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CLINICAL RESEARCH — Coronary Artery Disease

The Anti-Ischemic Mechanism of Action of Ranolazine in Stable Ischemic Heart Disease

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Objectives The purpose of this explanatory analysis was to investigate the relationship between ST-segment depression and the rate-pressure product (RPP) during exercise to determine whether ranolazine's mechanism of action was related to a reduction in myocardial oxygen demand or preservation of myocardial oxygen supply.

Background In patients with stable ischemic heart disease, ranolazine increases exercise duration and reduces maximal ST-segment depression while exerting minimal effects on heart rate and blood pressure, although its mechanism of action during exercise has not been investigated.

Methods Patients with stable ischemic heart disease (n = 191) were randomly allocated to a 4-period, double-blind, balanced Latin square crossover study to receive placebo, and ranolazine 500, 1,000, and 1,500 mg twice daily (bid) for 1 week each. Exercise treadmill tests were performed at baseline and at the end of each treatment period. The RPP and ST-segment depression were assessed before starting exercise, at each stage of exercise, and at maximal exercise.

Results Compared with placebo, ranolazine produced a dose-dependent reduction in ST-segment depression that became more marked as exercise-induced ischemia became more pronounced, associated with clinically minor decreases in heart rate and blood pressure. At 12-min exercise, the amount of ST-segment depression compared with placebo and controlled for RPP was reduced by 22.3% on ranolazine 500 mg bid ($p = 0.137$), by 35.4% on 1,000 mg bid ($p = 0.005$), and by 45.8% on 1,500 mg bid ($p < 0.001$).

Conclusions The progressive magnitude of ischemia reduction on ranolazine was proportionally more substantial than the minor reductions in heart rate or RPP, suggesting that ranolazine's beneficial mechanism of action is most likely primarily due to an improvement in regional coronary blood flow in areas of myocardial ischemia. (J Am Coll Cardiol 2010;56:934–42) © 2010 by the American College of Cardiology Foundation

Conventional antianginal medications reduce myocardial ischemia by significantly decreasing the determinants of myocardial oxygen demand, such as heart rate, blood pressure, or myocardial contractility at rest, during submaximal exercise, and during maximal exercise (1). Ranolazine is a novel antianginal and anti-ischemic medication approved for treatment of chronic angina. Although ranolazine has been shown to increase exercise duration, time to onset of angina, and time to ≥1-mm ST-segment depression (2–5) without clinically substantial changes in heart rate or blood pressure (3–5), the effect of ranolazine on the association between myocardial ischemia and oxygen demand during submaximal and maximal levels of exercise has not been

See page 943

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investigated. Pre-clinical evidence suggests that ranolazine's mechanism of action is in large part due to preservation of myocardial blood flow during ischemia through its effects on inhibition of the late inward sodium current, prevention of myocardial cellular sodium overload and, consequently, calcium overload, and thereby prevention of compression of intramyocardial nutritive blood vessels by diastolic myocardial stiffness (6). If ranolazine's beneficial mechanism of action is related to prevention of ischemia-induced reduction in myocardial blood flow, then ranolazine's anti-ischemia effects should become evident only once ischemia has developed and should become more marked, compared with placebo, as exercise and ischemia progresses.

The purpose of this new explanatory analysis was to assess the effects of ranolazine during submaximal and maximal exercise on exercise-induced ischemia, measured by ST-segment depression, and myocardial oxygen demand, measured as rate pressure product (RPP), utilizing a novel statistical approach to determine the timing and magnitude of the anti-ischemic effect of ranolazine. This new analysis sheds light on the mechanism of action of ranolazine to determine whether ranolazine's anti-ischemic effects were due to a decrease in myocardial oxygen demand or to improved myocardial perfusion.

