhythmic effect and QT prolongation</td>
</tr>
<tr>
<td>PKs:</td>
<td>Long t½ (26-107 days). Onset time 2 days-3 weeks (PO).</td>
</tr>
<tr>
<td></td>
<td>No renal adjustment. Consider therapy adjustment if significant hepatic concerns.</td>
</tr>
<tr>
<td></td>
<td>Food increases amiodarone absorption.</td>
</tr>
<tr>
<td></td>
<td>CYP3A4, CYP2C9, and P-glycoprotein inhibitor.</td>
</tr>
<tr>
<td>Dose:</td>
<td><strong>AF Maintenance:</strong> (unlabeled use) PO: 400–600 mg daily in divided doses for 2-4 weeks; followed by maintenance 100 – 200 mg daily.</td>
</tr>
<tr>
<td></td>
<td><strong>AF Conversion:</strong> (unlabeled use)</td>
</tr>
<tr>
<td></td>
<td>PO: 600-800 mg daily in divided doses – until 10 g total then 200 mg daily as maintenance dose. Numerous regimen variations in clinical practice.</td>
</tr>
<tr>
<td></td>
<td>IV: 150 mg over 10 minutes; then 1 mg/min for 6 hours; then 0.5 mg/min for 18 hours or change to oral maintenance dosing of 100-200 mg daily. After 24 hours of IV therapy, consider decreasing dose to 0.25 mg/min.</td>
</tr>
<tr>
<td>Clns:</td>
<td>Sinus or AV node dysfunctions; cardiogenic shock, bradycardia causing syncope or heart block (exception: patients with functioning artificial pacemakers); hypersensitivity.</td>
</tr>
<tr>
<td>SEs:</td>
<td>Hypotension (IV use), photosensitivity, fatigue, dizziness, headache, nausea, constipation, visual disturbances.</td>
</tr>
<tr>
<td></td>
<td>Risk of non-cardiac side effects, especially at higher doses.</td>
</tr>
<tr>
<td>Dis:</td>
<td>↑ digoxin concentration (P-glycoprotein inhibition) and ↑ warfarin concentration.</td>
</tr>
<tr>
<td>Notes:</td>
<td>Limited by long half-life and extra-cardiac side effects (including pulmonary toxicities, hepatic enzymes abnormalities, and thyroid disorders). Other unlabeled uses in prevention of postoperative AF and atrial flutter associated with cardiothoracic surgery.</td>
</tr>
</tbody>
</table>
RANOLAZINE

**Background**\(^\text{16}\)
- Ranexa® extended-release tablets (Gilead Sciences)
- (+)N-(2,6-dimethylphenyl)-4(2-hydroxy-3-(2-methoxyphenoxy)-propyl)-1-piperazineacetamid dihydrochloride
- Piperazine derivative
- FDA approval January 2006

**Approved Dosing and Indication**

**U.S.:** 500 - 1000 mg by mouth twice daily
- Treatment of chronic angina as a substitute if experiencing unacceptable side effects, inadequately controlled symptoms, or contraindication to initial treatment of BB therapy.
- May be used in combination with nitrates, DHP-CCBs, ACEI/ARBs, and antiplatelet and lipid-lowering therapies.\(^\text{16-17}\)

**Europe:** 375 - 750 mg by mouth twice daily
- Add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapy of BB, CCB, and nitrates.\(^\text{18}\)

**Mechanism of Action**
- The exact mechanism of action in chronic angina relief remains undefined – Available research evidence of anti-ischemic and metabolic properties.\(^\text{19-20}\)
- Exerts cardiac late inward sodium channels (\(I_{\text{NaL}}\)) inhibition at therapeutic drug levels.\(^\text{17}\)
  - \(I_{\text{NaL}}\): Na⁺ channels that exhibit slow or delayed inactivation in phase 2 and 3 of cardiac action potential.
  - Comprised of \(~1\%\) of all Na⁺ channels in a healthy cardiomyocyte.\(^\text{21}\)
  - Higher in cardiac disorders, including MI, HF, post-MI remodeling, and AF.
Pharmacokinetics Profile

Table 4  Pharmacokinetics profile of Ranolazine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Tablet bioavailability: 55-76%</td>
</tr>
<tr>
<td></td>
<td>Rate and extent of absorption unaffected by food</td>
</tr>
<tr>
<td>Distribution</td>
<td>Time to peak: 2-6 hours</td>
</tr>
<tr>
<td></td>
<td>t½: ~7 - 9 hours</td>
</tr>
<tr>
<td></td>
<td>~62% protein binding (incomplete clearance by hemodialysis)</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Extensive hepatic [CYP3A4 (major), 2D6 (minor); some intestinal</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urine: 75%, feces: 25%</td>
</tr>
</tbody>
</table>

Contraindications

**U.S.:**  concurrent use with CYP3A4 inducers or strong CYP3A4 inhibitors; liver cirrhosis.\(^{16}\)

**Europe\(^{18}\):**  U.S. contraindications, plus:
- severe renal impairment (CrCl <30 ml/min); moderate – severe hepatic impairment;
- concomitant administration of antiarrhythmics class Ia (example: quinidine) or class III (example: dofetilide, sotalol) other than amiodarone.

