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Electrophysiological Effects of Ranolazine, a Novel Antianginal Agent With Antiarrhythmic Properties

Charles Antzelevitch, PhD; Luiz Belardinelli, MD; Andrew C. Zygmunt, PhD; Alexander Burashnikov, PhD; José M. Di Diego, MD; Jeffrey M. Fish, DVM; Jonathan M. Cordeiro, PhD; George Thomas, PhD

Background—Ranolazine is a novel antianginal agent capable of producing antischismic effects at plasma concentrations of 2 to 6 μmol/L without reducing heart rate or blood pressure. The present study examines its electrophysiological effects in isolated canine ventricular myocytes, tissues, and arterially perfused left ventricular wedge preparations.

Methods and Results—Transmembrane action potentials (APs) from epicardial and midmyocardial (M) regions and a pseudo-ECG were recorded simultaneously from wedge preparations. APs were also recorded from epicardial and M tissues. Whole-cell currents were recorded from epicardial and M myocytes. Ranolazine inhibited $I_{Kr}$ (IC$_{50}$=11.5 μmol/L), late $I_{Na}$, late $I_{Ca}$, peak $I_{Ca}$, and $I_{Na-Ca}$ (IC$_{50}$=5.9, 50, 296, and 91 μmol/L, respectively) and $I_{Kr}$ (17% at 30 μmol/L), but caused little or no inhibition of $I_{K1}$ or $I_{Kr}$. In tissues and wedge preparations, ranolazine produced a concentration-dependent prolongation of AP duration of epicardial but abbreviation of that of M cells, leading to reduction or no change in transmural dispersion of repolarization (TDR). At [K+]o=4 mmol/L, 10 μmol/L ranolazine prolonged QT interval by 20 ms but did not increase TDR. Extrasystolic activity and spontaneous torsade de points (TdP) were never observed, and stimulation-induced TdP could not be induced at any concentration of ranolazine, either in normal or low [K+]o. Ranolazine (5 to 20 μmol/L) suppressed early afterdepolarizations (EADs) and reduced the increase in TDR induced by the selective $I_{Kr}$ blocker d-sotalol.

Conclusions—Ranolazine produces ion channel effects similar to those observed after chronic amiodarone (reduced $I_{Kr}$, $I_{K1}$, late $I_{Na}$, and $I_{Ca}$). The actions of ranolazine to suppress EADs and reduce TDR suggest that, in addition to its antianginal actions, the drug may possess antiarrhythmic activity. (Circulation. 2004;110:904-910.)

Key Words: ischemia ■ ion channels ■ intervals ■ depolarization

Ranolazine is the first of a new class of compounds shown to exert antianginal effects without causing significant bradycardia and/or lowering systemic blood pressure.1-3 The drug has been shown to increase left ventricular function in animals with chronic heart failure,4 and 2 clinical trials (Monotherapy Assessment of Ranolazine In Stable Angina [MARISA] and Combination Assessment of Ranolazine In Stable Angina [CARISA]) have established its effectiveness as an antianginal agent.1,2 Ranolazine is known to produce a modest prolongation of the QT interval, yet little is known about the electrophysiological actions of the drug.1 The present study was designed to assess the electrophysiological effects of ranolazine in myocytes, tissues, and arterially perfused wedge preparations isolated from the canine left ventricle.

Methods

See the online-only Data Supplement (listed with this article at http://www.circulationaha.org) for information about Methods.5,6

Results

Effect of Ranolazine on $I_{Kr}$, $I_{K1}$, $I_{to}$, Late $I_{Na}$, $I_{Ca}$, Late $I_{Ca}$, and $I_{Na-Ca}$

Figures 1 to 3 show the effect of ranolazine to inhibit $I_{Kr}$, late $I_{Na}$, $I_{Ca}$, late $I_{Ca}$, and $I_{Na-Ca}$ in canine left ventricular (LV) myocytes (midmyocardial and epicardial cells). Ranolazine inhibited both inward depolarizing and outward repolarizing currents. The potency (IC$_{50}$) of drug inhibition of late $I_{Na}$ ranged between 5 and 21 μmol/L, with a greater potency at more positive voltage-clamp test potentials and higher frequency of depolarization. Although ranolazine inhibited late $I_{Ca}$ with an IC$_{50}$ of 50 μmol/L, significant inhibition (25% to 30%) occurred within the therapeutic range (2 to 6 μmol/L). The drug weakly inhibited $I_{Na-Ca}$ (inward sodium-calcium exchange current), peak $I_{Ca}$, and the slow component of the delayed rectifier potassium current ($I_{K1}$; 17% inhibition at 30 μmol/L and 20% at 900 μmol/L), but produced no effect on the outward rectifier potassium current ($I_{Kr}$) or the transient outward potassium current ($I_{to}$).

