Effects of Ranolazine on Angina and Quality of Life Following PCI with Incomplete Revascularization

The Ranolazine for Incomplete Vessel Revascularization (RIVER-PCI) Trial

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For the RIVER-PCI Investigators
ClinicalTrials.gov NCT01442038
Background

- Incomplete revascularization (ICR) following PCI has been associated with a higher rate of recurrent ischemic events.

- Angina is also reported in >20% following PCI at 1 year, and is associated with lower QOL.

- In MERLIN, ranolazine reduced the risk of recurrent ischemic events among post-MI patients with a history of prior angina - including those treated with PCI – by up to 30% (HR 0.69; 95% CI 0.51-0.92)*

*Gutierrez et al Clin Cardiol. 2015;38:469–475
Patients with History of Chronic Angina AND Incomplete Revascularization After PCI
N=2600

1:1 Randomization
Strata: ACS vs. non-ACS, DM vs. non-DM

Ranolazine 1000 mg BID
245 sites 15 countries

Placebo

Primary Endpoint
Ischemia-driven revascularization or Ischemia-driven hospitalization

Event driven
Minimum 1 Year Follow-up

Standard Medical Therapy

Duke Clinical Research Institute

## Primary Endpoint

Ischemia-driven revascularization or ischemia-driven hospitalization

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>Ranolazine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1317</td>
<td>1287</td>
</tr>
<tr>
<td>3</td>
<td>1164</td>
<td>1165</td>
</tr>
<tr>
<td>6</td>
<td>1101</td>
<td>1098</td>
</tr>
<tr>
<td>9</td>
<td>1018</td>
<td>1028</td>
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<tr>
<td>12</td>
<td>945</td>
<td>960</td>
</tr>
<tr>
<td>15</td>
<td>891</td>
<td>879</td>
</tr>
<tr>
<td>18</td>
<td>813</td>
<td>788</td>
</tr>
<tr>
<td>21</td>
<td>500</td>
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<td>24</td>
<td>266</td>
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<tr>
<td>27</td>
<td>134</td>
<td>128</td>
</tr>
<tr>
<td>30</td>
<td>30</td>
<td>45</td>
</tr>
</tbody>
</table>

HR [95%CI] = 0.95 [0.82, 1.10]

p-value = 0.48

In MERLIN, patients with a history of prior angina demonstrated benefit from ranolazine across QOL domains, with greatest improvement in angina frequency (Mean SAQ difference 3.4, p <0.001)

We hypothesized that ranolazine would reduce angina frequency and improve QOL

Collected disease-specific health status and QOL measures at baseline and months 1, 6, and 12

QOL Population

Overall Trial Population
(2,604)

1,317 to ranolazine
103 questionnaires invalid
7 questionnaires not done
1,207 in QOL population

92%
QOL Population
(2,389)

1,287 to placebo
97 questionnaires invalid
8 questionnaires not done
1,182 in QOL population

78% (1,864) complete data at all time points
QOL Analysis

1º endpoint was SAQ Angina Frequency (Score 0-100)
- No Angina (SAQ score = 100)
- Monthly Angina (SAQ score 61–99)
- Weekly Angina (SAQ score 31–60)
- Daily Angina (SAQ score ≤30)

2º endpoints were SAQ Angina Treatment Satisfaction and Duke Activity Status Index

Treatment differences (ranolazine minus placebo) were generated with least squares means at each post-baseline time point and with repeated measures overall

