Ranolazine: New Treatment Paradigm for Myocardial Dysfunction, Arrhythmias, and Myocardial Ischemia

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Ischemia-induced Increase in $[\text{Na}^+]_i$ and Post-ischemia Recovery of LV Function in Rat Isolated Hearts

$^{23}\text{Na}$ NMR Spectroscopy

(Imahashi K. et al., Circ Res. 1999;84:1401)
Time Course of Changes in Intracellular [Na⁺] and Uptake of Ca²⁺ During Ischemia and Reperfusion.

(Tani and Neely, Circ. Res. 1989;65:1045)
Intracellular Na⁺-dependent Calcium Overload Due to Enhanced Late $I_{Na}$

Undrovinas AI, Fleidervishe IA, Makielski JC. Inward sodium current at resting potentials in single cardiac myocytes induced by the ischemic metabolite lysophosphatidylcholine. Circ Res. 1992;71:1231-1241.


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Ischemia is associated with disruptions in cellular sodium and calcium homeostasis.

An enhanced late sodium current is likely to contribute to the sodium overload observed in ischemia. Late phase sodium channels have been shown to remain open longer in ischemic conditions. Sodium overload may result from decreased efflux and increased influx during ischemia, with greater intracellular accumulation of sodium as the duration of ischemia increases.

This is followed by an increase in intracellular Calcium through the Na/Ca exchanger on the myocyte wall.


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Ranolazine Prevents Left Ventricular (LV) Dysfunction of Contraction and Relaxation Caused by ATX-II

ATX-II is a toxin that promotes late I_{ca}, and mimics the effects of ischemia on that channel.

Rat isolated ejecting/working heart
M Fraser, J McVeigh, L Seidman, 2004

ATX-II alone (12 nM) n=13
ATX II + Ran (8.6 μM) n=6
Ranolazine Prevents Left Ventricular (LV) Dysfunction of Contraction and Relaxation Caused by ATX-II

ATX-II is a toxin that promotes late L-type, and mimics the effects of ischemia on that channel.

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Ranolazine Prevents Left Ventricular (LV) Mechanical Dysfunction Caused by ATX-II

Rat isolated ejecting/working heart
M Fraser, J McVeigh, L Belardinelli, 2004
Role(s) of Oxygen Free Radicals in Pathophysiological Processes

**Ischemia/Reperfusion Injury**
"Stunned Myocardium"
*Development and Progression of HF*

Increased $O_2$ free radicals in the myocardium
- increase late $I_{\text{Na}}$
- cause $Ca^{2+}$ influx via reverse mode of NCX
- induce severe diastolic dysfunction
Ranolazine Improves LV Diastolic Compliance in Patients with Ischemic Heart Disease

Cellular calcium overload causes impaired contractility and, more significantly, impaired relaxation.

Sustained contraction of the ischemic cardiomyocyte during diastole, or diastolic relaxation failure, consumes energy.

This increases the demand for oxygen and worsens ischemia and angina.

Sustained contraction of the ischemic cardiomyocyte during diastole, or diastolic relaxation failure, also causes compression of the intramural vessels that supply the myocardium with blood and oxygen.

This significantly reduces myocardial blood flow and oxygen supply, since most blood flow to the heart occurs during diastole.

As a consequence, ischemia and angina become worse.


Reversal by Ranolazine of the Effect of ATX-II on Coronary Flow

Coronary Blood Flow

Rat isolated ejecting/working heart
H Fraser, L Belardinelli, AS Clanachan, 2004
Ranolazine Reduces Lactate Production Caused by ATX-II

Rat isolated ejection/working heart
H Fraser, J McVeigh, L Belardinelli, 2004

Confidential
Ranolazine Improves Myocardial Blood Flow During Reperfusion

*Isolated Perfused Rabbit Heart*

**Coronary Flow**
- Baseline
- Untreated: 24±1.3 ml/min
- Ranolazine: 20±1.2 ml/min

![Graph showing coronary flow during ischemia and reperfusion](image)

*(Cianachan AS et al. Eur J. 2005)*
Nature and Location of Limitations to Coronary Blood Flow

(Kern in Braunwald Heart Disease 2005)
Myocardial Injury Results Both From Ischemia Injury and Reperfusion Injury

Myocardial Ischemia:
Sites of Action of Anti-Ischemia Medication

**Development of Ischemia**

↑ O₂ Demand
- Heart rate
- Blood pressure
- Preload
- Contractility

↓ O₂ Supply

**Consequences of Ischemia**

- Electrical instability
- Myocardial dysfunction
  (↓ systolic function/
  ↑ diastolic stiffness)

**Ischemia (Ca²⁺ overload)**

**Ranolazine**

Compression of nutritive blood vessels

Conventional anti-ischemic medications
- β blockers
- Nitrates
- Ca²⁺ blockers

(Stone, 2004)
Monotherapy With Ranolazine Increases Exercise Performance at Trough and Peak: MARISA

N = 175, All/Near Completers population; L3 means ± SE.
**p < 0.01 vs placebo; ***p < 0.001 vs. placebo

