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Coronary Artery Disease

Anti-Ischemic Effects and Long-Term Survival During Ranolazine Monotherapy in Patients With Chronic Severe Angina

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OBJECTIVES The primary objective of the Monotherapy Assessment of Ranolazine In Stable Angina (MARISA) trial was to determine the dose-response relationship of ranolazine, a potentially new anti-anginal compound, on symptom-limited exercise duration.

BACKGROUND Fatty acids rise precipitously in response to stress, including acute myocardial ischemia. Ranolazine is believed to partially inhibit fatty acid oxidation, shift metabolism toward carbohydrate oxidation, and increase the efficiency of oxygen use.

METHODS Patients (n = 191) with angina-limited exercise discontinued anti-anginal medications and were randomized into a double-blind four-period crossover study of sustained-release ranolazine 500, 1,000, or 1,500 mg, or placebo, each administered twice daily for one week. Exercise testing was performed at the end of each treatment during both trough and peak ranolazine plasma concentrations.

RESULTS Exercise duration at trough increased with ranolazine 500, 1,000, and 1,500 mg twice daily by 94, 103, and 116 s, respectively, all greater ($p < 0.005$) than the 70-s increase on placebo. Dose-related increases in exercise duration at peak and in times to 1 mm ST-segment depression at trough and peak and to angina at trough and peak were also demonstrated (all $p < 0.005$). Ranolazine had negligible effects on heart rate and blood pressure. One year survival rate combining data from the MARISA trial and its open-label follow-on study was 96.3 ± 1.7%.

CONCLUSIONS In chronic angina patients, ranolazine monotherapy was well tolerated and increased exercise performance throughout its dosing interval at all doses studied without clinically meaningful hemodynamic effects. One-year survival was not lower than expected in this high-risk patient population. This metabolic approach to treating myocardial ischemia may offer a new therapeutic option for chronic angina patients. (J Am Coll Cardiol 2004;43:1375–82)

Acute myocardial ischemia is characterized by a number of maladaptive metabolic responses that amplify the direct deleterious effects of an imbalance between oxygen supply and demand. Fatty acid levels rise abruptly, promoting their myocardial uptake and oxidation. Because more oxygen is required to phosphorylate a given amount of adenosine triphosphate during fatty acid oxidation than during carbohydrate oxidation, this abrupt elevation in circulating free fatty acids causes an inefficient use of the already limited oxygen supply. In addition, elevated free fatty acids directly suppress the myocardial uptake and oxidation of more oxygen-efficient carbohydrate fuels such as glucose, lactate, and pyruvate, further exacerbating both the oxygen wasting and the accumulation of lactate (Fig. 1A) (1).

Ranolazine, an investigational treatment for angina, is not a beta-adrenergic receptor blocker, a calcium channel antagonist, or a vasodilator. Rather, ranolazine appears to shift adenosine triphosphate production away from fatty acid oxidation in favor of more oxygen-efficient carbohydrate oxidation (2) (Fig. 1B), especially when free fatty acids are elevated, as they are during ischemia (3). This shift in substrate selection should reduce the oxygen required to support any level of cardiac work. Furthermore, preferential use of the available oxygen for carbohydrate metabolism during ischemia should maintain the coupling of glycolysis to pyruvate oxidation, minimizing lactate accumulation (and subsequent tissue acidosis) (Fig. 1B) (1).

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Abbreviations and Acronyms

ANOVA = analysis of variance
BP = blood pressure
CARISA = Combination Assessment of Ranolazine In Stable Angina trial
ECG = electrocardiogram/electrocardiographic
ETT = exercise treadmill test
HR = heart rate
MARISA = Monotherapy Assessment of Ranolazine In Stable Angina trial
SR = sustained release

Ranolazine has demonstrated anti-ischemic activity in a variety of in vitro and in vivo systems (2,4–13). In earlier clinical studies, an immediate-release formulation of ranolazine, in combination with other anti-anginal medications, increased exercise treadmill test (ETT) performance in patients with chronic angina without decreases in blood pressure (BP) or heart rate (HR), both at rest and at peak exercise, but only at times associated with peak ranolazine plasma concentrations (1 to 3 h after dosing) (14,15). None of the earlier studies evaluated the drug prospectively as monotherapy for angina, and none reported long-term follow-up data. Subsequently, a sustained-release (SR) formulation was developed to maintain effective plasma concentrations with twice daily administration.

