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## Ranolazine for the Treatment of Chronic Angina and Potential Use in Other Cardiovascular Conditions

Bernard R. Chaitman, MD

Chronic angina, a condition that impairs quality of life and is associated with decreased life expectancy, affects  $\approx 6.4$  million Americans.<sup>1</sup> Current therapies that reduce angina frequency and nitrate consumption and increase the threshold at which demand-induced myocardial ischemic symptoms become evident include drugs (nitrates,  $\beta$ -blockers, calcium antagonists), exercise conditioning, enhanced external counterpulsation, and coronary revascularization.<sup>1-3</sup> Several new investigational drugs are being tested for the treatment of chronic angina.<sup>4-9</sup> This review will focus on sustained-release ranolazine, a drug that reduces angina symptoms, with a mechanism of action different from that of currently available pharmacological therapies.<sup>8-29</sup> Ranolazine was approved on January 27, 2006, in the United States for use in patients with chronic angina who continue to be symptomatic on  $\beta$ -blockers, calcium antagonists, or nitrates.

### Ranolazine

Ranolazine ([(+)-*N*-(2,6-dimethylphenyl)-4(2-hydroxy-3-(2-methoxyphenoxy)-propyl)-1-piperazine acetamide dihydrochloride]) is an active piperazine derivative that was patented in 1986 and is available in an oral and intravenous form (Figure 1). The immediate-release ranolazine (not in current use) had an average terminal elimination half-life ranging from 1.4 to 1.9 hours and a 10-fold peak/trough difference with dosing of 240 to 400 mg 3 times per day.<sup>19</sup> Early studies with immediate-release ranolazine provided evidence of antiischemic/antianginal properties in patients with chronic angina without clinically significant changes in heart rate or blood pressure and are reviewed elsewhere.<sup>20-24</sup> Unless otherwise stated, the remainder of this review refers to sustained-release ranolazine.

Ranolazine (Ranexa; CV Therapeutics Inc, Palo Alto, Calif) is manufactured in a sustained-release form that has a prolonged absorption phase with maximal plasma concentrations ( $C_{\max}$ ) typically seen 4 to 6 hours after administration. The average terminal elimination half-life is  $\approx 7$  hours after multiple dosing to steady state, and the peak/trough difference is 1.6-fold with dosing of 500 to 1000 mg twice daily.<sup>16-18</sup> Steady state is generally achieved within 3 days of twice-daily dosing. Ranolazine plasma concentrations that are therapeutically effective for chronic angina are in the range of 2 to 6  $\mu\text{mol/L}$ .<sup>8,9</sup>

### Ranolazine Metabolism

Exposure to ranolazine is not affected by food. Oral bioavailability is in the range of 30% to 55%. Plasma protein binding (mainly to  $\alpha 1$ -acid glycoprotein) is  $\approx 65\%$ . The cytochrome P450 (CYP) 3A4-mediated pathway accounts for the majority of ranolazine biotransformation.<sup>16-18</sup> Additional pathways include metabolism by CYP2D6 (10% to 15%), glucuronidation ( $<5\%$ ), and excretion of unchanged ranolazine by the kidneys ( $<5\%$ ) (Figure 1). Three phase I metabolites (CVT-2512, CVT-2514, CVT-2738) and 1 phase II metabolite of ranolazine in plasma occur at concentrations  $>10\%$  of the parent compound. The 4 most abundant metabolites in plasma have elimination half-life periods of 6 to 22 hours. At least 11 metabolites have been identified with a plasma disposition in humans  $>1\%$  relative to ranolazine.

Ketoconazole, a potent competitive reversal inhibitor of CYP3A isoenzymes, increases ranolazine exposure at steady state 2.5- to 4.5- fold on average.<sup>17</sup> The metabolite to ranolazine area under the curve from time 0 to 12 hours ( $\text{AUC}_{12}$ ) ratio decreased 5.6-fold, 2.1-fold, and 4.6-fold for CVT-2512, CVT-2514, and CVT 2738, respectively. Adverse events, generally mild to moderate, but occasionally intolerable, such as headache, dizziness, and nausea, are significantly increased with the concomitant administration of ketoconazole 200 mg twice daily to ranolazine 1000 mg twice daily. Average increases in plasma ranolazine concentrations are 1.2-fold at steady state after paroxetine, a potent inhibitor of the CYP2D6 enzyme system. Clearance of ranolazine is reduced by renal insufficiency and moderate hepatic impairment.<sup>16,25</sup> Ranolazine  $C_{\max}$  at steady state is 1.7- to 2-fold greater in patients with moderate to severe renal insufficiency ( $<30$  mL/min), resulting in significant increases in  $C_{\max}$  from time 0 to 12 hours ( $\text{AUC}_{12}$ ) compared with healthy subjects ( $>81$  mL/min).<sup>16</sup> A 10- to 15-mm Hg increase in mean diastolic blood pressure was observed in 6 patients with severe renal insufficiency on ranolazine 500 mg twice daily. In 8 subjects with moderate hepatic impairment (Child-Pugh grade B), ranolazine  $C_{\max}$ ,  $\text{AUC}_{12}$ , and  $C_{\text{trough}}$  were increased by 51% ( $P=0.01$ ), 76% ( $P<0.001$ ), and 123% ( $P<0.001$ ) compared with healthy subjects.<sup>25</sup> In 8 subjects with mild hepatic impairment (Child-Pugh grade A), ranolazine pharmacokinetics were not significantly altered. There are no

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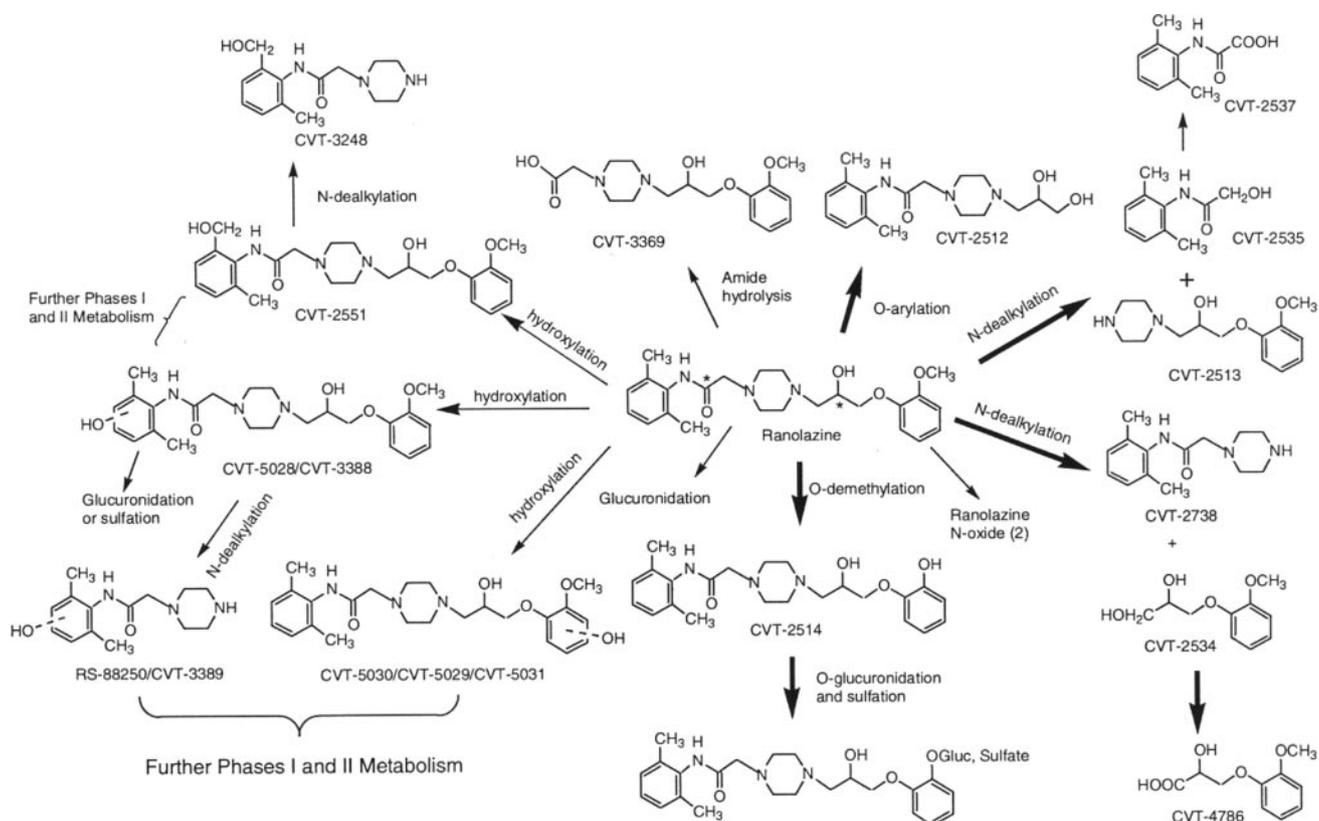