Therapy Modification\(^{16}\)

*Use with moderate CYP3A4 inhibitors (example: diltiazem, verapamil):* max dose 500 mg PO BID.
*Use with P-glycoproteins inhibitors (example: cyclosporine):* titrate therapy based on response.
*Use with simvastatin:* recommended maximum simvastatin dose of 20 mg daily.
*Use with digoxin:* ranolazine may increase digoxin plasma concentration – monitor therapy.
*Use with metformin:* limit metformin to 1,700 mg/day if also taking 1,000 mg ranolazine daily.

Side Effects

**Minimal to no effect on heart rate and blood pressure.**\(^{16-18}\)
No substantial proarrrhythmic effects.\(^{23}\)
Generally well-tolerated. Common side effects: dizziness, headache, constipation, and nausea.
Syncope incidence 0.5%.\(^{16,18}\)
Inhibition of $I_{\text{NaL}}$ reduces sodium influx (consequently decrease calcium influx into the myocardocyte via the sodium-calcium exchange pumps) = reduces delayed afterdepolarization episodes and further suppresses triggered ectopic activities that causes arrhythmias.\textsuperscript{8,21,25}

- Ranolazine is the most potent clinical inhibitor of $I_{\text{NaL}}$ at this time.\textsuperscript{21}
- Active research regarding ranolazine’s other potential mechanism of actions: inhibition of outward rectifier potassium currents ($I_{\text{Kr}}$) as well as late inward calcium currents ($I_{\text{Ca}}$).\textsuperscript{21,26}
- Favorable AF-suppressing effects in \textit{in vitro} and \textit{in vivo} experimental studies in non-human models.
- Minor dose-dependent QT interval prolongation (QTc mean increase 6 ms with 1,000mg BID dose).\textsuperscript{27}

Previous Evidence

\textit{Post-hoc analysis} of MERLIN-TIMI 36 study\textsuperscript{28} demonstrates that, in the studied non-ST-elevation ACS population, ranolazine therapy is associated with:

- statistically significant \textit{lower} incidences of supraventricular tachycardia compared to placebo (ranolazine 44.7% vs. placebo 55%; RR, 0.81; 95% CI, 0.77 to 0.85; $P<0.001$)
- trend toward \textit{fewer} new-onset AF (ranolazine 1.7% vs. placebo 2.4%; RR, 0.74; 95% CI, 0.52 to 1.05; $P=0.08$)

Refer to \textit{APPENDIX D}
Objective: To assess the relative benefit of prophylactic amiodarone versus ranolazine for the prevention of AF following CABG procedure.

Design: Single center, nonrandomized, retrospective cohort study

Aspirus Wausau Hospital, Wausau, Wisconsin
June 2008 – April 2010
393 patients (211 in amiodarone group; 182 in ranolazine group)
Dosage and timing of drug initiation assigned at discretion of the treating physician
ECG monitored continuously throughout hospital stay following CABG

| Pre-op: amiodarone 400 mg PO daily x 7D | VS | ranolazine 1,500 mg PO the day before Post-op: amiodarone 200 mg PO BID x 10-14D | ranolazine 1,000 mg PO BID x 10-14D |

Outcomes

Primary endpoint: identified AF after CABG procedure
Secondary endpoint: 30-day readmission rate and 30-day mortality rate

Inclusion Criteria
No history of permanent AF
CABG procedure without concomitant valve surgery

Exclusion Criteria
N/A

Baseline Features
- Amiodarone group have lower EF compared to ranolazine (54.7±12.7% vs. 57.7±9.8%; P=0.01)
- Amiodarone group included more NYHA class IV HF patients (8.5% vs. 2.8%; P=0.02)
- Statistically comparable in other baseline characteristics: >70% men; mean age 65-66; concomitant HTN and DM, and history of previous MI as well as AF.

Table 5 | Baseline Characteristics - Miles RH et al. 2011

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Amiodarone</th>
<th>Ranolazine</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>211</td>
<td>182</td>
<td>NA</td>
</tr>
<tr>
<td>Men</td>
<td>77%</td>
<td>70%</td>
<td>0.12</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.9 ± 10.9</td>
<td>66.7 ± 9.3</td>
<td>0.08</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>54.7 ± 12.7%</td>
<td>57.7 ± 9.8%</td>
<td>0.01</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>13.7%</td>
<td>7.9%</td>
<td>0.07</td>
</tr>
<tr>
<td>Class IV heart failure</td>
<td>8.5%</td>
<td>2.8%</td>
<td>0.02</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>41.7%</td>
<td>32.6%</td>
<td>0.07</td>
</tr>
<tr>
<td>Any previous atrial fibrillation/atrial flutter</td>
<td>7.6%</td>
<td>4.5%</td>
<td>0.21</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>20.4%</td>
<td>19.1%</td>
<td>0.73</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>24.2%</td>
<td>19.8%</td>
<td>0.29</td>
</tr>
<tr>
<td>Hypertension</td>
<td>86.3%</td>
<td>87.1%</td>
<td>0.66</td>
</tr>
<tr>
<td>Previous coronary artery bypass grafting</td>
<td>5.7%</td>
<td>5.1%</td>
<td>0.78</td>
</tr>
<tr>
<td>Diabetes</td>
<td>36.0%</td>
<td>39.3%</td>
<td>0.50</td>
</tr>
</tbody>
</table>
**Statistical Analysis**

Multiple logistic regression model
Significance (α) at 0.05 with a two-tailed test to interpret effect in either direction
SPSS, v16.0