The Monotherapy Assessment of Ranolazine In Stable Angina (MARISA) trial—a multi-national, randomized, double-blind, placebo-controlled study—is the first trial of ranolazine SR monotherapy in patients with chronic angina. Its purpose was to assess the tolerability of three doses of ranolazine SR compared to placebo and their effects on treadmill exercise performance and to provide long-term survival data in patients that completed the trial.

METHODS

Patient selection. Patients were at least 21 years of age, had well-documented coronary artery disease, and had at least a three-month history of effort angina responding to beta-blockers, calcium channel blockers, and/or long-acting nitrates. All patients discontinued anti-anginal treatment during the study (except sublingual nitroglycerin as needed) and provided written informed consent. Key exclusion criteria were: conditions that might compromise electrocardiogram (ECG) or ETT interpretation (e.g., treatment with digoxin, ≥1 mm ST-segment depression at rest, left bundle branch block, pacemaker rhythm); New York Heart Association functional class III or IV congestive heart failure; unstable angina, myocardial infarction, or any coronary revascularization procedure within two months of enrollment; corrected QT interval (QTc) >500 ms or any medication known to prolong the QTc interval; or requirement for medication or food known to affect metabolism by cytochrome P450 3A4. Appropriate precautions were taken for women of childbearing potential.

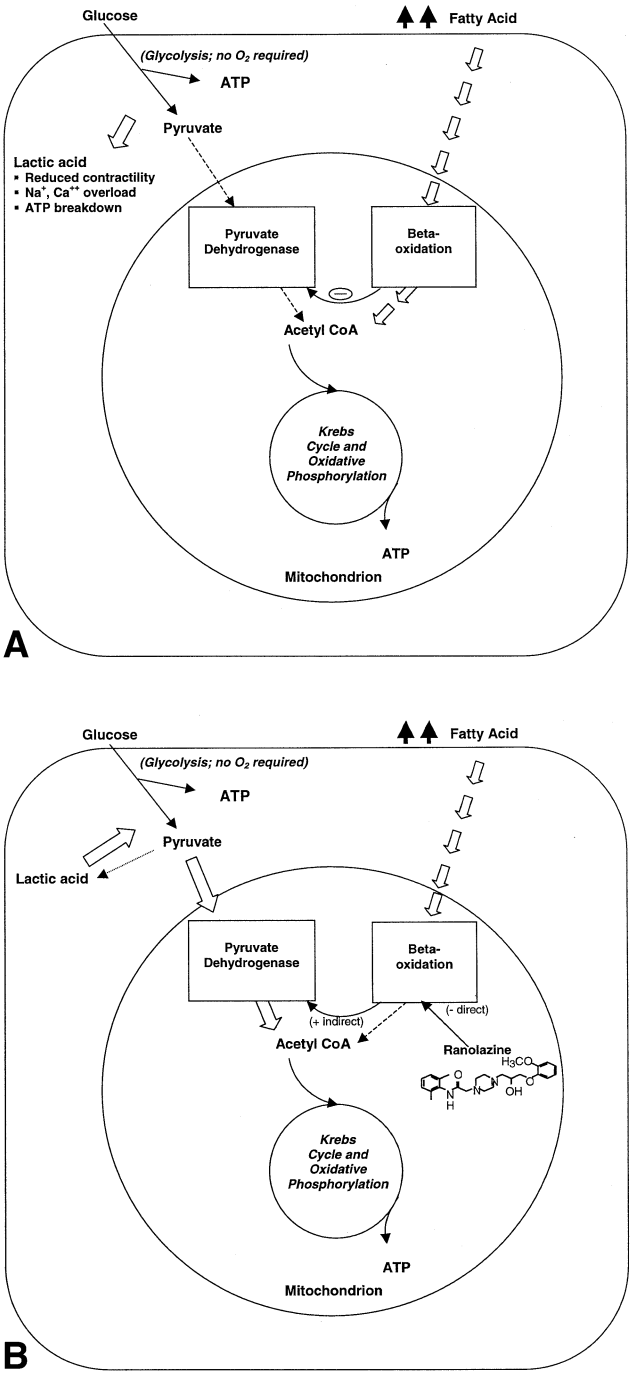

Figure 1. Regulation of carbohydrate metabolism by fatty acid oxidation. Predominating pathways are represented by **open arrows**; inhibited pathways are represented by **dotted arrows**. **(A)** When fatty acid levels are elevated, the end products of beta-oxidation reduce the activity of pyruvate dehydrogenase, the enzyme that mediates the conversion of pyruvate to acetyl CoA and permits its entry into the Krebs cycle. As a result, oxygen-wasting fatty acid oxidation predominates, pyruvate oxidation is inhibited, and lactate accumulates with deleterious consequences. **(B)** Inhibiting fatty acid oxidation with ranolazine should relieve the inhibition of pyruvate dehydrogenase, promoting oxidation of glucose and lactate, which phosphorylates a given amount of ATP using less oxygen than fatty acid oxidation. In addition, the coupling of pyruvate formation via glycolysis to pyruvate oxidation in the Krebs cycle is improved so that lactate accumulation is diminished.

After discontinuation of all prophylactic anti-anginal medications, eligible patients entered a single-blind placebo-treatment qualifying phase during which they had two modified Bruce ETTs (16) conducted one week apart. Patients were randomized into the double-blind phase of the study if they developed exercise-limiting angina and ≥1 mm horizontal or downsloping ST-segment depression below the isoelectric line between 3 and 9 min during each qualifying ETT and the difference in exercise duration between the two tests did not exceed 20% of the longer test or 1 min. In patients with permitted baseline ST-segment depression at rest (<1 mm), qualifying ST-segment depression was defined as additional ST-segment depression ≥1 mm below the resting value.