Methods

Study design. The dataset from the MARISA (Monotherapy Assessment of Ranolazine In Stable Angina) trial (2) was used for this analysis. The MARISA study was a multicenter, randomized, double-blind, balanced Latin square crossover trial in which patients received placebo and sustained-release ranolazine formulation at doses of 500, 1,000, and 1,500 mg twice daily (bid) for 1 week each in random order. Its treatment sequence groups for the order of the 1-week periods in which the treatments were invoked were as follows: 500, 1,000, 1,500, placebo; 1,000, placebo, 500, 1,500; 1,500, 500, placebo, 1,000; and placebo, 1,500, 1,000, 500 so that each treatment followed each of the other treatments in exactly 1 sequence group. An exercise treadmill test (ETT) was performed at baseline and at the end of each 1-week treatment period. Although the 1,500 mg bid dose is not approved by the Food and Drug Administration for routine clinical use because of excessive side effects (2), we included the 1,500 mg dose in this analysis because this higher dose provided another efficacy data point, enhancing our ability to address the concept of ranolazine's dose-response relationship and because the complete data utilizing 1,500 mg bid daily were present in the dataset.

Study population. As previously reported, the MARISA trial (2) enrolled patients who were 21 years of age or older with coronary artery disease and at least a 3-month history of stable exertional angina. After an initial single-blind placebo qualifying phase, ETTs were performed, and patients who had exercise-limiting angina and ST-segment depression ≥1 mm between 3 and 9 min during the tests were randomly assigned to the double-blind phase of the trial. Exclusion criteria included resting ST-segment depression ≥1 mm in any lead that would preclude accuracy of interpretation of ST-segment changes, class III or IV congestive heart failure, unstable angina, myocardial infarction, or a coronary revascularization procedure in the 2 months preceding the trial.

Abbreviations and Acronyms

bid = twice daily
ECG = electrocardiogram
ETT = exercise treadmill test
RPP = rate-pressure product

Exercise protocol. The ETTs were conducted according to the modified Bruce protocol (i.e., progressive 3-min stages starting at 1.7 mph at a 0% gradient, increasing to 1.7 mph at a 5% gradient, then 1.7 mph at a 10% gradient, and finally 2.5 mph at a 12% gradient). A supine 12-lead electrocardiogram (ECG) was obtained before each test, and standing ECGs were monitored throughout exercise testing. Resting ECGs were classified according to the Minnesota code, and customized software was used to analyze the exercise ECGs (7). Measurements of heart rate and blood pressure were made at 3-min intervals during each exercise test. The ETTs were conducted 4 and 12 h after dosing to correspond with peak and trough ranolazine plasma concentrations. The ST-segment depression was determined in 11 leads (excluding aVR) at baseline, at the end of each stage of exercise, and at maximal exercise.

Statistical analysis. This new explanatory analysis explicitly examines the stages of exercise and the associated ST-segment deviations on the different regimens of ranolazine. Analyses must first incorporate possible covariance structures that could accommodate both the variability among the periods and increasing variability in the measures as the study subject reaches (or does not reach) longer durations of exercise. We used the ETT data collected at the time of peak plasma concentrations of ranolazine. The RPP (heart rate in beats/min × systolic blood pressure in mm Hg) was calculated before exercise, at each stage of exercise, and at maximal exercise. The ST-segment changes from pre-exercise assessments were expressed as the sum across the 11 leads.

The RPP and change in ST-segment depression compared with the pre-exercise values were analyzed using a mixed-model repeated-measures analysis of variance with fixed effects for treatment sequence, treatment, crossover period, exercise stage and the interaction of treatment with exercise stage, and a repeated-measures covariance structure specified for STAGE and PERIOD within SUBJECT; an expanded model supported equality of any carryover effects of the treatments and thereby the omission of this factor from the model. The use of the mixed model accounts for missing data with the minimal assumption that the data are missing at random (which corresponds to the missing data being only dependent on the observed data) (8). Moreover,

this explanatory analysis is mainly to describe the variation for the observed data (rather than to have a predictive structure that encompasses both the observed and missing data).

A relevant component of the model for this purpose is the interaction of treatment with exercise stage as it enables the estimation of treatment differences separately within each of the respective exercise stages, with the recognition that the missing data are mainly due to some patients not reaching the later exercise stages. As in all situations with missing data, more caution for interpretation is necessary where missing data are more extensive such as the later stages of exercise. The RPP and change in ST-segment depression at each exercise stage were estimated from the mixed model by least squares means. Results throughout this paper are expressed as least square means ± SE. The same mixed model is used to summarize stage and treatment effects for heart rate and systolic blood pressure (8).