Pre-specified subgroups: age, sex, ACS indication for PCI, diabetes, and categories of baseline angina frequency
## QOL Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Ranolazine (n=1207)</th>
<th>Placebo (n=1182)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63.3 ± 10.4</td>
<td>63.3 ± 10.0</td>
</tr>
<tr>
<td>Female</td>
<td>20.3%</td>
<td>19.7%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>92.6%</td>
<td>93.6%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>33.1%</td>
<td>32.0%</td>
</tr>
<tr>
<td>HTN</td>
<td>84.7%</td>
<td>87.3%</td>
</tr>
<tr>
<td>ACS indication PCI</td>
<td>33.5%</td>
<td>36.3%</td>
</tr>
<tr>
<td>Anti-ischemic meds (2-3)</td>
<td>32.7%</td>
<td>33.2%</td>
</tr>
<tr>
<td>Prior MI</td>
<td>47.3%</td>
<td>47.8%</td>
</tr>
<tr>
<td>Prior Revascularization (any)*</td>
<td>50.8%</td>
<td>46.5%</td>
</tr>
<tr>
<td>Angina Frequency (SAQ mean)**</td>
<td>67.3</td>
<td>69.7</td>
</tr>
</tbody>
</table>

All p>0.05 except *p=0.04, **p=0.03
SAQ Angina Frequency

Mean Treatment Difference (Ranolazine – Placebo) – Adjusted for baseline

- Study Visit (Months): 1, P = 0.06
- Study Visit (Months): 6, P = 0.17
- Study Visit (Months): 12, P = 0.51
SAQ Angina Treatment Satisfaction

Mean Treatment Difference (Ranolazine – Placebo) - Adjusted for Baseline

P = 0.76
P = 0.62
P = 0.80
Duke Activity Status Index

Mean Treatment Difference (Ranolazine – Placebo) - Adjusted for Baseline
SAQ Angina Frequency - Subgroups

Mean Treatment Difference - Repeated Measure Adjusted for Baseline

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1.0 (-0.2, 2.2)</td>
</tr>
<tr>
<td>Age &lt;75 years</td>
<td>1.1 (-0.1, 2.4)</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>-0.2 (-3.6, 3.3)</td>
</tr>
<tr>
<td>Men</td>
<td>1.2 (-0.1, 2.5)</td>
</tr>
<tr>
<td>Women</td>
<td>-0.2 (-2.9, 2.4)</td>
</tr>
<tr>
<td>Non-ACS PCI indication</td>
<td>1.2 (-0.3, 2.7)</td>
</tr>
<tr>
<td>ACS PCI indication</td>
<td>0.6 (-1.2, 2.5)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>0.2 (-1.2, 1.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.7 (0.5, 4.9)</td>
</tr>
<tr>
<td>Angina Monthly/None (SAQ &gt;60)</td>
<td>0.1 (-1.1, 1.4)</td>
</tr>
<tr>
<td>Angina Weekly/Daily (SAQ ≤60)</td>
<td>2.3 (0.0, 4.6)</td>
</tr>
</tbody>
</table>
SAQ Angina Frequency – Diabetes and Baseline Angina
Ranolazine – Placebo (Adjusted for Baseline Score)

Interaction
P=0.02

Interaction
P=0.02
Limitations

- Incomplete Revascularization (ICR) was defined anatomically, without documentation of ischemia or FFR-based functionality.

- Angina questionnaires were administered at discrete times, and were not collected prior to repeat revascularization or hospitalization.

- Most patients were taking more than one other anti-ischemia agent at baseline.

- Ranolazine treated patients were more likely to prematurely discontinue study drug (27% vs. 21%, p<0.001*), possibly biasing the results towards the null.

*At 12 months*
Conclusions

- Despite incomplete revascularization following PCI, there was no incremental benefit on angina or QOL measures with the addition of ranolazine in this angiographically-identified population.

- Significant and sustained improvements in angina were observed in both arms following PCI, with most patients having rare or no angina by one month.

- Additional research is needed to understand the relationship between patient-reported angina and ischemia-driven events.
November 10, 2015 in Circulation

Original Article

Effects of Ranolazine on Angina and Quality of Life After Percutaneous Coronary Intervention With Incomplete Revascularization

Results From the Ranolazine for Incomplete Vessel Revascularization (RIVER-PCI) Trial

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