Study design and procedures. The protocol was approved by the institutional review board at each participating institution and written informed consent was obtained from each patient. Randomized patients received double-blind treatment with ranolazine SR at doses of 500, 1,000, and 1,500 mg or placebo (CV Therapeutics, Palo Alto, California), each administered twice daily for one week, according to a four-period, balanced Latin Square crossover design. At the end of each treatment period, ETTs were performed at times approximating peak and trough ranolazine plasma concentrations: 4 and 12 h after dosing (hereafter referred to as peak and trough, respectively). Sublingual nitroglycerin was not permitted for at least 60 min before testing.

Standing HR and systolic BP were measured at rest and at maximal exercise during each trough and peak ETT. A supine 12-lead ECG was obtained before each ETT and standing ECGs were monitored throughout ETT testing. A core ECG laboratory (St. Louis University, St. Louis, Missouri) interpreted all rest and exercise ECGs blinded to treatment assignment. All rest ECGs were classified using the Minnesota code. All exercise ECGs were analyzed using customized software as previously described (17).

Blood samples for analysis of plasma ranolazine concentrations were collected before each ETT during double-blind treatment. Clinical evaluations and adverse event monitoring occurred throughout the study. Laboratory tests were performed at screening and the final visit.

Of 191 patients randomized in the MARISA trial, 168 (88.0%) completed all four cross-over periods. Of these, 143 (85.1%) patients agreed to participate in an open-label study consisting of a 1- to 6-week titration phase starting with ranolazine monotherapy at 750 mg twice daily, escalating to 1,000 mg twice daily as needed based on angina relief, and then addition of other anti-anginal medication if necessary.

Statistical analysis. The primary efficacy end point of the study was total exercise duration at trough. Other efficacy end points included time to onset of angina and time to 1 mm ST-segment depression at trough, and the same three ETT end points at peak. The primary efficacy analysis population included patients who completed at least three of their four double-blind study periods. Randomized patients who received at least one dose of study drug were included in the safety evaluation.

For the primary efficacy analysis, adjustment for multiple comparisons of each ranolazine dose to placebo was addressed by a three-stage step-down procedure. This was based on closed testing and intersection union principles and maintained the experiment-wise type I error rate at 0.05 (18,19). All p values reflect comparisons versus placebo.