Figure 1. Chemical structure and metabolism of ranolazine. Reprinted with permission from *J Clin Pharmacol.* 2005;45:422–433.<sup>17</sup>

apparent gender differences in ranolazine pharmacokinetics, nor are pharmacokinetics significantly altered by diabetes mellitus or heart failure (in the absence of renal insufficiency). Ranolazine clearance decreases modestly with age.

### Drug–Drug Interaction

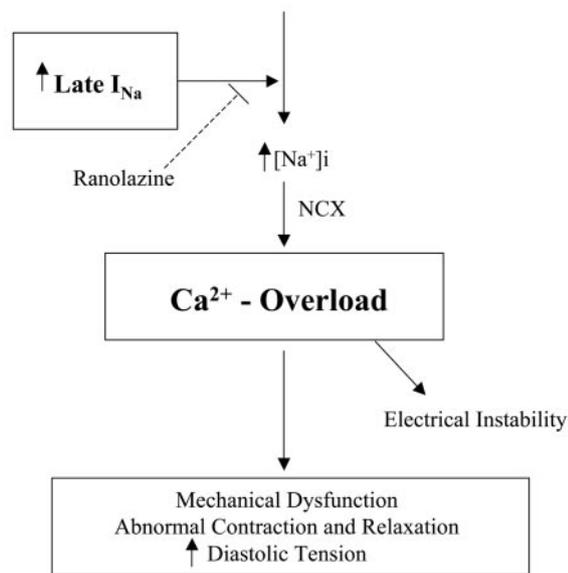
Drugs such as diltiazem ( $\geq 240$  mg daily), a moderate CYP3A inhibitor, increase ranolazine plasma levels, in a dose-dependent manner,  $\approx 1.5$ -fold; ranolazine has no significant effect on diltiazem pharmacokinetics.<sup>17</sup> Ranolazine is a substrate and an inhibitor of P-glycoprotein. Verapamil ( $\geq 360$  mg daily), a drug that inhibits P-glycoprotein, increases the absorption of ranolazine with a 2.3-fold increase in ranolazine plasma levels. The drug label indicates that ranolazine is contraindicated in patients on potent and moderately potent CYP3A inhibitors such as ketoconazole, diltiazem, verapamil, macrolide antibiotics, HIV protease inhibitors, and grapefruit juice. Ranolazine increases digoxin concentrations 1.4- to 1.6-fold at trough and  $\approx 2$ -fold at peak plasma levels, presumably through competition for intestinal and renal P-glycoprotein. Ranolazine is a weak inhibitor of CYP3A4 and CYP2D6. Simvastatin  $C_{\max}$  is increased  $\approx 2$ -fold after ranolazine; simvastatin has no significant effect on ranolazine pharmacokinetics.<sup>17</sup> In phase II studies of ranolazine with patients on statin drugs, significant increases in creatine kinase, clinical myositis, or elevated liver function tests have not been reported. No drug–drug interactions with warfarin have been reported.

### Proposed Mechanisms of Action for Ranolazine

The mechanism of action of ranolazine is unknown. Initially, ranolazine was thought to exert its therapeutic efficacy primarily through partial inhibition of fatty acid oxidation.<sup>8,20,24,28</sup> These pharmacological effects, however, were generally observed at concentrations in excess of therapeutic plasma concentrations in human clinical trials ( $> 10 \mu\text{mol/L}$ ).<sup>29</sup> MacInnes et al<sup>29</sup> reported that ranolazine at a concentration of  $20 \mu\text{mol/L}$  improved postischemic cardiac function in an isolated working rat heart perfused with a buffer containing a relatively high concentration of free fatty acid without a decrease in fatty acid oxidation. At a concentration of  $100 \mu\text{mol/L}$ , ranolazine inhibited fatty acid oxidation by only 12%. Thus, the contribution of substrate utilization effects (partial inhibition of fatty acid oxidation) to the therapeutic efficacy of ranolazine as an antianginal drug has not been established.

More recent evidence suggests that ranolazine reduces calcium overload in the ischemic myocyte through inhibition of the late sodium current ( $I_{\text{Na}}$ ). Myocardial ischemia produces a cascade of complex ionic exchanges that can result in intracellular acidosis, excess cytosolic  $\text{Ca}^{2+}$ , myocardial cellular dysfunction, and, if sustained, cell injury and death. Activation of the adenosine triphosphate–dependent  $\text{K}^+$  current during ischemia results in a strong efflux of  $\text{K}^+$  ions from myocytes. Sodium channels are activated on depolarization, leading to a rapid influx of sodium into the cells. The inactivation of  $I_{\text{Na}}$  has a fast component lasting a few

## Ischemia and Pathological States Linked to Imbalances of O<sub>2</sub> Supply and Demand



**Figure 2.** Increases in intracellular sodium concentration ( $[Na^+]_i$ ) in ischemic cardiac myocytes cause calcium ( $Ca^{2+}$ ) overload via the  $Na^+$ - $Ca^{2+}$  exchanger (NCX) leading to contractile dysfunction and cellular injury. A pathologically enhanced late  $Na^+$  current (late  $I_{Na}$ ) contributes to the  $[Na^+]_i$ -dependent  $Ca^{2+}$  overload. Ranolazine, by decreasing the magnitude of the pathologically enhanced late  $I_{Na}$ , prevents or reduces  $Ca^{2+}$  overload and attenuates the accompanying deleterious consequences. Ranolazine does not alter function of the normal heart, in which late  $I_{Na}$  is a small current. Thus, the action of ranolazine may be classified as cytoprotective. Adapted with permission from *Eur Heart J*. 2004;6(suppl 1):13–17.<sup>12</sup>

milliseconds and a slowly inactivating component that can last hundreds of milliseconds. The late  $I_{Na}$  is the inward current caused by the influx of  $Na^+$  that persists throughout the plateau of the action potential, ie, the  $Na^+$  that passes through voltage-gated  $Na$  channels that fail to inactivate completely and remain “open” at a time when the  $Na^+$  channels normally remain closed.<sup>12</sup> Under normal conditions, late  $I_{Na}$  constitutes only 1% of peak  $I_{Na}$ . In an isolated ventricular myocyte canine heart failure model, the delayed or incomplete inactivation of late  $I_{Na}$  of the sodium channel contribution was substantially augmented.<sup>10–12</sup> Late  $I_{Na}$  is also known to be increased by a number of conditions associated with the pathological milieu of ischemia (Figure 2). Regulation of intracellular  $Na^+$  homeostasis (ion channels, exchangers, transporters) during an episode of myocardial ischemia is complex and the subject of some debate, but the rise in intracellular  $Na^+$  is likely the result of several processes that include both the  $Na^+$ - $H^+$  exchanger and the nonactivating  $Na^+$  channels (ie, late  $I_{Na}$ ).<sup>26,27</sup>