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From the Masonic Medical Research Laboratory, Utica, NY (C.A., A.C.Z., A.B., J.M.D., J.M.F., J.M.C., G.T.), and CV Therapeutics, Inc, Palo Alto, Calif (L.B.).

The online-only Data Supplement, which contains information about the Methods used in the study, can be found at this article at http://www.circulationaha.org.

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Figure 3 shows the superimposed concentration-response curves for all of the currents for which such a relationship could be obtained. The plot highlights the overlap between the inhibition by ranolazine of $I_{Kr}$, late $I_{Na}$, and late $I_{Ca}$ at clinically relevant therapeutic concentrations (2 to 6 $\mu$mol/L), suggesting that the effect of the drug to block outward repolarizing current, which prolongs action potential duration (APD), is substantially counterbalanced by its effect to inhibit the inward current, which is expected to abbreviate the action potential.

**Effect of Ranolazine in Isolated Canine Ventricular Tissues**

Ranolazine caused no change in resting membrane potential, action potential amplitude, or overshoot in either midmyocardial (M) or epicardial cells, except at very high concen-
trations (100 μmol/L), considerably above the plasma concentrations encountered in clinical use (Table 1).

Figure 4 illustrates the effect of ranolazine on the maximal rate of increase of the upstroke (V_max) of the action potential recorded from free-running canine Purkinje fibers. Significant inhibition, presumably because of the effect of ranolazine to inhibit rapidly activating delayed rectifier potassium current (I_{Kr}), late sodium current (I_{Na}), peak calcium current (I_{Ca}), late I_{Ca}, and sodium-calcium exchange current (I_{Na-cCa}).

The effects of ranolazine on the action potential of canine ventricular M cell and epicardial tissues are illustrated in Figure 5. The drug caused a small concentration-dependent prolongation of APD in epicardium but an abbreviation or biphasic effect in M cell preparations. Thus, ranolazine caused a concentration-dependent reduction of transmural dispersion of APD. Higher concentrations of the drug produced a depression of the plateau of the action potential, probably because of the effect of ranolazine to inhibit I_{Kr} and late I_{Ca}. The preferential prolongation of epicardial APD was more apparent at a [K⁺]o of 2 mmol/L than at 4 mmol/L (Figure 5, right). Early afterdepolarizations (EADs) were not observed at any concentration of ranolazine, not even under bradycardic and hypokalemic conditions known to potentiate the effect of I_{Kr} blocker to induce EADs.

These concentration- and rate-dependent characteristics of ranolazine distinguish it from other agents that block I_{Kr}. Whereas selective I_{Kr} blockers invariably produce a concentration-dependent prolongation of APD that is greater in Purkinje fibers and M cells than in epicardial cells, the multi-ion channel block produced by ranolazine causes a concentration-dependent abbreviation of Purkinje and M cell APD but a slight prolongation of APD of epicardial cells.

Figure 6 illustrates another important distinction between typical I_{Kr} blockers and ranolazine. E-4031, a highly selective I_{Kr} blocker, caused a reverse rate-dependent prolongation of APD that is much greater in M cells than in epicardial cells, leading to a bradycardia-dependent accentuation of transmural dispersion of APD (TD-APD), typical of the actions of I_{Kr} blockers. In contrast, ranolazine produced a largely rate-independent prolongation of APD in epicardium and abbreviation in M cells, leading to a rate-independent reduction of transmural dispersion of APD. The reverse rate-dependent prolongation of APD and accentuation of TD-APD by E-4031 were still more dramatic at a [K⁺]o of 2 mmol/L (Figure 6, right). In contrast, ranolazine persisted in causing a rate-independent reduction of TD-APD at the lower [K⁺]o. These results are consistent with the clinical finding that prolongation of QTc by ranolazine, unlike that of pure I_{Kr} blockers, is not reverse rate dependent. Thus, although ranolazine modestly prolongs APD and QTc, it is fundamentally different from other I_{Kr} blockers, which are typically associated with proarrhythmic actions.