Treadmill parameters, ECG intervals, and hemodynamic parameters were assessed using standard analysis of variance (ANOVA) models for a crossover study design with treatment, period, pooled site, and patient within pooled site as factors. Estimates of the treatment differences (i.e., ranolazine vs. placebo) for each ranolazine dose and the associated statistical significance were obtained. The balanced Latin Square study design allowed a secondary analysis to be conducted in the context of an ANOVA to determine the presence or absence of a first-order carry-over effect. The McNemar's test was used for the analysis of dichotomous paired data (e.g., reason for stopping the ETT categorized as angina or not angina). All other data were summarized descriptively. Treatment means and differences are least-squares means from the ANOVA model unless otherwise noted.

A survival curve was prepared using Kaplan-Meier estimates (20). All patients who received at least one dose of ranolazine were included on an intent-to-treat basis. Patients were censored at one day after their last treatment with ranolazine.

RESULTS

The study began in December 1997 and ended in May 1999; long-term follow-up is reported through October 15, 2001. A total of 191 patients were enrolled at 52 investigational sites in four countries (U.S., Czech Republic, Poland, and Canada) and received at least one dose of double-blind study medication.

Patient characteristics are summarized in Table 1. Of the 191 randomized patients, all received at least one dose of double-blind medication and were evaluated for safety; 175 (91.6%) completed three of the four treatment periods and were thus included in the primary efficacy analysis population as defined prospectively in the protocol. Compliance, defined as receiving 67% to 125% of study drug, was observed in more than 96% of patients during each treatment period.

Twenty-three patients (12%) discontinued the study before completing all treatment periods: 15 patients (7.9%) for adverse events, 4 patients (2.1%) by elective withdrawal, 2 patients (1.0%) for other reasons, 1 patient (<1%) because of death, and 1 patient (<1%) because of inappropriate enrollment.

Exercise treadmill tests. Compared to placebo, treatment with ranolazine at all doses significantly improved total exercise duration, time to angina, and time to 1 mm

Table 1. Patient Characteristics (n = 191)

Parameter	All Enrolled Patients
Men	73.3%
Age (yrs)	
Mean (±SD)	64.3 ± 9.4
Range	39–85
Caucasian	91.1%
Antianginal drugs discontinued before randomization	
Long-acting nitrates	58.1%
Beta-adrenergic receptor antagonists	56.5%
Calcium-channel antagonists	38.2%
One of the above	37.2%
Two of the above	47.6%
All three of the above	6.8%
Baseline electrocardiographic findings by (Minnesota Code)	
Pathologic Q waves	15.7%
Major ST-T abnormalities (without pathologic Q waves)	14.7%
Minor ST-T abnormalities (without pathologic Q waves)	27.2%
No pathologic Q waves or significant ST-T abnormalities	42.4%
Prior myocardial infarction	52.3%
Congestive heart failure (class I/II)	16.8%
Prior coronary artery bypass grafting	27.7%
Prior coronary angioplasty	32.5%
Hypertension	64.4%
Diabetes	24.1%
Intermittent claudication	9.4%
Chronic obstructive pulmonary disease/asthma	6.8%

ST-segment depression at both the trough and peak time points (Table 2, Fig. 2A). A dose-response relationship for all three exercise parameters was apparent.

At trough, 71.8%, 67.2%, 60.3%, and 56.8% of patients receiving placebo or ranolazine 500, 1,000, or 1,500 mg, respectively, stopped exercising because of angina. At peak, these percentages were 70.3%, 64.9%, 62.6%, and 52.4%, respectively. The differences in proportions versus placebo were significant for the 1,000 and 1,500 mg ranolazine treatments at both trough and peak (all $p < 0.04$).

For all treadmill efficacy times, the first-order carryover effect assessed via ANOVA models was not significant at the 0.1 level, indicating that there was no significant effect of the preceding treatment on the effect of the subsequent treatment.

Hemodynamic changes at rest and maximal exercise. No clinically significant changes in rest or exercise HRs or BPs were observed. The 500 mg dose had no effect on any of these values. At peak, ranolazine 1,500 mg twice daily decreased resting HR by <3 beats/min ($p = 0.001$), resting systolic BP by <3 mm Hg ($p < 0.05$), and exercise systolic BP by <7 mm Hg ($p < 0.001$). At trough, ranolazine 1,500 mg twice daily decreased resting HR by <3 beats/min ($p < 0.001$) and exercise systolic BP by <6 mm Hg ($p < 0.001$).