For all of these explanatory analyses, p values describe strengths of relationships through the extent to which they are small, rather than being criteria for formally testing pre-specified hypotheses. Accordingly, the results from these analyses do not have formal control for type I error, although those with $p < 0.001$ would not seem to be due to chance, particularly in view of the positive findings of the MARISA trial for its primary and key secondary end points (2).

We chose this statistical approach since previously reported analyses of the trial for efficacy end points used single summary measures, for example, maximum exercise duration, for the results from the entire crossover period for a dose. These analyses did not specifically address the multiple stage measurements at 3, 6, 9, and 12 min of exercise within the cross-over periods. These analyses also did not need to deal with any missing measurements at longer planned exercise times.

Results

Study participants. These analyses include the 175 of the 191 randomized patients in the MARISA trial who completed at least 3 of the 4 treatment periods.

Effects of ranolazine on RPP and ST-segment depression. Changes in myocardial oxygen demand (RPP) as a function of the dose of ranolazine and duration of exercise are presented in Figure 1A. During placebo and active ranolazine therapy, RPP increased approximately linearly with increasing duration of exercise. Changes in heart rate and blood pressure as a function of dose of ranolazine and duration of exercise are presented in Table 1. Ranolazine treatment was associated with minor reductions in both heart rate and systolic blood pressure.

At submaximal exercise compared with placebo, ranolazine 500 mg bid had little or no effect on RPP (Table 2). Ranolazine 1,000 mg bid produced small reductions in RPP that ranged from 3.8% at 3 min (13,693 ± 183 vs. 14,237 ± 184; $p = 0.002$) to 7.2% at 9 min of exercise (18,529 ± 264 vs. 19,969 ± 276; $p < 0.001$) (Table 2). Ranolazine 1,500 mg produced slightly greater reductions in RPP that ranged from 7.5% at 3 min (13,164 ± 185 vs. 14,237 ± 184; $p < 0.001$) to 10.6% at 9 min of submaximal exercise (17,859 ± 266 vs. 19,969 ± 276; $p < 0.001$) (Table 2). At maximal exercise (12-min duration), both ranolazine 1,000 and 1,500 mg produced a significant reduction in RPP compared with placebo (21,963 ± 493 and 21,588 ± 480, respectively, vs. 23,933 ± 527; $p < 0.001$ for each) (Fig. 1A, Table 2).

The effects of ranolazine on myocardial ischemia during exercise, as measured by change from pre-exercise levels of ST-segment depression, are presented in Figure 1B and Table 2. As exercise progressed, during submaximal exercise ischemic ST-segment depression became more marked on placebo, while on ranolazine, there was progressively less substantial ischemic ST-segment depression in a marked dose-dependent manner. At maximal exercise (12 min), ranolazine 1,500 mg reduced ischemic ST-segment depression from baseline by 41.0% compared with placebo (5.09 ± 0.62 mm vs. 8.63 ± 0.73 mm; $p < 0.001$).

The relationship between change in ST-segment depression during the exercise protocol and RPP is presented in Figure 2. The estimated mean change in ST-segment depression at each exercise stage is plotted against the estimated mean RPP at the same stage. With increasing levels of myocardial oxygen demand, ranolazine produced clear, dose-dependent decreases in myocardial ischemia compared with placebo, but only after a substantial amount of cardiac work was achieved and ischemic ST-segment depression had occurred.

The relationship between changes in ST-segment depression and the respective treatments with adjustment for RPP throughout the exercise protocol was evaluated with an expanded mixed model that additionally included 14 separate and connected RPP slopes per 1,000 for RPP values from 10,000 to 23,000 (8). Parallelism of RPP relationships for the 4 treatments was assessed and provided reasonable support. This explanatory analysis provided a comprehensive description of the relationship between ST-segment change and RPP, and its results are presented in Table 3 and Figures 3 and 4. During the early phase of exercise (e.g., the first 3 min) there was a small reduction in ST-segment depression only on ranolazine 1,000 and 1,500 mg bid compared with placebo. As exercise progressed, however, the amount of ischemic ST-segment depression decreased in a dose-dependent manner, and the reduction was even more pronounced with ranolazine 1,000 and 1,500 mg bid, compared with placebo. At peak exercise and maximum RPP achieved, there remained a dose-dependent decrease in the magnitude of ischemic ST-segment depression. At 12-min exercise, the amount of ST-segment depression compared with placebo and controlled for RPP was reduced by 22.3% on ranolazine 500 mg bid ($p = 0.137$), by 35.4% on 1,000 mg bid ($p = 0.005$), and by 45.8% on 1,500 mg bid ($p < 0.001$). The data suggested that given the same