The increase in intracellular sodium triggers an increase in the influx of calcium via the reverse mode of  $Na^+$ - $Ca^{2+}$  exchanger, resulting in intracellular calcium overload. Increased intracellular  $Ca^{2+}$  results in increased left ventricular diastolic tension and the potential for compression of the vascular space and further reduction of nutrient coronary blood flow to the ischemic territory. A more detailed expla-

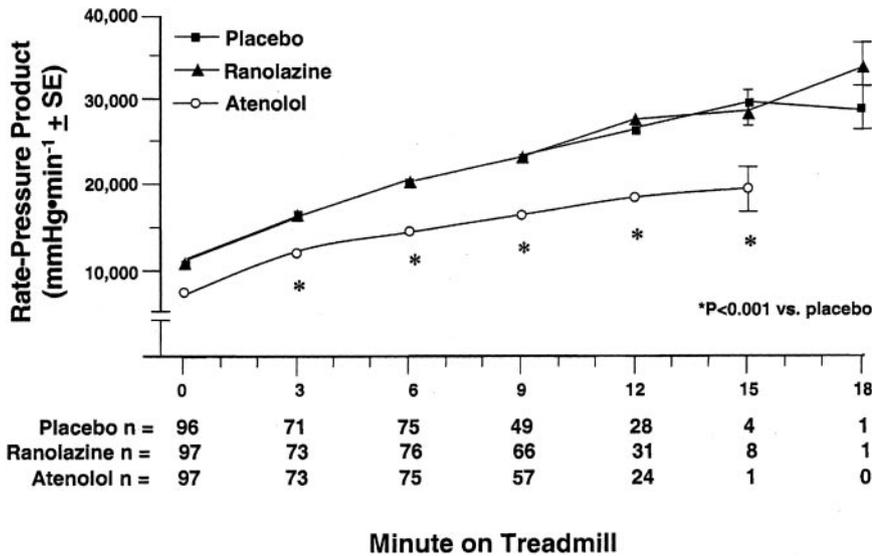
nation of the ionic exchanges that take place during myocardial ischemia and other pathological conditions (eg, heart failure) as they pertain to intracellular  $Na^+$  homeostasis is beyond the scope of this article and is reviewed elsewhere.<sup>26,27</sup>

In ventricular myocytes from dog and guinea pig hearts, ranolazine, at therapeutically relevant concentrations (up to 10  $\mu$ mol/L), has been shown to selectively inhibit late  $I_{Na}$  ( $IC_{50}$ =5 to 21  $\mu$ mol/L) without affecting either the fast sodium current responsible for the upstroke of the action potential ( $IC_{50}$  value of 244  $\mu$ mol/L for peak  $I_{Na}$ ) or the  $Na^+$ - $H^+$  and  $Na^+$ - $Ca^{2+}$  exchangers.<sup>10</sup> Thus, ranolazine is a relatively selective inhibitor for late  $I_{Na}$ . In isolated ventricular myocytes in which the late  $I_{Na}$  was pathologically augmented, ranolazine prevented or reversed the induced mechanical dysfunction, as well as ameliorated abnormalities of ventricular repolarization.<sup>10,11,14,15</sup> Ranolazine inhibition of late  $I_{Na}$  is discernible at therapeutic plasma concentrations in healthy cells, particularly in M cells and Purkinje fibers, where this current is most prominent. However, in healthy nonischemic, nonfailing myocytes, where the contribution of late  $I_{Na}$  is small, the drug does not have a measurable effect on cardiovascular performance at therapeutic plasma concentrations. The effect of ranolazine on late  $I_{Na}$  is more pronounced in ischemic or failing myocytes in which the current is amplified. Impaired left ventricular relaxation and increased left ventricular end-diastolic pressure are early manifestations of myocardial ischemia, caused in part by calcium overload. In patients with chronic angina and demand-induced ischemia, ranolazine has the potential to partially disrupt the consequences of cell hypoxia during transient myocardial ischemia by reducing excess late  $Na^+$  influx, thereby reducing calcium overload and ultimately reducing the concomitant increase in left ventricular wall tension. Reduction in diastolic left ventricular wall tension would decrease myocardial oxygen requirements in marginally ischemic myocytes and has the potential to reduce vascular compression, allowing more coronary blood flow to the affected area. Additional research is necessary to confirm this latter hypothesis.

In radioligand binding studies of rat hearts and guinea-pig lungs, ranolazine exhibits negligible affinity for  $\alpha_1$ ,  $\beta_1$ , and  $\beta_2$  adrenoreceptors and weak  $\beta_1$ - and  $\beta_2$ -antagonist activity in the rat cardiovascular system.<sup>30</sup> It has weak calcium channel antagonist activity.<sup>31</sup> Thus, its mechanism of action to alleviate angina is different from the currently available drug classes that affect heart rate, inotropic state, or hemodynamic state or increase coronary blood flow. At the dosage used in clinical trials, ranolazine does not have a clinically significant effect on resting or exercise heart rate or blood pressure.<sup>8,9</sup>

### Ranolazine in Chronic Angina

Published data on the efficacy of the immediate-release form of ranolazine are reviewed elsewhere.<sup>20,21</sup> The findings established a dose–response relationship and illustrated differences in the hemodynamic response to exercise in patients treated with ranolazine compared with  $\beta$ -blockers, as well as comparative efficacy in treating demand-induced ischemia. Rousseau et al<sup>19</sup> compared immediate-release ranolazine 400



**Figure 3.** In contrast to current antianginal drugs that alter heart rate and blood pressure at rest and during exercise, ranolazine does not result in a significant change in rate-pressure product in patients with chronic angina exercising at submaximal workloads. Reprinted with permission from *Am J Cardiol.* 2005;95:311–316.<sup>19</sup>

mg TID with atenolol 100 mg QD or placebo in a 1-week double-blind, 3-period, placebo-controlled, crossover study in 158 patients with chronic angina. Ranolazine and atenolol significantly improved exercise duration and time to exercise-induced myocardial ischemia when tested 1 hour after oral administration of study drug 7 to 10 days after treatment. However, unlike the expected decrease in both exercise heart rate and blood pressure observed with atenolol, ranolazine increased exercise duration and decreased exercise-induced ischemia without a clinically significant change in rate-pressure product (Figure 3).