Safety. ADVERSE EVENTS. The overall adverse event rate for the 500 mg dose was similar to that for placebo (15.6% on placebo vs. 16.0% on ranolazine 500 mg) (Table 3); adverse events increased with higher doses. Specific dose-related adverse events included dizziness, nausea, asthenia, and constipation; these occurred substantially more frequently on 1,500 mg twice daily than on 1,000 mg twice daily. Early withdrawal from the study because of adverse events also occurred predominantly during dosing with 1,500 mg twice daily (11 patients) compared with two, one, and one patient during treatment with placebo, ranolazine 500 mg twice daily, and ranolazine 1,000 mg twice daily, respectively.

ELECTROCARDIOGRAPHIC FINDINGS. Minor dose-related ECG changes were observed with ranolazine treatment. Mean differences in QTc interval (Bazett correction) versus placebo were 6, 7, and 11 ms at trough and 5, 6, and 14 ms at peak for the ranolazine 500, 1,000, and 1,500 mg twice

Table 2. Mean Exercise Treadmill Test Parameters in Seconds* (n = 175)

	Placebo		Ranolazine Treatment					
			500 mg b.i.d.		1,000 mg b.i.d.		1,500 mg b.i.d.	
	(Duration or Time)		(Difference From Placebo)					
Parameter	Trough	Peak	Trough	Peak	Trough	Peak	Trough	Peak
Exercise duration (s)								
Mean	505.7	501.7	23.8	29.3	33.7	50.1	45.9	55.5
Standard error	5.7	5.2	7.9	7.2	8.0	7.2	8.0	7.3
p Value	—	—	0.003	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Time to angina (s)								
Mean	407.3	416.3	27.0	35.5	45.9	56.4	59.6	68.5
Standard error	6.8	6.1	9.5	8.5	9.5	8.5	9.6	8.6
p Value	—	—	0.005	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Time to 1 mm ST-segment depression								
Mean	443.4	436.4	27.6	38.8	44.5	55.6	64.6	69.0
Standard error	5.7	5.9	8.1	8.2	8.1	8.2	8.2	8.4
p Value	—	—	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

*Mean durations or times receiving placebo, differences from placebo, and standard errors are least squares mean estimates from the analysis of variance model including effects for treatment, period, pooled site, and patient within pooled site; associated p values are reported. The unadjusted mean baseline exercise duration for the population was 440.1 s at trough and 442.7 s at peak.

b.i.d. = twice daily.