(Chaitman, et al JACC 2004;43:1075)
Ranolazine is at Least as Effective as Atenolol 100 mg Daily

- Time to onset of angina
- Time to 1-mm ST-depression
- Exercise duration

LS mean ± SE, sec

- Placebo
- Ranolazine IR 400 mg tid (1741 ± 1020 ng base/mL)
- Atenolol 100 mg qd

N = 154 patients

(Roussou, et al. AJC 2005;05:311)
Combination regimen of ranolazine with:
- Atenolol 50 mg qd, or
- Diltiazem 120 mg qd, or
- Amlodipine 5 mg qd

(CARISA)

**N = 781, ITT/LOCF; LS mean ± SE.**

*"p < 0.05; **p ≤ 0.01; ***p ≤ 0.001 vs placebo.*

(Chaitman, et al. JAMA 2004;291:309)
Values are least square means ± SE from a mixed-model repeated measures analysis of variance.
### Ranolazine: Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n=552)</th>
<th>Ranolazine (n=835)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation (%)</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Nausea (%)</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Dizziness (%)</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Headache (%)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Pts discontinuing Rx (%)</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

*Ranolazine prolongs the QTc an average of about 6 msec.*
*(No episode of torsades de pointes has been observed.)*
Drug-induced torsade de pointes: major electrophysiologic events
Electrophysiologic Effects of Ranolazine

### Ion Current Effects—$I_{Kr}$ and Late $I_{Na}$

<table>
<thead>
<tr>
<th>Ion current</th>
<th>Effect on action potential</th>
<th>Effect on ECG</th>
<th>Ranolazine potency $IC_{50}$</th>
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<td>$I_{Kr}$ Inhibition</td>
<td>Lengthens</td>
<td>$\uparrow$ QT</td>
<td>12 $\mu$M</td>
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<td>Late $I_{Na}$ inhibition</td>
<td>Shortens</td>
<td>$\downarrow$ QT</td>
<td>$\geq$ 5 $\mu$M</td>
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*Average therapeutic concentration range 850 to 2500 ng/mL (~2 to 6 $\mu$M)*
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**Late $I_{Na}$ effect mitigates $I_{Kr}$ effect**

Average therapeutic concentration range
850 to 2500 ng/mL (~2 to 6 µM)
The effect of RAN to inhibit EAD activity and to abbreviate the AP is also nicely demonstrated in this study by Song et al.
Suppression by Ranolazine of H$_2$O$_2$-induced EADs in a Guinea Pig Ventricular Myocyte

(A. Control) (B. H$_2$O$_2$ (200 μM))

(C. H$_2$O$_2$ + Ranolazine (10 μM)) (D. H$_2$O$_2$ Ranolazine Washout)

(Song Y, et al.; ACC, 2006)
Transmural Differences of Ventricular Repolarization—A Mechanism for Arrhythmias

Shimizu et al., JCF, 1999;10:154-164
Transmural Differences of Ventricular Repolarization—A Mechanism for Arrhythmias

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Transmural Differences of Ventricular Repolarization—A Mechanism for Arrhythmias

LV chamber

Epicardium

Mid-myocardium

Endo-endothium

APD, msec

Normal  $I_K$ blocker

230  261

289  359

271  326

Dispersion 59

$t$-Sotalol ($I_K$ blockers) 100 μM.
Transmural Differences of Ventricular Repolarization—A Mechanism for Arrhythmias

<table>
<thead>
<tr>
<th>Location</th>
<th>Normal</th>
<th>I&lt;sub&gt;Kr&lt;/sub&gt; Blocker&lt;sup&gt;†&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epicardium</td>
<td>230</td>
<td>261</td>
</tr>
<tr>
<td>Mid-myocardium</td>
<td>289</td>
<td>359</td>
</tr>
<tr>
<td>Endocardium</td>
<td>271</td>
<td>326</td>
</tr>
</tbody>
</table>

Dispersion: 59 vs. 98

†d-Sotalol (I<sub>Kr</sub> blockers) 100 µM.
Transmural Differences of Ventricular Repolarization—A Mechanism for Arrhythmias

APD, msec
Normal

I_{Kr} blocker

Epicardium
Mid-myocardium
Endocardium

230
289
271
261
359
325

Dispersion
59
98

Arrhythmias enabled

†d-Sotalol (I_{Kr} blockers) 100 µM.
# Effect of Ranolazine on Transmural Dispersion of Refractory Periods

**Canine LV Wedge Preparation**

<table>
<thead>
<tr>
<th>Ranolazine Concentration</th>
<th>QT (msec)</th>
<th>Transmural Dispersion of Repolarization (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>277</td>
<td>33</td>
</tr>
<tr>
<td>1 µmol/L</td>
<td>284 *</td>
<td>29</td>
</tr>
<tr>
<td>5 µmol/L</td>
<td>295 *</td>
<td>31</td>
</tr>
<tr>
<td>10 µmol/L</td>
<td>301 *</td>
<td>31</td>
</tr>
<tr>
<td>100 µmol/L</td>
<td>307 *</td>
<td>28</td>
</tr>
</tbody>
</table>