**Controlled Clinical Trials With Sustained-Release Ranolazine**

The Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) and subsequent Combination Assessment of Ranolazine in Stable Angina (CARISA) trials enrolled patients with chronic effort angina for at least 3 months who had reproducible treadmill-induced exercise-induced angina and ST-segment depression at low exercise workloads (<5 metabolic equivalents [METs]) with the use of a modified Bruce protocol at baseline.<sup>8,9</sup> The primary efficacy end point for both studies was symptom-limited exercise duration at trough plasma concentrations ≈12 hours after dosing. Patients with recent unstable angina, NYHA class III to IV heart failure, and acute coronary syndrome/revascularization within the prior 2 months were excluded, as were patients on drug therapy known to prolong the QT interval or who had a QTc interval >500 ms at baseline. The study design and baseline characteristics of patients enrolled in the MARISA, CARISA, and the subsequent Efficacy of Ranolazine In Chronic Angina (ERICA) trials in chronic angina are illustrated in Tables 1 and 2.

**MARISA**

MARISA was a monotherapy study that tested a 3-fold dose range of ranolazine.<sup>8</sup> An exercise test was conducted at trough (12 hours after dose) and peak (4 hours after dose) at the end of each treatment week. All 3 doses resulted in a significant increase in exercise duration at trough compared

with placebo ( $P \leq 0.005$ ) in a dose-dependent fashion. Exercise duration increased with progressive increase in plasma concentrations, although the incremental benefit was attenuated at dosage >1000 mg twice daily<sup>8</sup> (Figure 4).

**CARISA**

The CARISA study tested 823 patients with chronic angina on once-daily atenolol (50 mg), once-daily diltiazem (180 mg), or once-daily amlodipine (5 mg).<sup>9</sup> Eligible patients were stratified according to their background therapy. Exercise tests were performed 2, 6, and 12 weeks after randomization at trough and 2 and 12 weeks at peak. The results showed that, compared with placebo, ranolazine significantly increased symptom-limited exercise duration (mean increase 24 to 34 seconds) (Figure 5).

The improvement was sustained over the 12 weeks of therapy, indicating lack of tolerance over this time interval. At enrollment, 43%, 31%, and 26% of the patients were on background atenolol, amlodipine, or diltiazem therapy. The treatment-by-background interaction term indicated no evidence of differential treatment effect according to background therapy received. However, it should be noted that the number of patients and power to test differences between the 3 background treatment strategies were relatively small and that the absolute increase in exercise time from baseline was slightly greater with background calcium antagonist therapy. No clinically meaningful changes compared with placebo on rest or exercise heart rate or blood pressure were noted, although some small changes achieved statistical significance. At baseline, the average number of angina attacks per week was 4.5 in all groups. The mean number of weekly angina attacks and nitroglycerin use over the 12 weeks of treatment with ranolazine was significantly reduced in a dose-dependent fashion (3.3 for placebo compared with 2.5 [ $P = 0.003$ ] and 2.1 [ $P < 0.001$ ] for ranolazine 750 and 1000 mg BID, respectively). At the end of the 12-week double-blind treatment phase, patients entered a 2-day rebound assessment phase during which half of the patients on active double-blind ranolazine were continued on that therapy for an additional 2 days, and the others were switched in a double-

**TABLE 1. Sustained Release Ranolazine Trials in Chronic Angina**

	MARISA	CARISA	ERICA
Design	4-wk, double-blind, 4-group, crossover, placebo-controlled (n=191)	12-wk, double-blind, 3-group, parallel-group, placebo-controlled (n=823)	6-wk, double-blind, parallel-group, 3-phase, placebo-controlled (n=564)
Treatment	Ranolazine 500, 1000, or 1500 mg or placebo BID	Ranolazine 750 or 1000 mg or placebo BID on a treatment regimen of diltiazem 180 mg QD, or atenolol 50 mg QD, or amlodipine 5 mg QD; combination $\beta$ -blockers and calcium antagonists not permitted	Ranolazine 500 mg BID or placebo for 1 wk; ranolazine 1000 mg BID or placebo for 6 wk; all patients treated with amlodipine 10 mg QD for entire 7 wk; $\beta$ -blockers not permitted
Primary efficacy measure	Exercise duration on treadmill at trough ranolazine concentration	Exercise duration on treadmill at trough ranolazine concentration	Average weekly frequency of angina attacks
Secondary efficacy measures	Time to angina onset and time to 1-mm ST-segment depression at trough and peak; exercise duration at peak	Time to angina onset; time to 1-mm ST-segment depression at trough and peak; frequency of angina attacks; exercise duration at peak; frequency of nitroglycerin use	Average weekly nitroglycerin consumption scores and 5 dimensions of Seattle Angina Questionnaire
Excluded/permitted concomitant medications	Antianginal medications prohibited from 48 h before study entry to end of study	Required use of atenolol or amlodipine or diltiazem but not their combination; all other antianginal drugs (except sublingual nitroglycerin) discontinued	Antianginal drugs excluded (except amlodipine and long-acting nitrates or isosorbide mononitrate) 5 d before screening and to end of study

blind fashion to placebo. All patients had their final exercise test at trough. Abrupt withdrawal of ranolazine did not result in a rebound worsening of the patient's underlying angina. The therapeutic effect of ranolazine on exercise duration was no longer evident within 2 days after therapy was withdrawn.

The antianginal efficacy of ranolazine was examined in several patient subsets in the MARISA and CARISA trials.

**TABLE 2. Demographic and Baseline Characteristics in Ranolazine MARISA, CARISA, and ERICA Studies**

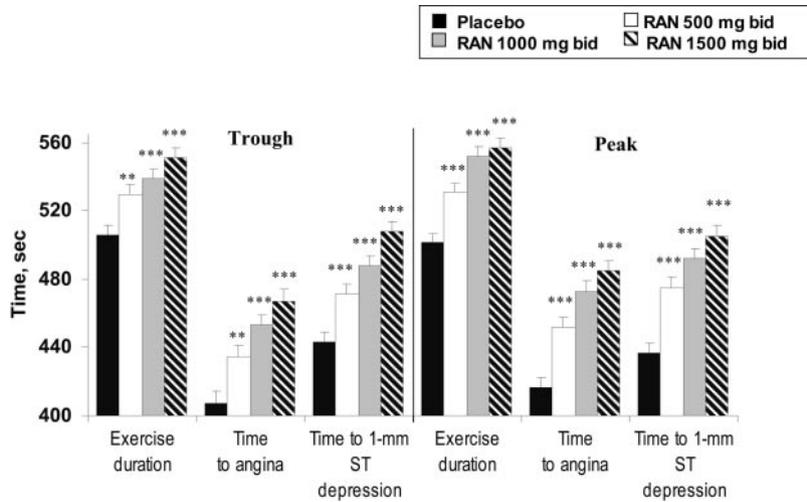
Category	MARISA All Patients (n=191)	CARISA All Patients (n=823)	ERICA All Patients (n=564)
Gender			
Male	140 (73.3)	638 (77.5)	409 (72.5)
Female	51 (26.7)	185 (22.5)	155 (27.5)
Age, mean, y	64.3	63.9	61.5
Race			
White	174 (91.1)	803 (97.6)	558 (99.0)
Nonwhite	17 (8.9)	20 (2.4)	6 (1.0)
Underlying disease			
Diabetes mellitus	46 (24.1)	189 (23.0)	106 (19.0)
Congestive heart failure	32 (16.8)	242 (29.4)	291 (51.5)
Prior unstable angina	37 (19.4)	177 (21.5)	198 (35.1)
Previous MI	100 (52.4)	474 (57.6)	446 (79.0)
Hypertension	123 (64.4)	527 (64.0)	497 (88.1)
PTCA	62 (32.5)	152 (18.5)	59 (10.4)
CABG	53 (27.7)	145 (17.6)	62 (10.9)

Values are number (percentage) of patients. MI indicates myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; and CABG, coronary artery bypass graft.