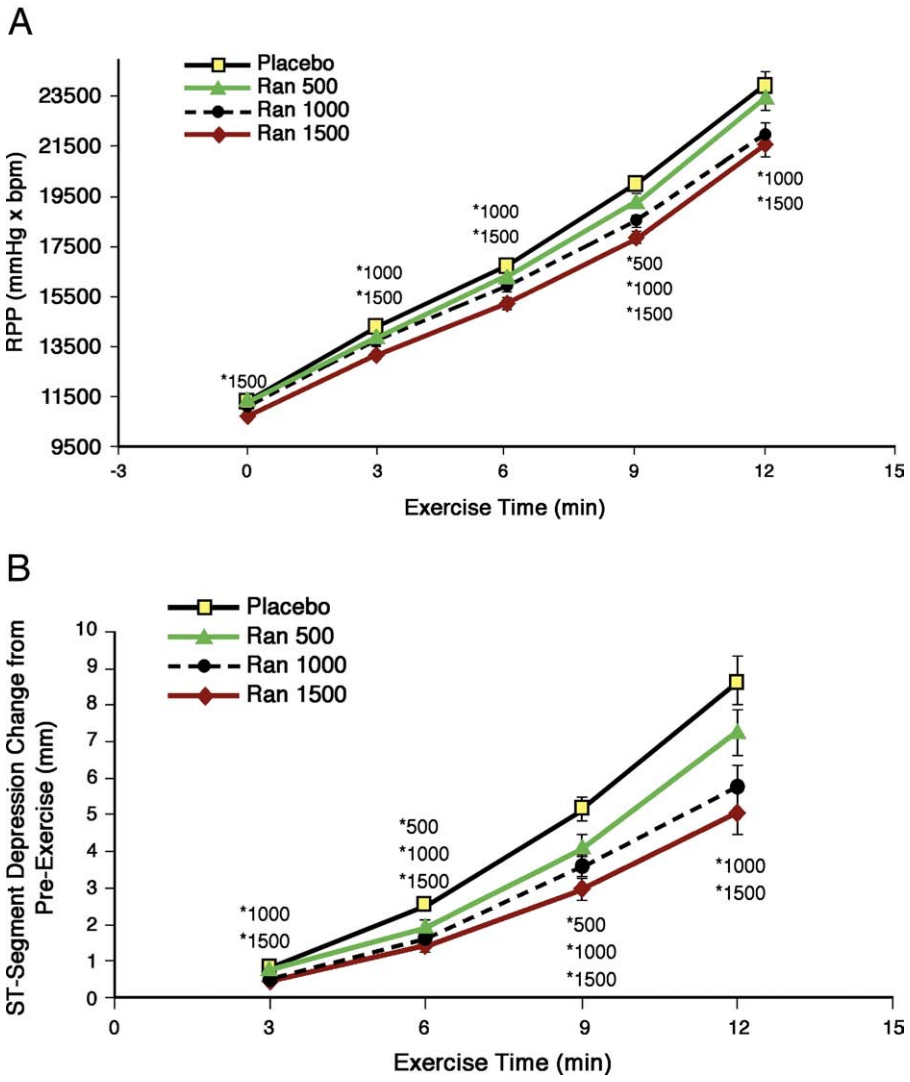

Figure 1 **Effects of Ranolazine on RPP and ST-Segment Depression During Exercise**

Effects (least square means ± SE) of ranolazine (Ran) on rate-pressure product (RPP) and exercise-induced ischemia during submaximal and maximal exercise in patients with stable chronic angina. **(A)** Effects of exercise duration and ranolazine dose on RPP. **(B)** Effects of exercise duration and ranolazine dose on myocardial ischemia (ST-segment depression summed over 11 leads). *$p < 0.05$ versus placebo. Specific p values for each comparison are presented in Table 2. **Yellow squares** = placebo; **green triangles** = ranolazine 500 mg; **black circles** = ranolazine 1,000 mg; **red diamonds** = ranolazine 1,500 mg. Figure by Craig Skaggs.

myocardial oxygen demand (RPP), myocardial ischemia may be further reduced by ranolazine in a dose-dependent manner.