* p<0.05 vs control

*No torsade could be provoked during endo- or epicardial pacing, even in setting of hypokalemia*

## Association of Increased Transmural Dispersion of Repolarization (TDR) and EADs in Canine LV Myocardium with Occurrence of Torsade de Pointes (TdP) in Humans

<table>
<thead>
<tr>
<th></th>
<th>Effect in canine LV</th>
<th>Effect in Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EADs</td>
<td>↑ TDR</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cisapride</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Quinidine, low concentration</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sotalol</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mibefradil</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

MERLIN TIMI-36 (N=6500)

UA/NSTEMI
CP < 48h, ST-Dep or +cTn, or DM, or TRS ≥ 3
Standard Therapy

Ranolazine
IV to PO

RANDOMIZE (1:1)
Double-blind

Placebo
Matched IV/PO

Holter at enrollment x 7d

Follow-up
Q4 mo
(Avg 8.12 mo)

Primary End Point
Cardiovascular death, MI
or recurrent ischemia

Duration
(Event-driven)

Follow-up Visits:
Day 14, Months 4,
Q4 Months

Final Visit

Additional endpoints: Exercise performance, extent of myocardial injury,
angina questionnaire, quality of life, arrhythmia
Effect of Ranolazine in Patients with ACS: 
the MERLIN Trial

6500 pts with ACS: randomized to IV, then PO ranolazine vs placebo
Followup median 348 days

Composite 1° Endpoint
(Death, MI, Recurrent Ischemia)
HR 0.92 (p=0.11)

Components of 1° Endpoint
CV Death/MI
HR 0.99 (p=0.87)
Recurrent Ischemia
HR 0.87 (p=0.03)

(Morrow, et al. ACG 2007)
Baseline BNP and Clinical Outcomes

CV Death, MI, or Recurrent Ischemia (%)

Days from Randomization

BNP > 80 pg/ml

BNP ≤ 80 pg/ml

P < 0.001

Morrow DA. AHA 2007, Orlando, FL
Baseline BNP and Effect of Ranolazine on Primary Endpoint

CV Death, MI, or Recurrent Ischemia (%)

*KM cumulative incidence (%) at 12 months

Morrow DA. AHA 2007, Orlando, FL
Baseline BNP and Effect of Ranolazine on Primary Endpoint

CV Death, MI, or Recurrent Ischemia (%)

Days from Randomization

*KM cumulative incidence (%) at 12 months

Morrow DA. AIHA 2007, Orlando, FL
Baseline BNP and Effect of Ranolazine on Primary Endpoint

CV Death, MI, or Recurrent Ischemia (%)

Days from Randomization

P-interaction = 0.05

*KM cumulative incidence (%) at 12 months

Morrow DA. AHA 2007, Orlando, FL
K-M Estimated Rates of First Occurrence of Ventricular Tachycardia > 8 Beats

MERLIN Study of 6560 Patients Treated within 48 Hrs of ACS

# Effect of Ranolazine on Tachyarrhythmias

<table>
<thead>
<tr>
<th></th>
<th>Ranolazine</th>
<th>Placebo</th>
<th>RR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ventricular Arrhythmias</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VT &gt; 4 beats &gt; 100 bpm (%)</td>
<td>20.9</td>
<td>29.5</td>
<td>0.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VT &gt; 8 beats, &lt; 30 sec (%)</td>
<td>5.3</td>
<td>8.3</td>
<td>0.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sustained VT (%)</td>
<td>0.4</td>
<td>0.4</td>
<td>1.01</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>Supraventricular Arrhythmias</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial Fib (%)</td>
<td>1.7</td>
<td>2.4</td>
<td>0.74</td>
<td>0.08</td>
</tr>
<tr>
<td>Other SVT (%)</td>
<td>44.7</td>
<td>55.0</td>
<td>0.81</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Ranolazine: Drug interactions

Ranolazine is primarily metabolized by CYP3A. Potent or moderately potent inhibitors of this enzyme will increase ranolazine plasma levels and QTc. Their concomitant administration should be avoided.

Less potent CYP3A inhibitors such as simvastatin and cimetidine did not increase the exposure to ranolazine in healthy volunteers.

Plasma concentrations are not significantly altered by concomitant digoxin at 0.125 mg qd.
Summary: Ranolazine’s Unique Pharmacologic Profile to Improve Myocardial Function, Ischemia, and Arrhythmias

- Prevents Na⁺-induced Ca²⁺ overload in ischemia and heart failure
  - Improves diastolic dysfunction
  - May have a more primary role in improving myocardial function
- Anti-anginal and anti-ischemic efficacy
- Anti-ischemic properties do not depend on changes in:
  - heart rate
  - blood pressure
- Complementary to existing agents that depend on hemodynamic mechanisms
- Safe and well-tolerated
- Prolongs QTc: slightly, but stabilizes myocardial repolarization
  - No evidence for torsade de pointes
  - May even have a primary anti-arrhythmic effect