Diabetes mellitus did not affect the beneficial effect of ranolazine on improvement of exercise parameters.<sup>32</sup> The probability values for the treatment-by-subgroup interaction for exercise duration were 0.77 in MARISA and 0.89 in CARISA, indicating no statistical evidence of a differential treatment effect by history of diabetes mellitus. The side effect profile and frequency of adverse events was also similar. HbA<sub>1c</sub> values were obtained from 160 of 189 diabetic patients (85%) at baseline and 140 of 189 diabetic patients (74%) at 12 weeks in the CARISA trial. Ranolazine 750 and 1000 mg reduced HbA<sub>1c</sub> compared with placebo by 0.48 $\pm$ 0.18% ( $P=0.008$ ) and 0.70 $\pm$ 0.18% ( $P=0.002$ ), respectively. When the diabetic patients in CARISA were stratified by insulin treatment, the reduction in HbA<sub>1c</sub> compared with placebo in those receiving insulin was greater. Although these preliminary post hoc observations in the diabetic cohort from the CARISA trial are clearly of interest, HbA<sub>1c</sub> values in CARISA were not a prespecified efficacy variable, and this finding will need to be validated in a larger, prospectively designed study. Similar analyses were conducted by prior history of heart failure (NYHA class I and II), gender, and age ( $\geq 65$  and  $< 65$  years).<sup>21</sup> Although the relative number of patients is relatively small, there is no evidence that the treatment effects of ranolazine within any of these particular subgroups were inconsistent with the results observed in the overall population, although the placebo-corrected increase in treadmill exercise duration on ranolazine was less in women than in men.

#### Open-Label Run-On Studies With Ranolazine

Of 899 eligible patients who completed MARISA and CARISA, 744 (83%) agreed to participate in an open-label run-on study.<sup>8,9,21</sup> The 1-year mortality estimate associated



LS means ± SE. \*\*p < 0.01 vs placebo; \*\*\*p < 0.001 vs placebo

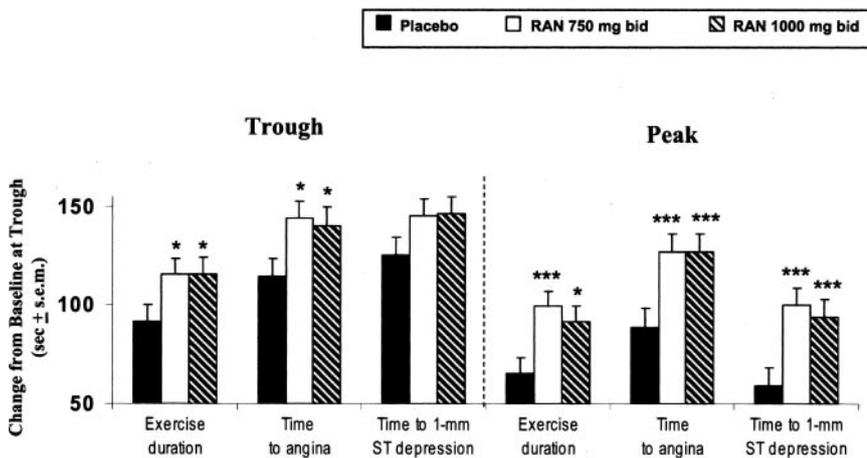
**Figure 4.** Symptom-limited exercise duration at trough and peak in MARISA. Exercise duration, time to onset of angina, and time to 1-mm ST-segment depression significantly increased with increased dose. The relative increase was greater at peak than at trough. Probability values for comparison of ranolazine to placebo are shown. Least-square (LS) means and probability values from ANOVA model with effects for pooled site, patient within pooled site, period, and treatment are shown (n=175). RAN indicates ranolazine. Adapted with permission from *J Am Coll Cardiol.* 2004;43:1375–1382<sup>8</sup> (copyright 2004, American College of Cardiology Foundation) and reprinted with permission from *J Cardiovasc Pharmacol Ther.* 2004;9(suppl 1):S47–S64.<sup>21</sup>

with ranolazine treatment in the observational database from the MARISA and CARISA trials and respective follow-up studies was 2% (95% CI, 96.9% to 99%); the 2-year mortality estimate was <5%.<sup>8,9,21</sup> In the open-label extension studies, at least 639 patients have been exposed to ranolazine for >1 year and 372 subjects for >3 years. To determine whether ranolazine is effective in decreasing mortality and preventing cardiovascular end points such as myocardial infarction in patients with chronic ischemic heart disease and angina, long-term randomized, placebo-controlled trials would be required.

**ERICA**

The third trial of sustained-release ranolazine in chronic angina differed from both earlier studies in that treadmill-induced angina and ischemic ST-segment depression were not required as entry criteria, and, in contrast to the CARISA trial, 10 mg of amlodipine was used once daily rather than 5 mg.<sup>33</sup> The primary efficacy variable for ERICA was the average number of angina attacks per week, unlike the

MARISA and CARISA trials, in which the primary end point was symptom-limited exercise duration at trough plasma concentrations. At baseline, the mean number of angina attacks was 5.5 per week, and mean nitroglycerin use was 4.3 tablets or sprays per week; 45% of patients were taking concomitant long-acting nitrates. During the 6-week treatment phase, the mean number of angina episodes per week decreased to 3.2 in the placebo group and 2.8 in the ranolazine group (P=0.028). Mean nitroglycerin use per week decreased to 2.6 in the placebo group and 2.0 in the ranolazine group (P=0.014) without a significant change in heart rate or blood pressure. The magnitude of symptomatic improvement was greater in patients with more angina attacks per week at baseline. The Seattle Angina Questionnaire revealed significant improvement in angina frequency dimension on ranolazine compared with placebo (mean change in score from baseline, 22.5 versus 18.5; P=0.008). The treatment effect of ranolazine appeared to be consistent across subgroups of gender, age (<65 versus ≥65 years), and concomitant use of long-acting nitrates. Early withdrawal due



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

**Figure 5.** In CARISA, exercise duration, time to onset of angina, and time to 1-mm ST-segment depression significantly increased with each ranolazine dose compared with placebo. The differences were statistically significant for all exercise parameters at peak and were statistically significant for all exercise parameters at trough with the exception of time to 1-mm ST-segment depression. Probability values for comparison of ranolazine versus placebo are shown. Least-square means and probability values from ANCOVA model with effects for treatment, baseline covariates, pooled site, and background therapy are shown (n=791).<sup>9</sup> RAN indicates ranolazine. Reprinted with permission from *J Cardiovasc Pharmacol Ther.* 2004;9(suppl 1):S47–S64.<sup>21</sup>