In the MARISA trial (2), the overall adverse event rate on ranolazine 500 mg bid was 16.0%, which was similar to that on placebo (15.6%). At ranolazine 1,000 mg bid, the adverse event rate was 21.7%, and on 1,500 mg bid, it was 34.2%. Most of these adverse events were minor, especially at the 500 and 1,000 mg bid regimens. The side effect profile observed in the MARISA trial is similar to that observed in much larger placebo-controlled clinical trials of ranolazine conducted and published subsequent to the MARISA trial (5,9,10).

Discussion

The development of more effective pharmacologic treatments to reduce myocardial ischemia remains an important healthcare priority. Recent studies underscore that revascularization strategies, especially percutaneous coronary interventions, do not reduce cardiac morbidity or mortality beyond that achieved with pharmacologic management alone (11,12). Yet, pharmacologic therapy is often inadequate to prevent episodes of angina and the consequences on emotional and physical well-being (13). Ranolazine is an important new anti-ischemic agent that significantly improves exercise duration, time to angina, and time to

Table 1 Effects of Ranolazine on Heart Rate and Systolic Blood Pressure at Each Stage of Exercise

	Heart Rate (Beats/Min)				Systolic Blood Pressure (mm Hg)			
Exercise Duration	Placebo	Ran 500 mg	Ran 1,000 mg	Ran 1,500 mg	Placebo	Ran 500 mg	Ran 1,000 mg	Ran 1,500 mg
Pre-exercise	83.68 ± 0.89 (n = 172)	83.82 ± 0.88 p = 0.862 (n = 174)	82.14 ± 0.88 p = 0.049 (n = 174)	81.02 ± 0.89 p = 0.001 (n = 166)	134.99 ± 1.17 (n = 172)	134.61 ± 1.16 p = 0.755 (n = 174)	134.79 ± 1.17 p = 0.870 (n = 172)	132.84 ± 1.18 p = 0.079 (n = 166)
3 min	96.04 ± 0.85 (n = 170)	94.88 ± 0.84 p = 0.119 (n = 174)	93.62 ± 0.84 p = 0.001 (n = 173)	91.66 ± 0.85 p < 0.001 (n = 167)	147.69 ± 1.24 (n = 170)	146.92 ± 1.24 p = 0.551 (n = 174)	145.97 ± 1.24 p = 0.181 (n = 173)	143.33 ± 1.25 p = 0.001 (n = 167)
6 min	105.38 ± 0.90 (n = 140)	103.94 ± 0.89 p = 0.073 (n = 151)	102.01 ± 0.89 p < 0.001 (n = 155)	100.06 ± 0.90 p < 0.001 (n = 145)	157.65 ± 1.28 (n = 140)	156.88 ± 1.26 p = 0.561 (n = 151)	155.28 ± 1.25 p = 0.074 (n = 155)	151.38 ± 1.27 p < 0.001 (n = 145)
9 min	117.56 ± 1.03 (n = 73)	115.87 ± 1.01 p = 0.075 (n = 89)	112.98 ± 1.00 p < 0.001 (n = 101)	110.57 ± 1.00 p < 0.001 (n = 106)	168.58 ± 1.63 (n = 73)	166.02 ± 1.56 p = 0.139 (n = 89)	163.30 ± 1.53 p = 0.002 (n = 101)	160.47 ± 1.54 p < 0.001 (n = 106)
12 min	135.60 ± 2.10 (n = 15)	133.62 ± 2.41 p = 0.451 (n = 9)	129.66 ± 1.97 p = 0.007 (n = 18)	127.46 ± 1.92 p < 0.001 (n = 20)	177.12 ± 2.81 (n = 15)	175.23 ± 3.32 p = 0.623 (n = 9)	170.31 ± 2.62 p = 0.035 (n = 18)	170.08 ± 2.54 p = 0.031 (n = 20)

Note: Least squares means estimates (± SE) and contrast *t* test p values for comparisons with placebo from mixed-model repeated-measures analysis of variance with fixed effects for treatment sequence, treatment, crossover period, exercise stage and the interaction of treatment with exercise stage, and with covariance structure specified by "REPEATED STAGE PERIOD/subject=SUBJECT UN@CS" (for unstructured of stages and compound symmetry on periods) in PROC MIXED in SAS version 9.1.2 (SAS Institute, Cary, North Carolina).
Ran = ranolazine.