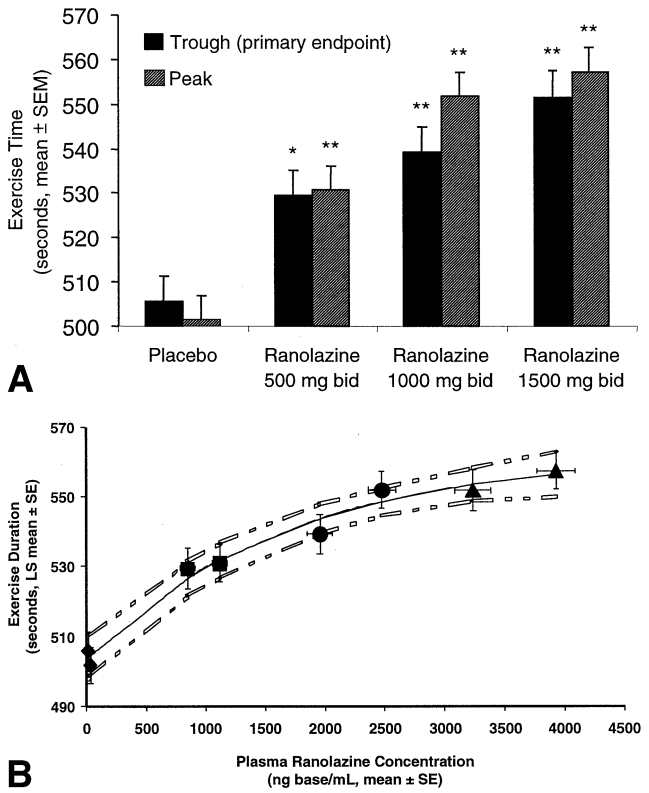

Figure 2. Symptom-limited exercise duration: dose and plasma concentration relationships. **(A)** Exercise duration versus ranolazine dose. Data are shown at trough (**solid bars**, primary end point) and peak (**lined bars**). Statistically significant increases were observed on each ranolazine dose versus placebo (*$p < 0.005$ vs. placebo; **$p < 0.001$ vs. placebo). A dose-response relationship was evident with greater increases at peak than at trough. Similar data were observed for time to onset of angina and time to 1 mm ST-segment depression (Table 2). **(B)** Exercise duration versus ranolazine plasma concentration. Mean exercise duration increases with mean plasma ranolazine concentrations. From **left to right**, values on each treatment at trough and peak, respectively, are represented by **diamonds** (placebo), **squares** (500 mg twice daily), **circles** (1,000 mg twice daily), and **triangles** (1,500 mg twice daily). **Dotted lines** represent the 95% confidence intervals around the fitted curve.

daily treatments, respectively. No patient discontinued the study because of QTc prolongation, prospectively defined as an increase of >30% from baseline to a value >500 ms. The QT dispersion was unaffected by any dose of ranolazine.

CLINICAL LABORATORY RESULTS. Clinically significantly high eosinophil counts occurred in 6 of 169 patients with end-of-study data (3.6%). Counts in these patients ranged from 2.9% to 8.6% at baseline and increased from 13.2% to 23.0% at end study. All counts returned to normal during a follow-on study in which patients continued on open-label ranolazine.

Ranolazine plasma concentrations. There was a clear monotonic relationship between mean ranolazine plasma concentrations and mean exercise durations (Fig. 2B). The increase in exercise duration appears to plateau at the higher ranolazine concentrations.

Subgroup analyses. The effect of ranolazine in diabetic subjects was compared to the nondiabetic cohort to determine if the metabolic abnormalities associated with this condition had an impact on the beneficial increase in total exercise time observed or were associated with a different side-effect profile. Diabetics accounted for 24% of the total population enrolled in the MARISA trial. Total exercise duration at trough was 498.5 ± 13.9 s, 519.6 ± 13.9 s, 526.0 ± 13.9 s, and 530.4± 14.5 s in the diabetic group (n = 42) and 503.4 ± 6.3 s, 528.1 ± 6.3 s, 539.1 ± 6.3 s, and 553.8 ± 6.4 s in the nondiabetic group (n = 133) for the placebo, 500 mg, 1,000 mg, and 1,500 mg twice daily ranolazine doses, respectively. The p value of treatment by diabetes interaction was 0.77, indicating no statistical evidence of a differential treatment effect by history of diabetes. The side-effect profile and frequency of adverse events were similar in diabetics and nondiabetics, with asthenia, constipation, dizziness, and nausea being the most common side effects reported more frequently during treatment with ranolazine.

Similar analyses were conducted by gender, prior history of heart failure (NYHA functional class I or II), and age (≥65 and <65 years). As indicated by the non-statistically significant p values of treatment by subgroup interaction, there was no evidence that the treatment effects of ranolazine within any of these particular subgroups were inconsistent with that observed in the overall population. The respective p values of treatment by subgroup interaction were 0.65, 0.94, and 0.054 for gender, heart failure, and age.

Table 3. Most Frequently Occurring Adverse Events, Incidence ≥3% for Any Treatment* (n = 191)

		Ranolazine Treatment		
Adverse Event	**Placebo**	**500 mg b.i.d.**	**1,000 mg b.i.d.**	**1,500 mg b.i.d.**
Any adverse event	15.6%	16.0%	21.7%	34.2%
Dizziness	1.1%	1.1%	5.0%	12.3%
Nausea	0	<1%	1.1%	8.6%
Asthenia	2.2%	0	1.7%	6.4%
Constipation	0	0	1.7%	4.3%
Angina pectoris	5.0%	5.0%	1.7%	3.2%
Headache	2.2%	<1%	1.1%	2.7%
Sweating	0	0	0	2.7%

*Events counted for each treatment during which event was present, even if continued from an earlier period.
b.i.d. = twice daily.