**TABLE 3. Treatment-Emergent Adverse Events  $\geq 2\%$ : MARISA and CARISA**

	No. (%) of Angina Patients						
	MARISA				CARISA		
	BID Dosing for 1 wk Each Treatment				BID Dosing for 12 wk		
	Placebo (n=179)	500 mg (n=181)	1000 mg (n=180)	1500 mg* (n=187)	Placebo (n=269)	750 mg (n=279)	1000 mg (n=275)
Any adverse event	26 (14.5)	28 (15.5)	37 (20.6)	62 (33.2)	71 (26.4)	87 (31.2)	90 (32.7)
Body as a whole	10 (5.6)	6 (3.3)	9 (5.0)	25 (13.4)	28 (10.4)	22 (7.9)	29 (10.5)
Abdominal pain	1 (0.6)	1 (0.6)	2 (1.1)	1 (0.5)	2 (0.7)	2 (0.7)	7 (2.5)
Asthenia	3 (1.7)	0	3 (1.7)	11 (5.9)	6 (2.2)	5 (1.8)	13 (4.7)
Headache	4 (2.2)	1 (0.6)	2 (1.1)	5 (2.7)	4 (1.5)	7 (2.5)	6 (2.2)
Pain	0	2 (1.1)	4 (2.2)	1 (0.5)	3 (1.1)	2 (0.7)	1 (0.4)
Cardiovascular	6 (8.9)	9 (5.0)	11 (6.1)	20 (10.7)	29 (10.8)	35 (12.5)	28 (10.2)
Angina pectoris	8 (4.5)	8 (4.4)	2 (1.1)	6 (3.2)	12 (4.5)	11 (3.9)	8 (2.9)
Palpitation	3 (1.8)	0	1 (0.6)	4 (2.1)	2 (0.7)	2 (0.7)	1 (0.4)
Digestive system	3 (1.7)	2 (1.1)	8 (4.4)	25 (13.4)	18 (6.7)	36 (12.9)	41 (14.9)
Constipation	0	0	3 (1.7)	8 (4.3)	2 (0.7)	18 (6.5)	20 (7.3)
Dyspepsia	0	1 (0.6)	1 (0.6)	2 (1.1)	4 (1.5)	7 (2.5)	5 (1.8)
Nausea	0	1 (0.6)	2 (1.1)	16 (8.6)	2 (0.7)	9 (3.2)	14 (5.1)
Vomiting	0	0	1 (0.6)	4 (2.1)	1 (0.4)	2 (0.7)	4 (1.5)
Nervous system	4 (2.2)	3 (1.7)	15 (8.3)	29 (15.5)	9 (3.3)	17 (6.1)	28 (10.2)
Dizziness	1 (0.6)	2 (1.1)	9 (5.0)	22 (11.8)	5 (1.9)	10 (3.6)	19 (6.9)
Urogenital system	0	1 (0.6)	2 (1.1)	8 (4.3)	1 (0.4)	2 (0.7)	11 (4.0)
Urine abnormality	0	0	1 (0.6)	4 (2.1)	0	0	3 (1.1)

\*1500 mg BID is not proposed for clinical use.

to adverse events was observed in 1.1% of the ranolazine group and 1.4% of the placebo group. There was 1 death in each group. The study was conducted primarily in Eastern Europe, where 97% of the patients were enrolled. Both ERICA and CARISA determined that ranolazine reduces angina frequency in patients who remain symptomatic ( $\geq 3$  angina attacks per week) on amlodipine (5 mg or 10 mg) once daily. The use of calcium antagonists as first-line therapy for chronic angina is not common practice.  $\beta$ -Blockers are recommended as initial therapy in the absence of a contraindication.  $\beta$ -Blockers and calcium antagonists reduce myocardial ischemia "upstream" to prevent ischemic episodes from occurring. Ranolazine appears to work "downstream," reducing the extent or impact of the demand-induced ischemic episode after it has occurred.

### MERLIN

Ranolazine is currently being tested in a large acute coronary syndrome trial to determine its impact on death and recurrent ischemic events. The Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndrome (MERLIN TIMI 36) study is a large (>6000 patients) multinational end-point-driven trial of patients with an acute coronary syndrome receiving contemporary therapy, who have had chest pain within the 48 hours before randomization, ST depression or abnormal biomarkers, diabetes mellitus, or a TIMI risk score  $\geq 3$ .<sup>34</sup> The primary end point of the trial is the composite of cardiovascular death, myocardial infarction, or recurrent ischemia. Patients are randomized 1:1

in a double-blind design to intravenous followed by oral ranolazine or placebo with sequential follow-up visits every 4 months and an exercise study conducted 8 months after randomization. The study is expected to complete enrollment in 2006 and will make an important contribution to understanding the potential for ranolazine to reduce cardiac events in patients with more extensive cardiac ischemia in an acute occlusion/reperfusion setting.

### Adverse Events

Adverse events during the MARISA trial were reported in 14.5% and 15.5%, 20.6% and 33.2% of patients on placebo and ranolazine 500, 1000, and 1500 mg twice daily, respectively<sup>8</sup> (Table 3). Early withdrawal from the study because of adverse events occurred in 2, 1, 1, and 11 patients, respectively. At the 1500-mg dose compared with placebo, the most common adverse events reported were dizziness, nausea, asthenia, and constipation (Table 3). The adverse event profile at the 1500-mg twice-daily dose and the relatively modest incremental benefit in exercise time from the 1000-mg to 1500-mg twice-daily dose (Figure 5) led to the maximum dose of 1000 mg twice daily tested in subsequent trials. The most common adverse effects that occur more frequently than placebo over the dose range of 500 to 1000 mg twice daily are dizziness, constipation, nausea, asthenia, headache, dyspepsia, and abdominal pain. Adverse events in the doses tested are more frequent in the elderly (>65 years) and occur  $\approx 2$ -fold more than with placebo. Dizziness and

nausea are the most common reasons for discontinuation of ranolazine compared with placebo.

In the 12-week CARISA trial, in which patients were on either an intermediate dose of a calcium channel antagonist or a  $\beta$ -blocker, serious adverse effects occurred in 6% of placebo patients and 7% of patients on either ranolazine dose.<sup>9</sup> Adverse events were reported in 26.4%, 31.2%, and 32.7% of patients on placebo and ranolazine 750 and 1000 mg twice daily, respectively. Syncope was reported in 3 MARISA patients, all at a dose of 1500 mg twice daily, and in 5 patients aged  $\geq 65$  years in CARISA, all initially randomized to 1000 mg twice daily. Four of the 5 patients were taking diltiazem, which is known to increase plasma ranolazine concentrations, and all were taking an ACE inhibitor. In the 4 patients in whom plasma concentrations were available, the mean plasma concentration was 5913 ng/mL. Although little or no effect of ranolazine on mean blood pressures has been observed over the dose range of 500 to 1000 mg BID, postural hypotension and syncope have occurred in healthy volunteers given higher doses, up to 2000 mg BID, in the absence of cardiac arrhythmias or QT prolongation on monitoring. There is no evidence that any of the cases of syncope observed were associated with torsades de pointes; indeed, some cases of syncope occurred in patients during ECG monitoring with documented normal sinus rhythm. In the 6-week ERICA trial of chronic angina patients on background therapy of amlodipine 10 mg QD (44% treated with long-acting nitrates) initially started on ranolazine 500 mg twice daily for 1 week and then uptitrated to 1000 mg twice daily as tolerated, there were no cases of syncope.<sup>33</sup> There have been no cases of syncope reported in the 3 controlled trials at ranolazine doses  $< 1000$  mg twice daily. Therefore, syncope can be avoided by starting patients with chronic angina on a smaller dose of ranolazine initially (eg, 500 mg twice daily), increasing the dose as required for symptomatic relief in the absence of side effects, and explaining to patients who are on multiple drugs known to affect blood pressure or ranolazine metabolism that they should notify their physician if they experience lightheaded episodes or dizziness.

At higher plasma concentrations (eg,  $> 8000$  ng/mL), ranolazine may cause nausea, vomiting, dizziness, vertigo, abnormal vision, confusion, postural hypotension, and syncope.<sup>9,18</sup> Plasma levels that exceed 8000 mg/dL may be seen in patients taking concomitant ranolazine (1000 mg twice daily) and ketoconazole (200 mg twice daily).