ST-segment depression either as monotherapy (2) or in combination with currently available antianginal drugs (e.g., amlodipine, atenolol, diltiazem) (5), yet its mechanism of action remains unclear. The present analysis shows that ranolazine, in a dose-dependent manner, clearly decreases myocardial ischemia during submaximal and maximal exercise, after the onset of ischemic ST-segment depression. The progressive magnitude of ischemia reduction on ranolazine was proportionally more substantial than the minor reductions in heart rate or RPP, suggesting that ranolazine's beneficial mechanism of action is most likely primarily due to an improvement in regional coronary blood flow in areas of myocardial ischemia associated with submaximal and maximal exercise.

Conventional antianginal therapies (e.g., beta-blockers, calcium-channel blockers, and nitrates) reduce myocardial oxygen demand by reducing hemodynamic parameters, such as heart rate, blood pressure, cardiac contractility, and pre-load (14). Such therapies reduce the RPP at rest and during submaximal exercise compared with placebo. Active therapy enables the patient to exercise for longer durations of time as myocardial oxygen demand is reduced during submaximal exercise. Exercise-induced ischemia, therefore, is accordingly reduced throughout the exercise duration,

Table 2 Effects of Ranolazine on Rate Pressure Product and Change From Pre-Exercise in ST-Segment Depression at Each Stage of Exercise

	Rate Pressure Product (mm Hg/min)				Change From Pre-Exercise in ST-Segment Depression (mm) Sum Over 11 Leads			
Exercise Duration	Placebo	Ran 500 mg	Ran 1,000 mg	Ran 1,500 mg	Placebo	Ran 500 mg	Ran 1,000 mg	Ran 1,500 mg
Pre-exercise	11,278 ± 144 (n = 172)	11,272 ± 144 p = 0.965 (n = 174)	11,024 ± 144 p = 0.070 (n = 172)	10,746 ± 146 p < 0.000 (n = 166)				
3 min	14,237 ± 184 (n = 170)	13,969 ± 183 p = 0.134 (n = 174)	13,693 ± 183 p = 0.002 (n = 173)	13,164 ± 185 p < 0.001 (n = 167)	0.84 ± 0.10 (n = 167)	0.72 ± 0.10 p = 0.236 (n = 171)	0.49 ± 0.10 p < 0.001 (n = 168)	0.45 ± 0.10 p < 0.001 (n = 162)
6 min	16,675 ± 207 (n = 140)	16,347 ± 204 p = 0.102 (n = 151)	15,876 ± 204 p < 0.001 (n = 155)	15,203 ± 207 p < 0.001 (n = 145)	2.53 ± 0.18 (n = 143)	1.95 ± 0.18 p = 0.002 (n = 151)	1.60 ± 0.18 p < 0.001 (n = 158)	1.42 ± 0.18 p < 0.001 (n = 144)
9 min	19,969 ± 276 (n = 73)	19,344 ± 268 p = 0.023 (n = 89)	18,529 ± 264 p < 0.001 (n = 101)	17,859 ± 266 p < 0.001 (n = 106)	5.16 ± 0.31 (n = 83)	4.15 ± 0.30 p = 0.002 (n = 103)	3.59 ± 0.29 p < 0.001 (n = 109)	2.99 ± 0.30 p < 0.001 (n = 111)
12 min	23,933 ± 527 (n = 15)	23,540 ± 612 p = 0.568 (n = 9)	21,963 ± 493 p = 0.001 (n = 18)	21,588 ± 480 p < 0.001 (n = 20)	8.63 ± 0.73 (n = 15)	7.31 ± 0.69 p = 0.122 (n = 17)	5.74 ± 0.64 p < 0.001 (n = 21)	5.09 ± 0.62 p < 0.001 (n = 24)

Note: Least squares means estimates (± SE) and contrast *t* test p values for comparisons to placebo from mixed-model repeated-measures analysis of variance with fixed effects for treatment sequence, treatment, crossover period, exercise stage and the interaction of treatment with exercise stage, and with covariance structure specified by "REPEATED STAGE PERIOD/subject=SUBJECT UN@CS" (for unstructured of stages and compound symmetry on periods) in PROC MIXED in SAS version 9.1.2 (SAS Institute, Cary, North Carolina).
Ran = ranolazine.