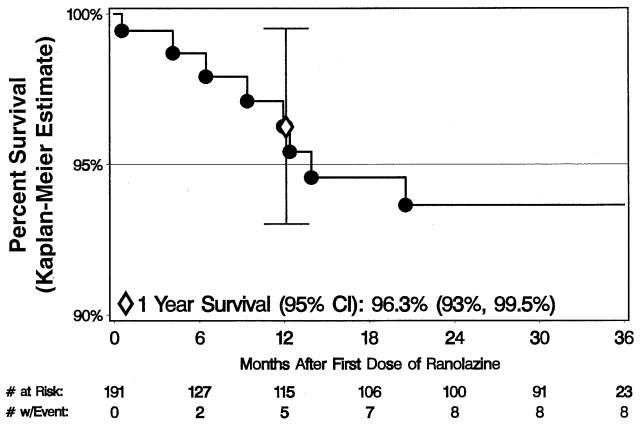

Figure 3. Survival during long-term ranolazine treatment. Kaplan-Meier survival curve including 191 patients who received ranolazine during the double-blind portion of the trial; 143 patients completed the double-blind study and continued on treatment with open-label ranolazine, as described in the Methods section. The curve was constructed from the first date of ranolazine treatment during the double-blind four-period crossover study, and includes a subsequent week of placebo treatment for the 140 patients who were not randomized to begin double-blind treatment with placebo. CI = confidence interval.

Long-term follow-up. Of the 143 patients participating in the open-label study, 115 (80.4%) and 100 (69.9%) were still receiving ranolazine at one year and two years after their first doses, respectively; the majority (>70%) were receiving 1,000 mg twice daily. Their one-year and two-year survival rate on ranolazine (95% confidence interval) were 96.3% (93.0% to 99.5%) and 93.6% (89.3% to 98.0%), respectively (Fig. 3).

DISCUSSION

The abrupt rise in free fatty acid levels during acute myocardial ischemia (1) and infarction (21) and its deleterious consequences (22,23) was first reported more than three decades ago but has yet to be fully exploited as a target for therapeutic intervention. Infusions of glucose, insulin, and potassium (intended to promote glucose uptake and oxidation and to reduce oxidation of free fatty acids) have achieved some success in the treatment of acute myocardial infarction (24–28) but are impractical for prophylaxis of chronic angina.

To date, few available therapies for chronic angina have been targeted specifically toward normalizing myocardial metabolism, and these have not achieved widespread use (29,30). Thus, an effective and well-tolerated metabolic anti-anginal agent remains an attractive therapeutic goal. First, metabolic intervention offers the potential to reduce the lactate accumulation and oxygen wasting associated with the precipitous ischemic rise in free fatty acids. Second, by reducing the oxygen demand necessary to support a given level of cardiac work, a metabolic mechanism might avoid reductions in BP, HR, or contractile function, effects of currently available anti-anginal agents that can be undesirable in some patients. Finally, many patients continue to have angina despite the best current therapy (31) and thus might benefit from a new agent with a mechanism complementary to those of existing drugs.

During exercise testing of patients with chronic angina, ranolazine, which partially inhibits fatty acid oxidation, significantly increased total exercise duration from 24 to 56 s more than placebo at doses of 500 to 1,500 mg twice daily. The symptoms and ECG evidence of myocardial ischemia during exercise testing were similarly delayed or prevented throughout the 12-h dosing interval (Table 2). Although the subgroup analyses contain relatively small numbers of patients, the beneficial effects on exercise tolerance time was observed in diabetics, patients who reported a prior history of mild heart failure, those over age 65 years, and in men and women, and were consistent with the overall study results.

These increases in exercise performance are similar to those reported for maximal doses of nitrates (32), beta-blockers (33,34), and calcium channel blockers (33,35,36) in similar patients. Comparisons of exercise data across different trials, however, should recognize that the increment in exercise performance versus placebo depends upon an interaction among several trial-specific factors, including the exercise protocol, the patient population, the uniformity of administration of the test, the criteria for a positive ischemic response, and the efficacy of the drug.