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**Results**

- AF occurred in 26.5% of the amiodarone group vs. 17.5% of the ranolazine group ($P=0.035$)
- No difference in 30-day readmission rate or 30-day mortality rate between treatment groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Amiodarone</th>
<th>Ranolazine</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative atrial</td>
<td>26.5%</td>
<td>17.5%</td>
<td>0.035</td>
</tr>
<tr>
<td>fibrillation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart block</td>
<td>0%</td>
<td>0%</td>
<td>1.0</td>
</tr>
<tr>
<td>Stroke or transient</td>
<td>0%</td>
<td>0.5%</td>
<td>0.87</td>
</tr>
<tr>
<td>ischemic attack</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal failure with</td>
<td>1.1%</td>
<td>0.9%</td>
<td>0.88</td>
</tr>
<tr>
<td>dialysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged ventilation</td>
<td>6.0%</td>
<td>3.8%</td>
<td>0.28</td>
</tr>
<tr>
<td>30-Day readmission</td>
<td>10.4%</td>
<td>10.4%</td>
<td>1.0</td>
</tr>
<tr>
<td>30-Day Mortality</td>
<td>1.09%</td>
<td>0.94%</td>
<td>0.88</td>
</tr>
</tbody>
</table>

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**Authors’ Conclusion**

Ranolazine is independently associated with a significant reduction of AF (34%) after CABG procedure in comparison to amiodarone with no difference in adverse events between the two treatments.

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**Reviewer’s Evaluation**

**Strengths:**
- >300 patient sample
- America
- Novel therapy approach with potential clinical practice implications

**Limitations:**
- Weak study design
- Inconsistent assigned treatment doses with possible clinician bias (amiodarone was the standard of care at study site)
- Lack of exclusion criteria (potential unaddressed ADRs or contraindications)
- Incomplete disclosure of medication history prior to procedure (example: previous or concurrent use of AAD, statins, CCB, or/and BB)
Comparison of Effectiveness of Ranolazine plus Amiodarone versus Amiodarone Alone for Conversion of Recent-Onset Atrial Fibrillation

Fragakis N, Koskinas KC, Katritsis DG, Pagourelis ED, Zografos T, Geleris P.


Objective
To compare the safety and efficacy of ranolazine added to amiodarone versus amiodarone alone for the conversion of recent-onset AF.

Design
Single center ( Greece ), randomized, prospective study
January – December 2011
51 patients (26 in amiodarone control group; 25 in amiodarone + ranolazine active group)
All participants provided informed consents
Trial approved by local ethics committee

### Control Group
- LD: amiodarone IV 5 mg/kg in 1 hour;
- MD: 50 mg/hour for 24 hours – (or until cardioverted in <24 hour)

### Active group
- amiodarone dose in control group
- PLUS ranolazine 1,500 mg PO x 1

Hospitalization management:
- Transthoracic echocardiography performed in all patients
- Discontinuation of amiodarone infusion if: QTc >550 ms; heart rate <40 beats per minute or symptomatic bradycardia; SBP <80 mmHg and not responding to IV fluid; or intolerable SE.
- Electrical conversion if AF persists after 24 hours
- Mandatory first 24-hour continuous ECG and BP monitoring in coronary care unit

Outcomes
- **Primary end point:** Proportion of patients with AF conversion to sinus rhythm within 24 hours
- **Secondary end points:**
  - Time to AF conversion
  - Occurrence of proarrhythmic events
    (defined as new-onset of sustained ventricular tachycardia, ventricular fibrillation, or torsades de pointes)

Inclusion Criteria
- Adults with symptomatic recent-onset AF (<48 hours duration)
- Suitable for pharmacologic cardioversion

Exclusion Criteria
- Cardiogenic shock
- Symptomatic bradycardia
- ACS
- Previous exposure to ranolazine
- Atrial flutter
- Hepatic, renal, or thyroid disorders
- Pacemaker
- Uncorrected electrolyte imbalance
- QTc >440 ms
- Cardiac surgery within 30 days before enrollment
- Concurrent strong cytochrome P450 (CYP3A) inhibitors therapy
- Use of class I or class III antiarrhythmic drug in preceding 24 hours

Baseline Features
No significant differences between the control group and the active group.

**Table 7 Baseline Characteristics – Fragakis et al. 2012**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Control Group (n=26)</th>
<th>Active Group (n=25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62 ± 8</td>
<td>64 ± 7</td>
<td>0.60</td>
</tr>
<tr>
<td>Men</td>
<td>18 (69%)</td>
<td>15 (60%)</td>
<td>0.49</td>
</tr>
<tr>
<td>1st AF episode</td>
<td>9 (35%)</td>
<td>7 (28%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Previous AF</td>
<td>17 (65%)</td>
<td>18 (72%)</td>
<td>0.61</td>
</tr>
<tr>
<td>HTN</td>
<td>20 (77%)</td>
<td>17 (68%)</td>
<td>0.47</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>58 ± 7</td>
<td>55 ± 9</td>
<td>0.44</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>4.3 ± 0.5</td>
<td>4.5 ± 0.5</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Ranolazine for Atrial Fibrillation: A New Indication? | 10
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**Control Group (n=26)** | **Active Group (n=25)** | **P**
--- | --- | ---
BB | 16 (61%) | 12 (48%) | 0.33
CCB | 4 (15%) | 6 (24%) | 0.44
Digoxin | 3 (12%) | 4 (16%) | 0.69
Statins | 16 (61%) | 13 (52%) | 0.49
ACEI/ARB | 8 (31%) | 12 (48%) | 0.21
QTc (ms) | 410 ± 20 | 406 ± 13 | 0.41

**Statistical Analysis**
Multivariable Cox proportional hazards regression model. α = 0.05. SPSS Statistics, v20.0
Log-ranked test to compare cumulative progression of primary endpoint.

