RANOLAZINE ADDED TO AMIODARONE FACILITATES EARLIER CONVERSION OF ATRIAL FIBRILLATION COMPARED TO AMIODARONE-ONLY THERAPY

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University of Thessaly
NO CONFLICT OF INTEREST DISCLOSURE
Frequently used and effective to convert AF in patients with or without heart failure.

Needs several hours or days for converting AF into sinus rhythm\(^1\)

Requires surveillance for liver, lung and thyroid toxicity\(^2\)

Ranolazine

NEW CLASS
“Late Cardiac Sodium Current Inhibitor”

Film-coated prolonged-release tablets containing 375 mg, 500 mg or 750 mg of ranolazine

2006 - FDA approval for Chronic Stable Angina
Revealed that RAN may suppress both supraventricular & ventricular arrhythmias.
Ranolazine and its Antiarrhythmic Actions

![Diagram showing the effects of ranolazine on atrial and ventricular actions.]

- **Atrial Selective Actions**
  - Peak $I_{Na}$ inhibition
  - $I_{Kr}$ inhibition
  - Late $I_{Na}$ inhibition
  - Increases ERP
  - Increases APD
  - Decreases EADs/DADs

- **Ventricular Effects**
  - Late $I_{Na}$ inhibition
  - $I_{Kr}$ inhibition
  - Decreases EADs/DADs
  - Increases APD/VF threshold
  - Decreases NSVT
  - Decreases proarrhythmia

*Cardiovascular & Hematological Agents in Medicinal Chemistry, 2015, Vol. 13, No. 1*
Current data of Ranolazine effect on AF

- Effectively suppressed AF in experimental studies

- Demonstrated efficacy superior to AMIO alone when used synergistically with AMIO+RAN (1500mg single oral dose) in pts with LA>46mm

- Demonstrated to reduce the incidence of post-operative AF following CABG or valve surgeries when it was or administered in combination with AMIO

1. JACC 2010, Vol.56, N.15
2. JAFIB 2014/Vol-6/Issue-5
4. AM J Cardiol 2011; 108: 673-676
OBJECTIVE

- Effectively restore SR in pts with recent-onset AF
- Fast and effective
- Minimal side effects and no proarrhythmia
HYPOTHESIS

Compare the antiarrhythmic effectiveness of AMIO+RAN vs AMIO alone irrespective of LA size
THE STUDY

- PROBE design

- Prospective
- Open-blinded
- Randomized
Recent onset AF (< 48 hrs duration)
  - Time onset range (2 – 26 hrs)

Eligible for pharmacologic cardioversion
**DOSE SCHEME**

- **Group 1**  \((n=81)\)
  
  Amiodarone infusion (standard scheme)
  
  (loading dose 5mg/kg in 100ml D/W 5% 30’ followed by maintenance infusion of 50mg/h)

- **Group 2**  \((n=92)\)
  
  Amiodarone infusion (standard scheme) plus Ranolazine 1g per os as a single dose
Primary Endpoint

Time to conversion of AF after treatment initiation in the AMIO versus AMIO + RAN group

Secondary Endpoint

The conversion rate of both treatments within 24 hours
Exclusion Criteria

pulmonary disease
cardiogenic shock
sick sinus syndrome
QTc > 440 ms
thyroid dysfunction
hypokalemia
renal failure (eGFR <30 mL/min/1.73 m²)
hepatic insufficiency
patients receiving CYP3A4 inhibitors
RESULTS
### Demographic and baseline clinical characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Amiodarone (n = 81)</th>
<th>Amiodarone Plus Ranolazine (n = 92)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>41/40</td>
<td>38/54</td>
<td>0.20</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67 ± 11</td>
<td>70 ± 10</td>
<td>0.05</td>
</tr>
<tr>
<td>HTN</td>
<td>53 (65%)</td>
<td>65 (71%)</td>
<td>0.46</td>
</tr>
<tr>
<td>IHD</td>
<td>13 (16%)</td>
<td>29 (31%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Obesity</td>
<td>32 (39%)</td>
<td>27 (29%)</td>
<td>0.16</td>
</tr>
<tr>
<td>T2DM</td>
<td>9 (11%)</td>
<td>7 (8%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Previous AF</td>
<td>33 (41%)</td>
<td>34 (37%)</td>
<td>NS</td>
</tr>
<tr>
<td>New-onset AF</td>
<td>48 (59%)</td>
<td>58 (63%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Medications**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Amiodarone (n = 81)</th>
<th>Amiodarone Plus Ranolazine (n = 92)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Blockers</td>
<td>32 (39%)</td>
<td>36 (39%)</td>
<td>0.96</td>
</tr>
<tr>
<td>ACEI/ARBs</td>
<td>55 (68%)</td>
<td>56 (61%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Digoxin</td>
<td>0 (0%)</td>
<td>2 (2%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Class III or la/lc antiarrhythmics</td>
<td>10 (12%)</td>
<td>12 (13%)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Data are expressed as mean SD or number (percentage).