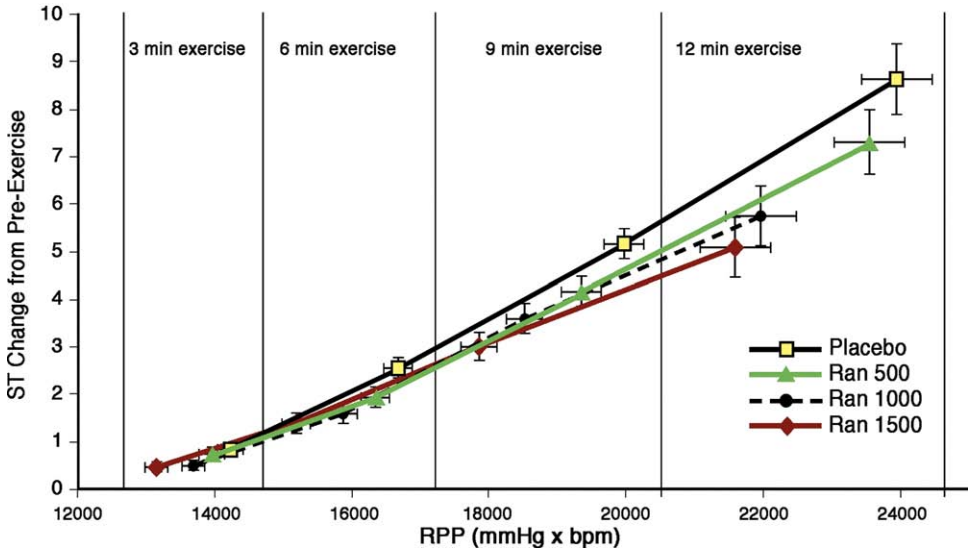

Figure 2 **Relationship Between Changes in ST-Segment Depression and RPP During Exercise**

Relationship (expressed by least square means ± SE) between change from pre-exercise in ST-segment depression and rate-pressure product (RPP) in patients with stable chronic angina treated with ranolazine (Ran) during submaximal and maximal exercise. **Yellow squares** = placebo; **green triangles** = ranolazine 500 mg; **black circles** = ranolazine 1,000 mg; **red diamonds** = ranolazine 1,500 mg. Figure by Craig Skaggs.

including submaximal and maximal exercise. At maximal exercise, however, the peak RPP reductions on placebo and active therapy may be the same, even though the active therapy enabled the patient to exercise longer to achieve that same RPP (15).

In contrast, pre-clinical evidence suggests that the anti-ischemia effect of ranolazine is due, at least in part, to preservation of myocardial blood flow during the ischemic process (6). As a consequence of myocardial ischemia, the late sodium channels remain open, leading to intracellular sodium overload (6). The myocyte extrudes the pathologic concentrations of sodium through the sodium-calcium exchange mechanism, leading to intracellular calcium overload, which leads to excessive exposure of the contractile elements to increased calcium ions and consequent increased tension in the myocyte and manifestations of diastolic relaxation failure. In pre-clinical studies, this increased diastolic myocardial stiffness results in prolonged extravascular compression of intramural vessels and decreased myocardial oxygen supply (16). Ranolazine inhibits the myocardial late inward sodium current asso-

Table 3 **Effects of Ranolazine on Change From Pre-Exercise in ST-Segment Depression at Each Stage of Exercise Controlled for Rate-Pressure Product**