### Table 1. Effects of Ranolazine on Phase 0 Amplitude, Resting Membrane Potential, and Overshoot of Action Potential in M Cell and Epicardial Preparations at a BCL of 500 ms

<table>
<thead>
<tr>
<th>Ranolazine Concentration, μmol/L</th>
<th>Control</th>
<th>1</th>
<th>5</th>
<th>10</th>
<th>50</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M cell</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplitude</td>
<td>107±6</td>
<td>109±4</td>
<td>114±4</td>
<td>113±4</td>
<td>104±3</td>
<td>91±8*</td>
</tr>
<tr>
<td>RMP</td>
<td>-86±2</td>
<td>-86±1</td>
<td>-86±1</td>
<td>-88±1</td>
<td>-84±2</td>
<td>-82±3</td>
</tr>
<tr>
<td>Overshoot</td>
<td>21±6</td>
<td>23±5</td>
<td>27±3</td>
<td>25±3</td>
<td>19±1</td>
<td>9±6</td>
</tr>
<tr>
<td><strong>Epicardial cell</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplitude</td>
<td>95±2</td>
<td>93±2</td>
<td>101±1</td>
<td>94±2</td>
<td>86±6</td>
<td>93±2</td>
</tr>
<tr>
<td>RMP</td>
<td>-84±2</td>
<td>-84±2</td>
<td>-89±1</td>
<td>-88±1</td>
<td>-86±1</td>
<td>-85±2</td>
</tr>
<tr>
<td>Overshoot</td>
<td>11±1</td>
<td>10±2</td>
<td>12±1</td>
<td>8±2</td>
<td>0±6</td>
<td>8±4</td>
</tr>
</tbody>
</table>

RMP indicates resting membrane potential. All values are in mV, mean±SEM. n=5 for all. *P<0.05 vs control.
Effect of Ranolazine in Canine Left Ventricular Wedge Preparation

Table 2 shows the effect of ranolazine in isolated canine left ventricular wedge preparations. In the presence of 4 mmol/L \([K^+o]\) and at a BCL of 2000 ms, ranolazine caused a small concentration-dependent prolongation of epicardial APD and a small biphasic effect in the M region, resulting in a 30-ms QT prolongation at the highest concentration tested (100 \(\mu\)mol/L). It is noteworthy that much of the QT-interval prolongation observed at the higher concentrations of ranolazine is a result of a slowing of conduction secondary to sodium channel inhibition. Transmural dispersion of repolarization (TDR) showed a tendency to diminish, although the decrease was not statistically significant. Under hypokalemic conditions (\([K^+o]=3 \text{ mmol/L}\)), ranolazine produced a much greater prolongation of the QT interval, but TDR showed a similar tendency to decrease.

Ranolazine did not induce either spontaneous or programmed electrical stimulation–mediated torsade de pointes (TdP) during endocardial or epicardial pacing of the canine left ventricular wedge preparation at any concentration up to 100 \(\mu\)mol/L. TdP did not develop, nor could it be induced, even in the presence of extremely low \([K^+o]\), (2 or 3 mmol/L) and high concentrations of ranolazine. In contrast, both spontaneous and stimulation-induced TdP have been shown to develop in the perfused wedge preparation in response to a wide variety of \(I_{Kr}\) blockers.

Neither early nor delayed afterdepolarizations were observed in either tissue or wedge preparations pretreated with any concentration of ranolazine. On the contrary, as illustrated in Figure 7, ranolazine proved to be effective in suppressing EADs in M cell and Purkinje fiber preparations pretreated with other \(I_{Kr}\) blockers, such as \(d\)-sotalol. 