**Results**

**Primary end point:**
The active group [amiodarone + ranolazine] demonstrates higher rate of conversion from AF to SR within 24 hours compared to the control group [amiodarone monotherapy] (88% or 22/25 patients vs. 65% or 17/26 patients; \( P = .056 \))

**Secondary end points:**
- **Time to AF conversion**
The active group [amiodarone + ranolazine] demonstrates shorter mean time to conversion from AF to SR within 24 hours compared to the control group [amiodarone monotherapy] (9.8 ± 4.1 hours vs. 14.6 ± 5.3 hours; \( P = .002 \))

**Occurrence of proarrhythmic events**
Although QTc interval increased from baseline to 24 hours in both treatment groups:
- Active group [amiodarone + ranolazine] baseline QTc 406 ± 13 \( \Rightarrow \) 426 ± 17 ms, p<0.001
- Control group [amiodarone monotherapy] baseline QTc 410 ± 20 ms \( \Rightarrow \) 428 ± 21 ms, p<0.001

Overall, QTc interval at time of conversion did not differ between treatment groups:
- Active group [amiodarone + ranolazine] 429 ± 19 ms
- versus Control group [amiodarone monotherapy] 432 ± 24 ms, p=0.44

**Safety Evaluation:**
- No patients required amiodarone discontinuation due to excessive QTc prolongation (pre−specified as >550 ms)
- No proarrhythmic events occurred throughout the study in either group

**Authors’ Conclusion**

**Statistical Impact:** The addition of a single dose of ranolazine increased conversion rate by 23% at 24 hours, significantly increased sinus rhythm restoration by >4 hours compared to amiodarone therapy.

**Clinical Impact:** The addition of ranolazine to standard amiodarone therapy is equally safe, demonstrates higher conversion rate, and promotes faster sinus rhythm restoration compared to amiodarone monotherapy in patients with recent-onset AF.

---

*Figure 8 Cumulative Progression and Time to AF Conversion – Fragakis et al. 2012*
### Reviewer’s Evaluation

#### Strengths:
- First clinical report of synergistic effect of amiodarone and ranolazine combination in patients with recent-onset AF
- Patient selection criteria

#### Limitations:
- Single-center study with low number of participants
- Statistically insignificant primary end point result
- Low clinical practice significance – SR conversion within 24 hours in both groups
- UK Single dose ranolazine 1,500 mg (vs. US maximum daily dose of 2,000 mg)
- “Our purpose was not to test the AF converting potential of ranolazine” alone
- Additional follow-up data are desired

#### Ranolazine enhances the Antiarrhythmic Activity of Amiodarone by Accelerating Conversion of New-onset Atrial Fibrillation after Cardiac Surgery


#### Objective
To assess the time to conversion of post-operative AF of combination ranolazine and amiodarone therapy versus amiodarone alone after CABG surgery.

#### Design
Single center (Greece), randomized, single-blind, prospective study
Undisclosed duration of trial
41 patients (21 in amiodarone control group; 20 in amiodarone + ranolazine active group)
All participants provided informed consents
Trial approved by local ethics committee

<table>
<thead>
<tr>
<th>Control Group</th>
<th>Active group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-conversion</strong></td>
<td>amiodarone IV 300 mg over 30 min; then amiodarone IV 750 mg within 24 hours</td>
</tr>
<tr>
<td><strong>Post-conversion</strong></td>
<td>amiodarone 200 mg PO BID x 1 week; then 200 mg PO daily for next 7 days (or physician discretion)</td>
</tr>
</tbody>
</table>

#### Perioperative management:
- Same surgical, anesthetic, and perfusionist team for all CABG procedures
- Post-op monitoring in coronary care unit with continuous ECG, daily chemistry panel
- ECG Holter monitoring for first 24-hour following transfer to medical floor; then ECG every 4 hours thereafter until discharge
- K+ level maintained in range of 4.6 – 5.0 mmol/L throughout hospital stay
- All medications, including ranolazine, were *crushed* to deliver via GI tube to intubated patients.
- All patients received regimen: aspirin 100 mg daily, atorvastatin 20-40 mg daily, metoprolol 50-100 mg daily, and perindopril 5-10 mg daily upon hospital discharge.

#### Outcomes
Time to normal sinus rhythm conversion of post-operative AF following CABG procedure

#### Inclusion Criteria
Development of post-operative AF following on-pump CABG procedure
Exclusion Criteria

<table>
<thead>
<tr>
<th>History of AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior AAD therapy</td>
</tr>
</tbody>
</table>

Baseline Features

No significant differences between the control group and the active group.