Ranolazine does not cause deleterious changes in laboratory parameters. Small mean increases in creatinine have been observed ( $> 0.1$  mg/dL) that appear to be due to modest inhibition of tubular secretion with no decline in glomerular filtration. Small mean decreases in hematocrit (1%) have been noted without evidence of red blood cell destruction or gastrointestinal blood loss. Mild transient eosinophilia has also been observed in a small number of patients.<sup>8</sup>

### Effects on the ECG

In CARISA, the average increase in QTc (Bazett) was 6.1 and 9.2 ms at the ranolazine doses of 750 and 1000 mg twice daily.<sup>9</sup> In population-based analyses, the QTc effect of



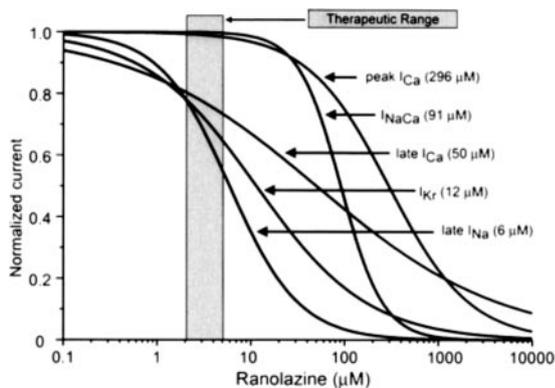
**Figure 6.** In this normal volunteer exposed to a high dose of ranolazine (2000 mg BID), T-wave notching is observed (arrow). Higher doses of ranolazine may also cause a reduction in T-wave amplitude. Reprinted with permission from *J Cardiovasc Pharmacol Ther.* 2004;9(suppl 1):S47–S64.<sup>21</sup>

ranolazine has been well characterized and remains linear over a concentration range up to 4 times greater than the peak concentrations produced by ranolazine at 1000 mg twice daily.<sup>18</sup> The slope of the relationship between QTc and plasma levels of ranolazine, with the use of the Fridericia QTc (a QT correction formula that provides a more accurate regression of QT/RR in the ranolazine population), was 2.4-ms prolongation of the QTc per 1000 ng/mL of ranolazine. In the dose range of 500 to 1000 mg twice daily, ranolazine increases the QTc (Fridericia) by an average of 2 to 5 ms. The slope was steeper in patients with moderate to severe hepatic impairment ( $\approx 7$  ms/1000 ng/mL).<sup>25</sup>

The incidence of “QTc outliers” in lead II with the use of the Fridericia correction for a QTc of  $> 500$  ms was 0.7% and 0.6% at the 1000- and 1500-mg twice daily doses, respectively; for a QTc increase of  $> 60$  ms, the rates were 2.3% and 3.7%, respectively. The likelihood of either event occurring at the 1000- or 1500-mg twice daily dose is 2.8% and 4.3%, respectively. Ranolazine is contraindicated in patients with preexisting QT prolongation, on QT-prolonging drugs, or with hepatic impairment. An ECG should be acquired at baseline and follow-up to evaluate effects on the QT interval. T-wave notching has been observed at high plasma ranolazine concentrations<sup>21</sup> (Figure 6). No cases of torsade de pointes have been seen in patients who received the drug in clinical trials to date. The mean change from baseline in the PR interval was 1.6 and 2.1 ms at 750 and 1000 mg twice daily, and the increase in the QRS duration was 0.7 and 1.2 ms, respectively.

### Electrophysiological Properties of Ranolazine

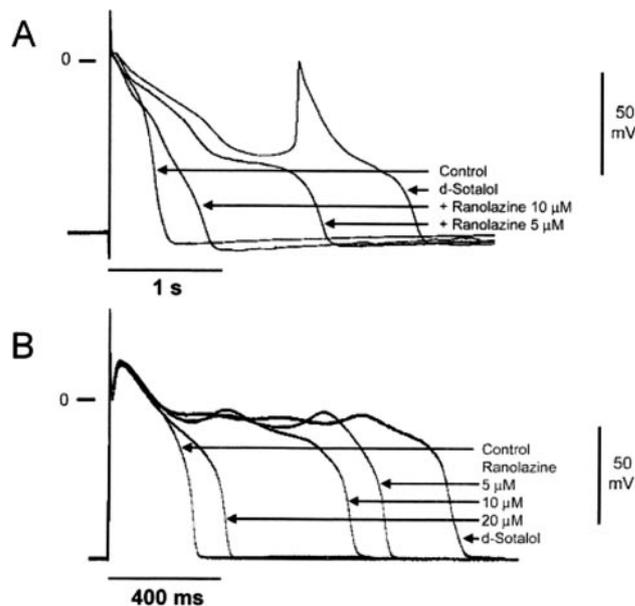
The electrophysiological properties of ranolazine have been tested in several different experimental preparations.<sup>10–15,35–37</sup> Ranolazine significantly inhibits the rapidly activating component of the delayed rectifier or  $I_{Kr}$  with a potency (ie,  $IC_{50}$ ) of 12  $\mu$ mol/L. The  $IC_{50}$  for ranolazine inhibition of late  $I_{Na}$  is  $\geq 6$   $\mu$ mol/L (Figure 7). The parent compound inhibits late  $I_{Na}$  and  $I_{Kr}$  equipotently at the low end of the therapeutic range



**Figure 7.** Summary of concentration-response relationships for effect of ranolazine to inhibit inward and outward ion channel currents in canine ventricular myocytes. Numbers inside parentheses are  $IC_{50}$  values for effect of ranolazine to inhibit rapidly activating rectifier potassium current ( $I_{Kr}$ ), late sodium current (late  $I_{Na}$ ), peak calcium current ( $I_{Ca}$ ), late  $I_{Ca}$ , and sodium-calcium exchange current ( $I_{Na-Ca}$ ). Reprinted with permission from *Circulation*. 2004;110:904–910.<sup>11</sup> Copyright 2004, American Heart Association.

but inhibits late  $I_{Na}$  more potently at the high end (Figure 7). The net effect is to prolong the action potential duration (APD) of epicardial and endocardial cells, in which late  $I_{Na}$  is relatively small, but to abbreviate or produce little change in the APD of the M cells, in which late  $I_{Na}$  is more prominent. The most abundant ranolazine metabolite is present at a plasma concentration of 30% to 40% that of the parent compound. Four of the metabolites produce a weak inhibition of  $I_{Kr}$  (40% to 50% at a concentration of 50  $\mu\text{mol/L}$ ) in canine cardiac myocytes. The  $IC_{50}$  values for  $I_{Kr}$  inhibition by the 11 metabolites tested were all  $>50 \mu\text{mol/L}$ . All 11 metabolites were found to inhibit late  $I_{Na}$  by 12% to 57% at a concentration of 10  $\mu\text{mol/L}$ . Because the metabolites inhibit late  $I_{Na}$  more potently than  $I_{Kr}$ , they are likely to produce less of a reduction in the net outward current than the parent compound and are unlikely to contribute to QT interval prolongation.<sup>10</sup>

Unlike its effect on ventricular myocardium, ranolazine does not prolong the APD of canine Purkinje fibers at any concentration, distinguishing it from other agents that block the  $I_{Kr}$ . The APD prolongation induced by ranolazine is rate independent (ie, does not display reverse use dependence) and is not associated with early afterdepolarizations (EADs), triggered activity, increased spatial dispersion of repolarization, or polymorphic ventricular tachycardia. In canine ventricular wedge preparations, ranolazine did not induce spontaneous torsades de pointes or permit programmed electrical stimulation induction at any concentration tested up to 100  $\mu\text{mol/L}$ .<sup>11</sup> Therefore, ranolazine does not have the electrophysiological profile commonly observed with other QT-prolonging drugs. In experimental preparations, Antzelevitch and colleagues<sup>11</sup> demonstrated a significant reduction in APD prolongation and suppression of EADs induced by *d*-sotalol when ranolazine at therapeutic concentrations (5 to 10  $\mu\text{mol/L}$ ) was added to a canine ventricular M cell preparation (Figure 8). Other experiments show reduced amplitude of early EADs with the use of 1 to 10  $\mu\text{mol/L}$  of ranolazine in