\(d\)-Sotalol (100 \(\mu\)mol/L) produced a remarkable prolongation of repo-
larization and induced EADs in both M cell and Purkinje fiber preparations. Ranolazine caused a concentration-dependent abbreviation of the action potential and abolished the EADs. A similar effect of ranolazine (5 to 20 μmol/L) to suppress EAD activity and abbreviate APD was observed in 4 of 4 M cell and 3 of 3 Purkinje fiber preparations. Moreover, ranolazine was found to be effective in reducing TD-APD, the interval between the peak and end of the T wave (\(T_{\text{peak}} - T_{\text{end}}\)) and TDR under long-QT conditions (\(d\)-sotalol, moxifloxacin, and sea anemone toxin [ATX]-II) (data not shown).

**Discussion**

The effects of ranolazine on cardiac ion currents at concentrations within the therapeutic range (ie, 2 to 6 μmol/L) include inhibition of \(I_{\text{Kr}}\), late \(I_{\text{Na}}\), and late \(I_{\text{Ca,L}}\). Inhibition of \(I_{\text{Kr}}\) by ranolazine prolongs APD, and its effect to inhibit late \(I_{\text{Na}}\) and late \(I_{\text{Ca,L}}\) abbreviates APD. The net effect and clinical consequence of inhibition of these ion channel currents is a modest increase in the mean QTc interval over the therapeutic range. The drug differs significantly from other agents that block \(I_{\text{Kr}}\) and induce TdP. Ranolazine-induced prolongation of the APD is rate independent (ie, does not display reverse

**TABLE 2. Summary of the Effects of Ranolazine on the Action Potential Duration, QT Interval, and Transmural Dispersion of Repolarization in the Canine Arterially Perfused Left Ventricular Wedge Preparation**

<table>
<thead>
<tr>
<th>Concentration</th>
<th>APD(_{50})</th>
<th>APD(_{90})</th>
<th>APD(_{50})</th>
<th>APD(_{90})</th>
<th>QT</th>
<th>TDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 mmol/L [K(^+)] (n=7 unless otherwise noted)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>180.4±8.0</td>
<td>219.7±9.6</td>
<td>218.0±7.5</td>
<td>270.3±9.6</td>
<td>276.7±8.7</td>
<td>33.4±3.2</td>
</tr>
<tr>
<td>1 μmol/L</td>
<td>185.6±7.5</td>
<td>228.0±9.5</td>
<td>216.6±5.0</td>
<td>271.4±8.6</td>
<td>283.8±8.6*</td>
<td>28.7±2.5</td>
</tr>
<tr>
<td>5 μmol/L</td>
<td>189.5±9.4</td>
<td>233.0±9.5</td>
<td>220.6±6.1</td>
<td>281.1±9.1</td>
<td>295.1±9.5*</td>
<td>31.0±3.8</td>
</tr>
<tr>
<td>10 μmol/L</td>
<td>188.9±10.1</td>
<td>238.3±10.2</td>
<td>219.6±5.8</td>
<td>284.9±9.8</td>
<td>301.3±9.0*</td>
<td>30.7±4.5</td>
</tr>
<tr>
<td>100 μmol/L</td>
<td>164.3±7.6</td>
<td>233.0±7.5</td>
<td>188.6±6.0*</td>
<td>278.0±8.1</td>
<td>306.9±11.7†</td>
<td>28.2±5.3</td>
</tr>
<tr>
<td>3 mmol/L [K(^+)] (n=5 unless otherwise noted)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>186.4±8.6</td>
<td>234.9±10.3</td>
<td>228.6±12.9</td>
<td>285.9±14.3</td>
<td>293.0±12.6</td>
<td>29.5±7.7</td>
</tr>
<tr>
<td>1 μmol/L</td>
<td>192.2±9.2</td>
<td>240.0±11.0</td>
<td>229.8±13.9</td>
<td>289.7±14.6</td>
<td>300.3±12.8</td>
<td>28.7±7.2</td>
</tr>
<tr>
<td>5 μmol/L</td>
<td>193.6±9.1</td>
<td>250.6±10.8</td>
<td>226.5±11.7</td>
<td>298.4±13.7</td>
<td>314.4±11.5*</td>
<td>26.0±5.4</td>
</tr>
<tr>
<td>10 μmol/L</td>
<td>198.9±7.7</td>
<td>262.1±8.2</td>
<td>236.4±8.9</td>
<td>307.9±7.0</td>
<td>318.8±8.8</td>
<td>25.0±5.6</td>
</tr>
<tr>
<td>100 μmol/L</td>
<td>181.6±14.7</td>
<td>285.3±10.1*</td>
<td>198.4±12.0</td>
<td>312.2±9.6</td>
<td>347.7±16.2‡</td>
<td>12.9±3.7</td>
</tr>
</tbody>
</table>

All values are in ms, mean±SEM. BCL=2000 ms.