<table>
<thead>
<tr>
<th>Table 8  Baseline Characteristics – Simopoulos et al. 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Group (n=20)</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Age; years</td>
</tr>
<tr>
<td>Gender (male)</td>
</tr>
<tr>
<td>LVEF; %</td>
</tr>
<tr>
<td>LAD; mm</td>
</tr>
<tr>
<td>Arterial blood pressure</td>
</tr>
<tr>
<td>DM</td>
</tr>
<tr>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>Aortic cross-clamp time; minutes</td>
</tr>
<tr>
<td>Serum K+; mEq/L</td>
</tr>
</tbody>
</table>

Statistical Analysis

1-way analysis of variance test used to assess the median time to sinus rhythm conversion Linear regression analysis used to determine the univariate association between variables Significance (α) at 0.05 with a two-tailed test to interpret effect in either direction GraphPad Prism, v5.01

Results

The active group [amiodarone + ranolazine] had significantly shorter time to conversion compared to the control group [amiodarone monotherapy] (19.9 ± 3.2 hours vs. 37.2 ± 3.9 hours; P <.001)

No premature discontinuation of combination therapy was needed (no hemodynamic deterioration or proarrhythmic effects throughout treatment period).

Authors’ Conclusion

The combination of ranolazine 375 mg twice daily with IV amiodarone has superior anti-arrhythmic efficacy in converting post-operative AF compared to IV amiodarone alone.

Reviewer’s Evaluation

Strengths:
- Adequate perioperative management protocol
- Similar patient baseline characteristics in both treatment groups
- Limited cohort to new-onset AF patients only (exclusion criteria)

Limitations:
- Crushing of ranolazine
- Single-center study with low number of participants
- Inconsistent assigned treatment doses with possible clinician bias
- Low daily dose of ranolazine (375 mg PO BID)
SUMMARY

- Atrial fibrillation remains a complex clinical challenge as the currently available treatment options deliver unsatisfactory results (bleeding risks associated with anticoagulants; proarrhythmic complications associated with antiarrhythmic medications; and variable success rates and higher risk of complications associated with ablation procedure).
- Inconsistencies in AAD therapy are prevalent – especially with the dosing of amiodarone, which is considered to be the most effective drug for sinus rhythm maintenance in paroxysmal or persistent AF.
- Ranolazine, an anti-angina medication with unique inhibitory effects of late inward sodium channels within the cardiomyocytes, demonstrates promising potential in AF treatment.
- Preliminary clinical evidence suggests efficacy and safety benefits of ranolazine as adjunctive therapy with multichannel AAD (specifically amiodarone) in recent-onset AF management.

CONCLUSION

CURRENT CHALLENGES

1. Urgent demand for well-designed clinical research trials to assess ranolazine’s role in AF therapy – both in recent-onset and chronic management.
2. Difficulty constructing the ideal AF patient to benefit from ranolazine therapy (weak external validities from available literature evidence).
3. Hardship in identifying the best treatment approach and most appropriate timing of AF therapy for individual patients.

FUTURE DIRECTIONS

1. Ongoing clinical research to expand ranolazine’s impact in cardiopharmacology.
2. Long-term efficacy, safety, and cost-effectiveness analysis of ranolazine in AF management are highly desired.
3. Novel therapeutic options with better efficacy and safety profile for AF management are needed.
STROKE RISK STRATIFICATION SCORES FOR AF PATIENTS

<table>
<thead>
<tr>
<th>CHADS2</th>
<th>CHF</th>
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<tbody>
<tr>
<td>HTN</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
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<td></td>
</tr>
<tr>
<td>DM</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Maximum Score</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>CHA2DS2-VASc</td>
<td>PLUS</td>
<td></td>
</tr>
<tr>
<td>Vascular disease (previous MI, PAD, or aortic plaque)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Age 65 – 74 years</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Maximum Score</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

**A. Antiplatelet Agents**

i. **Aspirin**
   - Limited evidence supporting aspirin monotherapy in preventing strokes in AF patients.
   - Not recommended for patients with CHA2DS2-VASc score= 0.1,9-10
   - Option for patients with CHADS2 or CHA2DS2-VASc score = 1.1,9-10
   - AVERROES trial: apixaban demonstrates greater stroke reduction compared to aspirin 81-325mg daily (1.6% vs. 3.7%, HR 0.45; p<0.001) without significant difference in major bleeding risks.31

ii. **Clopidogrel**
   - Warfarin is superior to combined therapy of clopidogrel and aspirin for stroke prevention in AF patients.32
   - Clopidogrel and aspirin combination is superior to aspirin alone for stroke prevention in AF patients.33 Similar bleeding risks between therapies.

**B. Anticoagulants**

a. **Warfarin**
   - Warfarin results in 64% RR (95% CI 49%-74%) for ischemic & hemorrhagic strokes compared to placebo.1
   - 37 patients needed to treat with warfarin for 1 year to prevent the first primary stroke event.1
     - o 12 patients needed to treat with warfarin for 1 year to prevent another stroke or heart attack.1
   - Warfarin (INR 2-3) for ≥3-weeks prior and 4-weeks after cardioversion for AF lasting ≥48 hours.
   - Limitations: regular INR monitoring, drug interactions, consistent dietary intake, bleeding risks.