For example, Stone et al. (33) studied placebo, propranolol, diltiazem, and nifedipine as anti-anginal monotherapies titrated to their maximum tolerated doses, each for two weeks in a crossover trial. At peak, only diltiazem significantly prolonged exercise duration, by 30 s versus placebo. Exercise durations on nifedipine and propranolol were no different from placebo in this trial. Increases versus placebo in time to 1 mm ST-segment depression were 6 s for all three drugs; increases in time to angina ranged from 18 to 30 s. Similarly, in the Angioplasty Compared to Medicine (ACME) study, combination therapy allowing all three major anti-anginal classes titrated to their maximum tolerated doses increased exercise duration by 30 s from baseline (37). In Randomized Intervention Treatment of Angina-2 (RITA-2), a trial comparing coronary angioplasty to medical therapy for angina relief, the average increase in exercise time three months after randomization to coronary angioplasty was 37 s greater than with medical therapy (38). Finally, long-acting nitrates are mechanistically incapable of maintaining a continuous anti-anginal effect and must be withdrawn daily to restore responsiveness to a subsequent dose (32). Thus, the increases in exercise duration of 24 to 56 s demonstrated throughout the dosing interval on ranolazine versus placebo in the current study appear to be clinically useful.

Consistent with the proposed metabolic mechanism that requires further study, improvements in exercise tolerance on ranolazine do not appear to be explained by effects on BP or HR. First, ranolazine 500 mg twice daily significantly increased all three treadmill efficacy variables at both peak and trough without any effects on BP or HR. Second,

changes in exercise HR were not observed at any of the doses studied. Finally, the small decreases in exercise systolic BP at the two higher ranolazine doses translated to small declines in maximum rate-pressure product; however, in comparable studies, calcium channel blockers, and in particular, beta-blockers generally cause larger decreases in double product to produce similar or smaller improvements in exercise performance (33).

Ranolazine also appeared to be generally well tolerated by the chronic angina patients in this trial, particularly at the lower two doses. Fewer than 8% of patients discontinued ranolazine because of adverse effects, and almost three-quarters of these withdrawals occurred at the 1,500 mg dose. Dose-related complaints of dizziness, nausea, asthenia, and constipation were also considerably more common on the 1,500 mg dose than on the lower two doses, suggesting that for most patients, the optimum dose for both efficacy and tolerability can be achieved by starting with 500 mg twice daily and titrating upwards to 750 mg twice daily and 1,000 mg twice daily as needed to control angina. A crossover design with relatively brief treatment periods (one week each) was employed in this study to allow a definitive, placebo-controlled assessment of the anti-anginal efficacy of ranolazine monotherapy while minimizing the exposure of these severely limited patients to placebo-only treatment. The interpretation of crossover studies may be confounded by carryover effects. In this study, however, first-order carryover effects were not statistically significant at the 0.1 level for each of the three major treadmill exercise variables at both trough and peak.

Studies with longer-term follow-up in a broader population of angina patients will better assess the continued efficacy, tolerability, and safety of the drug. In particular, the relative lack of hemodynamic effects and novel mechanisms of ranolazine may render it especially useful for concomitant administration with other anti-anginal therapies. A placebo-controlled trial of 12 weeks' treatment with ranolazine at 750 or 1,000 mg twice daily, in combination with a beta-blocker or a calcium channel blocker (the CARISA trial), also reported significant increases in treadmill exercise performance in association with significant decreases in angina frequency and nitroglycerin consumption (39). In the CARISA trial, there was no statistical evidence of a differential treatment effect among patients receiving different background therapies (treatment-by-background interaction $p = 0.63$).

A total of 143 patients in the MARISA trial participated in the open-label long-term ranolazine study. The average Duke treadmill score at entry was -13.7 ± 0.2, a score consistent with a prognostic high-risk patient cohort (40). Although the 3.7% first-year mortality rate observed on ranolazine compares favorably with the approximate 9% annual rate reported in historical controls with a Duke treadmill score worse than -10 (40), comparative treatment differences on survival would need to be addressed by randomized clinical trials

In summary, ranolazine at doses of 500 to 1,500 mg twice daily significantly improves exercise performance and delays or prevents the symptoms and ECG evidence of myocardial ischemia during exercise testing in patients with chronic angina. Consistent with ranolazine's proposed metabolic mechanism, these effects occur with no (or only minimal) changes in BP and HR, and the tolerability of ranolazine appears acceptable. We conclude that ranolazine shows promise as a new treatment for chronic angina.

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APPENDIX

For a list of the MARISA Publications Committee, the MARISA Rest and Exercise ECG/MI/Ischemia Classification Laboratory, Sponsor, and Investigators, please see the April 21, 2004, issue of *JACC* at http://www.cardiosource.com/jacc.html.