\(\*P<0.05\) vs control.

\(†n=5\).

\(‡n=3\).

Figure 6. Rate-dependent effect of ranolazine (10 μmol/L) and E-4031 (1 μmol/L) on APD in canine ventricular M cell and epicardial tissue slices in presence of 4 mmol/L (A and B) and 2 mmol/L (C and D) [K\(^+\)]. A and C, Rate-dependence of E-4031 and ranolazine-induced change in APD\(_{90}\) of M and epicardial cells, respectively. B and D, Rate-dependence of drug-induced change in transmural dispersion of APD (TD-APD\(_{90}\)). Values are mean±SEM.
The mechanisms underlying TdP have long been a matter of debate. Recent studies have identified dispersion of repolarization secondary to accentuation of electrical heterogeneities intrinsic to ventricular myocardium as the substrate and EADs as the trigger for the development of TdP.8,10,12–15 Ventricular myocardium is composed of at least 3 electrophysiologically distinct cell types: epicardial, M, and endocardial. M cells are distinguished by having action potentials similar in the 3 transmural cell types. M cells, like Purkinje fibers, develop EADs in response to agents and pathophysiological conditions that reduce the repolarization reserve of the ventricular myocardium. Epicardial and endocardial cells generally do not.

Most drugs that prolong the QT interval accentuate the normal transmural heterogeneity of final ventricular repolarization by causing a preferential prolongation of the action potential of M cells. Ik blockers, including d-sotalol, almokalan, E-4031, moxifloxacin, and erythromycin augment transmural dispersion of repolarization as a consequence. These agents cause relatively little prolongation of the AP of epicardial and endocardial cells, because these cell types possess a much more prominent Ik than the M cell. A similar preferential prolongation of the M cell AP is seen with agents that increase calcium current (I_{Ca}), such as Bay K 8644, as well as with agents that increase late Is, such as ATX-II, anthopleurin-A, and DPI 201-106. An exception to this rule applies to agents that block I_{Ks}, which cause a similar percentage of APD prolongation in the 3 transmural cell types.

A more complex electrophysiological effect is observed with drugs affecting 2 or more ion channels, such as amiodarone, sodium pentobarbital, quinidine, cisapride, and azimilide. Amiodarone is a potent antiarrhythmic agent used in the management of both atrial and ventricular arrhythmias. In addition to its β-blocking properties, amiodarone is known to block late I_{Ks}, I_{Ca}, and Ik. The efficacy of the amiodarone and its low incidence of proarrhythmia relative to other agents with class III actions are attributable to this complex multichannel inhibition.22 When administered chronically, amiodarone increases QT without augmenting spatial dispersion of repolarization, unlike other Ik blockers.23–25 In some cases, transmural dispersion of repolarization is reduced.23 Chronic amiodarone therapy can also suppress the effect of other Ik blockers, like d-sotalol, to increase TDR or induce EADs.23 Thus, chronic amiodarone alters the cellular electrophysiology of ventricular myocardium so as to reduce TDR and suppress EADs, especially under conditions in which they are accentuated. The drug’s potent inhibition of late I_{Ks} is thought to play a key role.

The multichannel inhibition, particularly the ability to potently block late I_{Ks}, has been suggested to underlie the effect of Ik blockers to prolong QT without creating the substrate or trigger for the development of TdP. Indeed, this feature could contribute to the suppression of EADs and reduction of spatial dispersion of repolarization, the substrate and trigger for TdP. This is the case for amiodarone and sodium pentobarbital, as well as for high concentrations of quinidine and cisapride.24,26–28 Our data suggest that ranolazine fits this pharmacological profile as well. Like amiodarone and sodium pentobarbital, ranolazine produces a preferential prolongation of epicardial APD_{M}, leading to a reduction in transmural dispersion of repolarization. The opposite effects of ranolazine on M cells and Purkinje fibers to that of epicardial APD is most likely because of the more prominent late I_{Ks} in the M cell and Purkinje fiber than in epicardial cells.20 Ranolazine is among the most potent late rate-dependent prolongation of APD) and is not associated with EADs, triggered activity, an increase in spatial dispersion of repolarization, or polymorphic ventricular tachycardia. Indeed, rather than displaying arrhythmogenic activity, ranolazine, via its actions to suppress EADs and reduce TDR, possesses significant antiarrhythmic activity, acting to suppress the arrhythmogenic effects induced by a variety of other QT-prolonging drugs.