b. **Newer oral anticoagulants**
   i. **Dabigatran** - Factor IIa (direct thrombin) inhibitor
      - RE-LY trial: dabigatran 150 mg BID was superior to warfarin (INR goal of 2.0-3.0) in stroke or systemic embolism prevention (1.11% per year vs. 1.69% per year, respectively; p<0.001).34
      - o Dabigatran 150 mg BID had similar rates of major hemorrhage compared to warfarin.34
      - FDA May 2014 Drug Safety: >134,000 Medicare patients review, dabigatran is associated with lower risk of clot-related strokes, bleeding in the brain, and death compared to warfarin. MI risk is similar in both drugs, but dabigatran demonstrated increased risk of major GI bleeding compared to warfarin. No changes to current medication label or recommendation for use.35
      - Consider reduce dose (to 75 mg BID) in renal-impaired patients with concurrent use of dronedarone.13
   
   ii. **Rivaroxaban** - Factor Xa inhibitor
      - AF: 20 mg PO daily with evening meal. Reduce dose to 15 mg in patients with CrCl 15-50 ml/min.13
      - ROCKET-AF trial: rivaroxaban is noninferior to warfarin for the prevention of stroke or systemic embolism in AF patients (1.7% vs. 2.2% per year; HR 0.79, 95% CI 0.66-0.96; p<0.001 for noninferiority).36 Rivaroxaban demonstrates statistically significant reduction in intracranial hemorrhage and fatal bleeding compared to warfarin.36
   
   iii. **Apixaban** - Factor Xa inhibitor
      - AF: 5 mg PO BID. Reduce dose to 2.5 mg BID in patients with ≥2 of the following factors: ≥80 years; weight ≤60 kg; SCr ≥1.5 mg/dL.13,14
      - ARISTOTLE trial: apixaban is superior to warfarin in the prevention of stroke or systemic embolism in AF patients (1.27% vs. 1.6% per year; HR 0.79, 95% CI 0.66-0.95; p<0.001 for noninferiority, p=0.01 for superiority).37 Apixaban demonstrates lower mortality and lower rate of hemorrhagic/ ischemic/ uncertain type of stroke compared to warfarin.37
i. **Beta blockers**
   - “most effective” and is the most frequently used therapy for AF rate control.\(^1\)
   - IV esmolol, propranolol, and metoprolol are effective options in acute AF management.
   - PO atenolol, metoprolol, nadolol, propranolol, or sotalol is appropriate therapy for chronic AF.
   - Concomitant use with digoxin demonstrates improvement in LV function.\(^1\)

ii. **Non-dihydropyridine calcium channel antagonists**
   a. Verapamil
   b. Diltiazem

iii. **Digitalis glycosides**
   a. **Digoxin**\(^1,13-14\)
   - MOA: Direct suppression of AV node conduction
   - ECG: ↓heart rate.
   - PKs: T½ dependent on age, renal clearance, and cardiac function
   - Onset >1 hour; time to peak 1-3 hours
   - Dosing: **AF Rate Control:** (unlabeled dose) 0.125-0.25 mg PO daily
     - Renal adjustment CrCl ≤50 ml/min
   - CIns: Hypersensitivity to drug formulation; ventricular fibrillation.
   - SEs: Digoxin toxicity. Rash, dizziness, headache, nausea, vomiting, and abdominal pain.
   - DIS: Amiodarone, propafenone, and NHP-CCB reduce digoxin excretion.
   - Notes:
     - Reduce dose by 20-25% when convert from PO to IV therapy.
     - Long term use associated with increased mortality risk (AFFIRM trial).\(^38\)
     - Increased risk of death in newly diagnosed AF patients (TREAT-AF trial).\(^39\)
     - Hypokalemia increases risk of digoxin toxicity.

iv. **Other:** when above therapies are ineffective or not tolerated and sinus rhythm is unachievable.
   a. Amiodarone
   b. Dronedarone
### APPENDIX C – Rhythm Control Therapy for AF Management

#### Figure 10 Rhythm Control Strategy for AF Management

<table>
<thead>
<tr>
<th>No Structural Heart Disease</th>
<th>Structural Heart Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dofetilide</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Cathodal ablation</td>
<td>Amodarone</td>
</tr>
<tr>
<td>Flecainide</td>
<td>Cathodal ablation</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Antidotal ablation</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>Isoproterol</td>
</tr>
<tr>
<td>Bisoprolol (monopolar 1kHz)</td>
<td>Antidotal ablation</td>
</tr>
</tbody>
</table>

**Figure 11 Action Potential of Cardiomyocytes**

<table>
<thead>
<tr>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Action Potential of Cardiomyocytes" /></td>
</tr>
</tbody>
</table>

#### a. Flecainide

- **MOA:** (1975) Vaughan Williams class lc agent. Potent Na⁺ channel blocker, vagolytic, anticholinergic, and mild (-) inotrope.
- **ECG:** ↓sinus rate; ↑PR and QRS duration.
- **PKs:** Hepatic metabolism. T½ 7-22 hours. Time to peak 1.5-3 hours. Renal adjust GFR ≤50 ml/min.
- **Dosing:**
  - **AF Maintenance:** 50 mg PO q12h – increase by 50 mg BID at 4-day interval. Max 400 mg daily.
  - **AF Conversion:** (unlabeled use) “pill in pocket” approach – give ≥ 30 minutes after BB or NHP-CCB therapy – 200 mg PO once (<70 kg) or 300 mg once (if ≥ 70 kg) in 24-hour period.
- **Cns:** structural heart disease, MI, and reduced LVEF due to risk of proarrhythmia (CAST trial).
- **SES:** Dizziness, visual disturbances, fatigue, rash, headache. Proarrhythmias risk.
- **Dis:** May ↑ digoxin level. May ↓ warfarin level.
- **Notes:**
  - “pill in pocket” (efficacy 50% within 3 hours)
  - Wait 2-4 t½ of another antiarrhythmic agent(s) to clear before starting flecainide therapy.