**Figure 8.** Effect of ranolazine to suppress *d*-sotalol-induced EADs in M cell and Purkinje fiber preparations. A, Superimposed transmembrane action potentials recorded from a Purkinje fiber preparation in presence of  $I_{Kr}$  block (100  $\mu\text{mol/L}$  *d*-sotalol) and after addition of increasing concentrations of ranolazine (5 and 10  $\mu\text{mol/L}$ ) in continued presence of *d*-sotalol.  $[K^+]_o = 3 \text{ mmol/L}$ , basic cycle length = 8000 ms. B, Superimposed transmembrane action potentials recorded from an M cell preparation under control conditions, in presence of  $I_{Kr}$  block (100  $\mu\text{mol/L}$  *d*-sotalol), and after increasing concentrations of ranolazine (5, 10, and 20  $\mu\text{mol/L}$ ) in continued presence of *d*-sotalol. Basic cycle length = 2000 ms. Reprinted with permission from *Circulation*. 2004;110:904–910.<sup>11</sup> Copyright 2004, American Heart Association.

guinea pig isolated ventricular myocytes and, in other experiments, suppression of the antiarrhythmic effects induced by a variety of QT-prolonging drugs.<sup>11,35–37</sup> The reader is referred to several publications for a more in-depth discussion of the antiarrhythmic potential of ranolazine.<sup>38–40</sup>

### Ranolazine in Heart Failure

In an isolated ventricular myocyte canine heart failure model, the delayed or incomplete inactivation of late  $I_{Na}$  of the sodium channel contribution was substantially augmented.<sup>10–12</sup> Ranolazine inhibits the late  $I_{Na}$  current and significantly improves left ventricular performance in experimental models of heart failure.<sup>41–45</sup> Sabbah et al<sup>43</sup> measured hemodynamics before and 40 minutes after an intravenous dose of 0.5 mg/kg of ranolazine followed by a continuous infusion of 1.0 mg/kg per hour in a canine model of heart failure induced by intracoronary microembolization to produce an average ejection fraction of 27%. Results in 13 experimental dogs were compared with those obtained in 8 normal healthy dogs. Ranolazine significantly decreased left ventricular end-diastolic pressure and increased left ventricular ejection fraction (27% versus 36%;  $P < 0.001$ ), peak LV  $+dP/dt$  (1712 versus 1900 mm Hg/s;  $P = 0.001$ ), and stroke volume (20 versus 26 mL) in the absence of any effects on heart rate or blood pressure. In normal dogs, there was no effect on indices of left ventricular function. The study was limited by the absence of

blinding and a placebo control. In subsequent experiments from the same laboratory, Chandler et al<sup>41</sup> reproduced these findings and determined that the improvement in left ventricular performance was not associated with an increase in myocardial oxygen consumption ( $\dot{M}\dot{V}O_2$ ) compared with an intravenous infusion of dobutamine that improved left ventricular performance to a similar extent but was associated with a significant increase in  $\dot{M}\dot{V}O_2$  requirements. In subsequent studies from the same laboratory in which a chronic canine heart failure model was used, pre/post 3-month comparison of oral ranolazine compared with placebo demonstrated decreased left ventricular end-diastolic pressure, negative LV  $-dP/dt$ , and left ventricular circumferential wall stress and increased deceleration time of early mitral inflow velocity (H. Sabbah, PhD, written communication, February 16, 2006).

In a study of 15 patients with prior myocardial infarction (average ejection fraction 35%) who received an intravenous ranolazine infusion (200 or 500  $\mu\text{g}/\text{kg}$ ), regional function was assessed in ischemic, infarcted, and normal left ventricular segments.<sup>44</sup> Global left ventricular function was not changed significantly after ranolazine infusion; left ventricular ejection fraction was 37% after dosing ( $P=\text{NS}$ ). However, ranolazine was associated with a significant increase in peak filling rate and regional wall lengthening during the isovolumic relaxation phase in ischemic left ventricular segments, suggesting evidence of improved regional diastolic function.

The MARISA and CARISA trials in chronic angina allowed enrollment of patients with a prior clinical history of NYHA class I/II heart failure (Table 1). Comparison of the exercise test results in patients with and without a prior history of heart failure did not reveal treatment effects inconsistent with the results observed in the overall population.<sup>8,9</sup> The treatment-by-subgroup interactions at trough for both studies were not statistically significant.

### Summary and Future Directions

Ranolazine is a relatively selective inhibitor of the late  $I_{\text{Na}}$  current and has effects on several other cardiac ion currents (eg, late  $I_{\text{Ca,L}}$ ,  $I_{\text{Kr}}$ ) at therapeutic plasma concentrations. This relatively unique mechanism of action merits further study in cardiovascular conditions in which the late  $I_{\text{Na}}$  is amplified such as heart failure, acute and chronic myocardial ischemia, certain types of cardiac sodium channel gene mutations, and ventricular and supraventricular arrhythmias. Other conditions such as left ventricular diastolic dysfunction with preserved systolic function and skeletal muscle ischemia (intermittent claudication)<sup>45</sup> should also be considered for study.

Ranolazine was recently approved in United States for the treatment of chronic angina. The label indicates that ranolazine should be reserved for patients who have not achieved an adequate response with other antianginal drugs because ranolazine is known to prolong the QT interval. Ranolazine should be used in combination with amlodipine,  $\beta$ -blockers, or nitrates. It should not be used as an alternative to  $\beta$ -blocker therapy in patients otherwise eligible for this form of therapy unless future studies demonstrate an indication. The therapeutic dose range of 500 to 1000 mg twice daily is generally

well tolerated, with constipation, nausea, asthenia, and dizziness being the most common adverse events reported (<7% excess frequency compared with placebo). The maximum recommended dose of ranolazine is 1000 mg twice daily. Ranolazine is extensively metabolized predominantly through the CYP3A4 pathway with a small amount (<5%) excreted in the urine unchanged. Ranolazine is contraindicated in patients with hepatic impairment, those with QTc prolongation or who are taking drugs known to prolong the QT interval, and those who are taking drugs that are moderately potent CYP 3A inhibitors. Patients who start ranolazine therapy and are receiving drugs known to inhibit this pathway or who have severe renal insufficiency should be more closely monitored for side effects if the patient is uptitrated to the maximum approved dose. An ECG should be acquired at baseline and during follow-up to evaluate any effects on the QT interval. Ranolazine has been studied in a wide range of clinical patient subgroups with chronic angina, is effective, and is generally well tolerated. There are few data in blacks, Hispanics, and Asians. The reduction in HbA<sub>1c</sub> levels in diabetic subjects that was observed in the CARISA trial requires prospective validation. The ongoing MERLIN TIMI 36 trial, scheduled to be completed in 2006, will address whether ranolazine can reduce the composite end point of cardiovascular death, myocardial infarction, or recurrent ischemia in high-risk patients with an acute coronary syndrome and will provide important data on the adverse event profile and safety in a large number of patients on multiple medications followed up for at least 1 year.

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