Drugs with QT-prolonging properties have attracted considerable attention in recent years because of their proclivity to induce life-threatening cardiac arrhythmias, such as TdP.9–11 More than 50 commercially available or investigational noncardiovascular and 20 cardiovascular nonantiarrhythmic drugs have been shown or are suspected to have proarrhythmic effects.

The mechanisms underlying TdP have long been a matter of debate. Recent studies have identified dispersion of repolarization secondary to accentuation of electrical heterogeneities intrinsic to ventricular myocardium as the substrate and EADs as the trigger for the development of TdP.8,10,12–15 Ventricular myocardium is composed of at least 3 electrophysiologically distinct cell types: epicardial, M, and endocardial. M cells are distinguished by having action potentials that prolong disproportionately relative to the action potentials of other ventricular myocardial cell types in response to a slowing of rate and/or in response to many QT-prolonging drugs.16–18 The ionic bases for these features include the presence of a smaller slowly activating delayed rectifier current (I_{k1}),19 a larger late I_{Na}20 and I_{Na-cx},21 Ik, and I_{Ks} are similar in the 3 transmural cell types. M cells, like Purkinje fibers, develop EADs in response to agents and pathophysiological conditions that reduce the repolarization reserve of the ventricular myocardium. Epicardial and endocardial cells generally do not.

Most drugs that prolong the QT interval accentuate the normal transmural heterogeneity of final ventricular repolarization by causing a preferential prolongation of the action potential of M cells. Ik blockers, including d-sotalol, almokalan, E-4031, moxifloxacin, and erythromycin augment transmural dispersion of repolarization as a consequence. These agents cause relatively little prolongation of the AP of epicardial and endocardial cells, because these cell types possess a much more prominent Ik than the M cell. A similar preferential prolongation of the M cell AP is seen with agents that increase calcium current (I_{Ca}), such as Bay K 8644, as well as with agents that increase late Is, such as ATX-II, anthopleurin-A, and DPI 201-106. An exception to this rule applies to agents that block I_{Ks}, which cause a similar percentage of APD prolongation in the 3 transmural cell types.
I_{Na} blockers reported. It causes a decrease in net inward current in the M cells and Purkinje fiber but a decrease in net outward current in epicardium. The effect of ranolazine to block late I_{Na} and late I_{Kr} most likely underlies its effect to suppress EAD activity. Thus, unlike other I_{Na} blockers, ranolazine does not lead to the development of TdP, either spontaneous or stimulation induced. Of note, ranolazine has recently been evaluated in an anesthetized dog model with acute complete atrioventricular block, a model susceptible to drug-induced polymorphic ventricular tachycardia. At doses that prolonged the QT interval by approximately 5% to 11% above control, ranolazine did not cause spontaneous TdP or TdP facilitated by an intravenous bolus of phenylephrine (which increases susceptibility to TdP) in 5 dogs, whereas sotalol induced TdP in all 5 dogs under these conditions.29 Recent studies involving isolated guinea pig and rabbit hearts have also reported failure of ranolazine to induce TdP but its effectiveness to suppress TdP induced by selective I_{Na} blockers (E-4031) and agents that augment late I_{Na} (ATX-II).29

In summary, the available data suggest that ranolazine, in addition to its antiangiinal actions, may possess important antiarrhythmic activity.

Acknowledgments

This study was supported by grant HL-47678 from the National Heart, Lung, and Blood Institute (Dr Antzelevitch) and grants from the American Heart Association (Dr Burashnikov, Fish, and Antzelevitch), CV Therapeutics (Dr Antzelevitch), and the NY State and Florida Grand Lodges of the Free and Accepted Masons.

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