#### b. Propafenone

- **MOA:** (1976) Vaughan Williams class lc agent. Potent Na⁺ channel blocker; some BB activity.
- **ECG:** ↓sinus rate; ↑PR and QRS duration.
- **PKs:** T½ 2-10 hours in extensive metabolizers. Hepatic metabolism. Time to peak 3-8 hours. No renal or hepatic dosing adjustments, but consider use with caution.
- **Dosing:**
  - **AF Maintenance:** IR tablet: 150-300 mg PO every 8 hours
    - ER capsule: 225-425 mg PO every 12 hours
  - **AF Conversion:** (unlabeled use) “pill in pocket” approach – use in conjunction with BB or NHP-CCB therapy – IR 450 mg once (<70 kg) or IR 600 mg (≥ 70 kg) in 24-hour period.
- **Cns:** Structural heart disease, post-MI, significant liver disease.
- **SES:** Dizziness, blurred vision, metallic taste.
- **Dis:** May ↑ digoxin level. May ↓ warfarin level.
- **Notes:** Consider withholding class la or class III agents for at least 5 t½ before starting propafenone.
- **Concurrent use with CYP2D6 or CYP3A4 inhibitors may increase flecainide levels.**
- **Food may increase drug serum concentration.**
- **Avoid in patients with prior MI (↑mortality risk) and LV dysfunction (negative inotrope effects).**
- **CYP2D6 substrate (~7-10% AF patients are poor metabolizers requiring 10-32 hours t½ elimination).**

#### c. Dofetilide

- **MOA:** (2000) Vaughan Williams class III agent. Potent K⁺ channel blocker only!!
- **ECG:** ↑QT.
- **PKs:** T½ ~10 hours – prolonged with renal impairment. Renal dosing adjustment based on CrCl.
- **Dosing:** Must have baseline QTc prior to therapy initiation. Rechecked QTc 2-3 hours after initial dose.
- **AF Maintenance or Conversion:** 500 mg PO BID.
- **May start at lower dose based on renal clearance and clinical judgment.**
- **Dose may be modified based on response to initial dofetilide treatment.**
- **Therapy should be discontinued if QTc >500 ms at any time.**
- **Cns:** CrCl ≤20 mL/min; congenital/acquired long QT syndrome; baseline QTc >440ms (or >500 ms in patients with ventricular conduction abnormalities).
- **SES:** Headache, dizziness, insomnia, torsades de pointes (high risk within first 3 days of therapy).
Ranolazine for Atrial Fibrillation: A New Indication?

Dis: CYP3A4 inhibitors (may ↑ serum concentration of dofetilide)
Use with caution together with medications secreted by the kidneys

Notes Unapproved therapy in Europe for atrial fibrillation.
3-day inpatient hospital admission is mandatory for ECG monitoring for therapy start/dose escalation.
Tikosyn® in Pharmacy System (T.I.P.S.) enrollment required for inventory and dispensing.
3-month washout period needed if dofetilide is started after amiodarone therapy failure.

d. Sotalol

MOA: (2000) Dual class II agent (β1- and β2-adrenoreceptor non-cardioselective antagonistic activity) and class III agent (K⁺ channels blocker, contributing to prolonging duration of cardiac action potential).
ECG: ↓sinus rate; ↑PR, ↑QT
PKs: T½ ~ 12 hours (longer if renal dysfunction exists). Food decreases absorption by 20-30%.
Renal dosing adjustment required. No hepatic dosing adjustment.

Dosing: AF Maintenance: 80-160 mg PO BID. Must calculate renal clearance for appropriate dosing.
AF Conversion: not effective for AF conversion to sinus rhythm.

CIns: AF specific: CrCl <40 mL/min; baseline QTc >450 ms; bronchospastic disorders; serum K⁺ <4 mEq/L.
All patients: Uncontrolled HF; congenital or acquired long QT syndromes; cardiogenic shock; AV heart block; bronchial asthma; sinus bradycardia; or hypersensitivity to drug formulation.

SEs: Bradycardia, hypotension, dizziness, dose-related fatigue and dyspnea, GI side effects.
Dis: Monitor therapy with concurrent antihypertensive therapies and/or diabetes medications
Avoid concomitant use with other QT prolonging medications
Notes: Dosing adjustment/reduction based on QTc to avoid toxicity.
Betapace AF® is not interchangeable with Betapace®
Recommend therapy initiation/re-initiation stay in hospital for at least 3 days for continuous ECG monitoring.
Avoid abrupt therapy withdrawal. Recommend gradually taper therapy to avoid side effects and complication.

e. Ibutilide

MOA: (1995) Vaughan Williams class III agent
Exact MOA unknown. Observed prolong action potential in cardiac tissues.
ECG: Continuous ECG monitoring for 4 hours following infusion (or longer if significant hepatic concerns)
PKs: Onset ~1.5 hours after infusion start (1/2 of sinus rhythm conversion take place during infusion)
Hepatic metabolism. Average t½ of 6 hours

Dosing: AF Conversion: 1 mg IV over 10 minutes. May repeat ONCE if needed.
Patients <60 kg: use 0.01 mg/kg.
No renal or hepatic dosing adjustments required.