*No statistically significant differences btw the Groups*
**ECHO and ECG characteristics after conversion of AF to SR**

<table>
<thead>
<tr>
<th>ECHO Parameters</th>
<th>AMIO</th>
<th>AMIO plus RAN</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAd (cm)</td>
<td>4.2 ± 0.5</td>
<td>4.1 ± 0.4</td>
<td>0.18</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>53 ± 8</td>
<td>52 ± 10</td>
<td>0.58</td>
</tr>
<tr>
<td>LVEF &lt;50%</td>
<td>7 (8%)</td>
<td>13 (14%)</td>
<td>0.26</td>
</tr>
<tr>
<td>ECG variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>74 ± 8</td>
<td>60 ± 7</td>
<td>0.00</td>
</tr>
<tr>
<td>PWD (ms)</td>
<td>88 ± 34</td>
<td>91 ± 26</td>
<td>0.63</td>
</tr>
<tr>
<td>PQ (ms)</td>
<td>182 ± 42</td>
<td>183 ± 42</td>
<td>0.70</td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>96 ± 15</td>
<td>96 ± 22</td>
<td>0.47</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>433 ± 27</td>
<td>418 ± 33</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*No statistically significant differences btw the Groups*
Cumulative progression of AF conversion into SR
Effect of AMIO and AMIO+RAN treatment on AF conversion rate (A) and time to conversion (B)
POST CONVERSION OF AF TO SR IN AMIO+RAN GROUP

- No bradycardia

- No significant QTc prolongation
SIDEB EFFECTS

- Overall well tolerated (both agents)
- 6 pts w/ Dizziness and mild transient hypotension (Ranolazine)

- Major side effects were not observed
Our data demonstrate faster sinus rhythm restoration and enhanced conversion rate of AF after AMIO plus RAN in patients with preserved ejection fraction and left atrial size, implicating a synergistic effect of the two agents.

This is explained by the ability of ranolazine to selectively depress atrial conduction and increase post-repolarization refractoriness more than amiodarone, thereby potentially enhancing the antiarrhythmic effect of amiodarone.
Ranolazine Added to Amiodarone Facilitates Earlier Conversion of Atrial Fibrillation Compared to Amiodarone-Only Therapy

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Background: Amiodarone is known to slow the ventricular rate during atrial fibrillation (AF) and to convert it into sinus rhythm. However, due to its delayed onset of action, ranolazine (RAN), a new antianginal agent with atrial-selective electrophysiologic properties, has recently been attempted as add-on therapy with AMIO to facilitate AF conversion.

Methods: To establish the role of this combination therapy, we enrolled 173 consecutive patients (68 ± 10 years, 54% male) with recent-onset (<48-hour duration) AF who were eligible for pharmacologic cardioversion. Patients were randomized to intravenous AMIO (loading dose 5 mg/kg in 1 hour followed by 50 mg/h; n = 81), or AMIO plus a single oral dose of RAN 1 g (n = 92).

Results: Mean left atrial diameter did not significantly differ between groups, AMIO and AMIO + RAN (4.2 ± 0.5 cm vs 4.1 ± 0.4 cm, P = 0.18). Patients were randomized to intravenous AMIO (loading dose 5 mg/kg in 1 hour followed by 50 mg/h; n = 81), or AMIO plus a single oral dose of RAN 1 g (n = 92). The AMIO + RAN group compared with the AMIO-only group showed significantly shorter time to conversion (8.6 ± 2.8 hours vs 19.4 ± 4.4 hours, P < 0.0001) and higher conversion rate at 24 hours (98% vs 58%, P < 0.001). Left ventricular ejection fraction did not markedly vary between the two groups and ranged within moderately reduced values. No serious clinically evident adverse effects were observed in any of the patients receiving either AMIO or the combination treatment.

Conclusions: Our data demonstrate faster sinus rhythm restoration and enhanced conversion rate of AF after AMIO plus RAN in patients with preserved ejection fraction and left atrial size, implicating a synergistic effect of the two agents. (PACE 2017; 00:1–7)
THANK YOU!