CIns: Hypersensitivity to formulation; QTc >440 ms
SEs: QT prolongation, hypotension, torsades de pointes, headache, nausea
Dis: Avoid combination with other class III agents or medications with QTc-prolonging effects.
Notes: Potentially fatal arrhythmias (black box warnings).
Chronic AF patients may not be the best candidate (black box warnings).

f. Dronedarone

MOA: (2009) multi-cardiac channels blocker (Na⁺, Ca²⁺, and K⁺ channels)
ECG: ↑QT
Dose: Paroxysmal or persistent AF: 400 mg PO twice daily with food

CIns: NYHA Class IV patients or symptomatic HF with recent decompensation requiring hospitalization (2x of death); AF patients who cannot be cardioverted into normal sinus rhythm; liver or lung toxicity with previous amiodarone use; bradycardia <50 bpm; concomitant use with strong CYP3A4 inhibitors or medications known to prolong the QT interval; severe hepatic impairment; QTc ≥500 ms or PR >280 ms

SEs: SCr bump (~0.1 mg/dL) within 7 days of start; bradycardia; weakness; diarrhea; nausea; vomiting.

Dis: ↑ serum digoxin levels (via inhibition of P-glycoprotein intestinal and renal excretion);
↑ serum creatinine (via renal organic-cation) transport;
CYP3A4, CYP2C9, and P-glycoprotein inhibition effects.

Notes: Structural analogue of amiodarone without the iodine moieties and less lipophilicity.
Do not use in severe heart failure patients (ANDROMEDA trial).
Average increase ~10 ms in QT interval.
Only AAD with stroke reduction benefits

Amiodarone - Refer to Table 3 (page 5) for additional drug information

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Ranolazine for Atrial Fibrillation: A New Indication? | 18
APPENDIX D -- MERLIN-TIMI 36 TRIAL

Effect of ranolazine, an antianginal agent with novel electrophysiological properties, on the incidence of arrhythmias in patients with non-ST-segment-elevation acute coronary syndrome: Results from the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-St-Elevation Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) randomized controlled trial


- Post-hoc analysis of MERLIN-TIMI 36’s safety data of continuous ECG for first 7 days after randomization
- Randomized, placebo-controlled, multinational, multisite, prospective study from 10/2004-5/2006
- Evaluation of incidence(s) of clinically significant arrhythmias detected by ECG monitoring
- 6,351 patients randomized to 1 treatment: 1 placebo therapies

<table>
<thead>
<tr>
<th>Control Group</th>
<th>Treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td>placebo</td>
<td>VS</td>
</tr>
<tr>
<td></td>
<td>LD: ranolazine 200 mg IV over 1 hour;</td>
</tr>
<tr>
<td></td>
<td>MD: ranolazine 80 mg/hour x 12–96 hours.</td>
</tr>
<tr>
<td></td>
<td>Then switch to ranolazine 1,000 mg PO BID</td>
</tr>
</tbody>
</table>

ABBREVIATIONS

AAD: antiarrhythmic drug
ACEI/ARB: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers
AF: atrial fibrillation
AFB: atrial fibrillation burden
AFFIRM: the Atrial Fibrillation Follow-up Investigation of Rhythm Management study
AFI: atrial flutter
AHA/ACC/HRS: American Heart Association/American College of Cardiology/Heart Rhythm Society
ANDROMEDA: Antiarrhythmic Trial with Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease study
ARISTOTLE: Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation study
AV: atrio-ventricular
AVERROES: Apixaban versus Acetylsalicylic Acid to Prevent Strokes study
BB: β-blocker therapy
BID: twice daily
BP: blood pressure
Ca++: calcium
CABG: coronary artery bypass graft
CAD: coronary artery disease
CAST: the Cardiac Arrhythmia Suppression Trial
CCB: calcium channel blocker therapy
CHF: congestive heart failure
CI: confidence interval
Clns: contraindications
CrCl: creatinine clearance
CV: cardiovascular
D: day
DHP: dihydropyridine
Dis: drug interactions
DM: diabetes mellitus
ECG or EKG: Electrocardiogram
EF: ejection fraction
ER: extended release
ESC: European Society of Cardiology
GFR: glomerular filtration rate
GI: gastrointestinal
HF: heart failure
HR: hazard ratio
HTN: hypertension
Ir: cardiac late inward sodium channel
INR: international normalized ratio
IR: immediate release
IV: Intravenous
K+: Potassium
LAD: left atrial diameter
LD: loading dose
LV: left ventricle
LVEF: left ventricular ejection fraction
MI: myocardial infarction
MOA: mechanism of action
ms: milliseconds
mV: millivolts
Na+: Sodium
NHP: non-dihydropyridine
NS: not significant
NYHA: New York Heart Association
PAD: peripheral arterial disease
PKs: pharmacokinetics
PO: by mouth
QTc: corrected QT interval
RE-LY: Randomized Evaluation of Long-Term Anticoagulation Therapy trial
ROCKET-AF: Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation study
RR: relative risk
SCr: serum creatinine
SEs: side effects
SR: sinus rhythm
SVT: supraventricular tachycardia
T½: half-life
TE: thromboembolism
TIA: transient ischemic attack
TMP: threshold membrane potential
TREAT-AF: the Retrospective Evaluation and Assessment of Therapies in AF study
VS: versus
VT: ventricular tachycardia
REFERENCES


Ranolazine for Atrial Fibrillation: A New Indication? | 20