	Change From Pre-Exercise in ST-Segment Depression (mm) Sum Over 11 Leads			
Exercise Duration	**Placebo**	**Ran 500 mg**	**Ran 1,000 mg**	**Ran 1,500 mg**
3 min	1.00 ± 0.10 (n = 167)	0.92 ± 0.10 p = 0.402 (n = 171)	0.71 ± 0.10 p = 0.003 (n = 168)	0.71 ± 0.11 p = 0.004 (n = 162)
6 min	2.35 ± 0.17 (n = 140)	1.77 ± 0.17 p = 0.001 (n = 146)	1.54 ± 0.17 p < 0.001 (n = 153)	1.38 ± 0.17 p < 0.001 (n = 141)
9 min	4.42 ± 0.33 (n = 72)	3.59 ± 0.31 p = 0.012 (n = 89)	3.23 ± 0.30 p < 0.001 (n = 98)	2.57 ± 0.30 p < 0.001 (n = 102)
12 min	7.12 ± 0.82 (n = 14)	5.53 ± 0.94 p = 0.137 (n = 9)	4.60 ± 0.73 p = 0.005 (n = 18)	3.86 ± 0.72 p < 0.001 (n = 19)

Note: Least squares means estimates (± SE) and contrast *t* test p values for comparisons with placebo from mixed-model repeated-measures analysis of variance with fixed effects for treatment sequence, treatment, crossover period, exercise stage, the interaction of treatment with exercise stage, 14 rate-pressure product (RPP) slopes per 1,000 for RPP values from 10,000 to 23,000, and with covariance structure specified by "REPEATED STAGE PERIOD/subject=SUBJECT UN@CS" (for unstructured stages and compound symmetry on periods) in PROC MIXED in SAS version 9.1.2 (SAS Institute, Cary, North Carolina).

Ran = ranolazine.

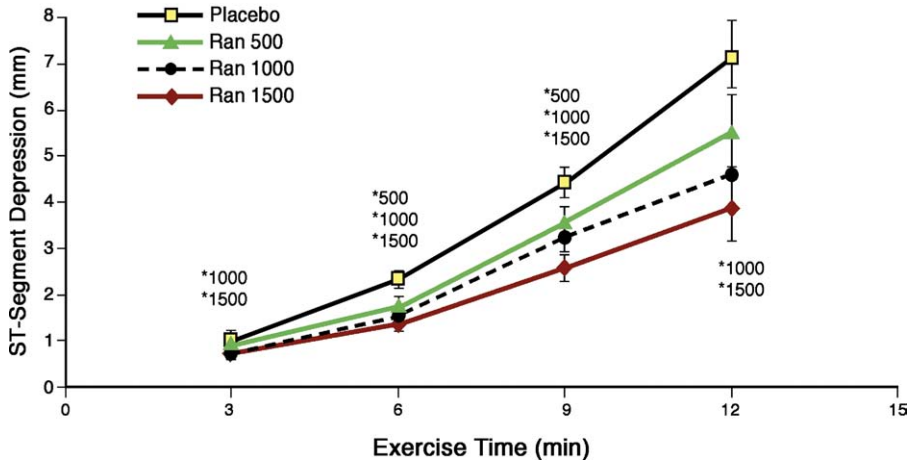

Figure 3 Relationship Between Changes in ST-Segment Depression and Exercise Time Adjusted for RPP

Relationship (expressed by least square means ± SE) between change in ST-segment depression and exercise time adjusted for rate pressure produce (RPP). *$p < 0.05$ versus placebo. Specific p values for each comparison are presented in Table 3. **Yellow squares** = placebo; **green triangles** = ranolazine (Ran) 500 mg; **black circles** = ranolazine 1,000 mg; **red diamonds** = ranolazine 1,500 mg. Figure by Craig Skaggs.

ciated with ischemia (17,18), and thereby inhibits the consequent calcium overload and the resultant diastolic stiffness. Thus, by inhibiting the late inward sodium current, ranolazine may preserve or increase diastolic myocardial oxygen delivery during ischemia.

The time course of the beneficial effect of ranolazine we observed during the exercise protocol supports this putative mechanism of action. During the early phase of exercise, in the context of minor ischemia, there is little effect of ranolazine. Basic pre-clinical studies indicate that in healthy, nonischemic myocytes, where the contribution of the late sodium current is small, ranolazine does not have a measurable effect at therapeutic concentrations (19). As exercise proceeds in patients with coronary disease, however, and ischemia becomes more pronounced, then ranolazine's anti-ischemic effects become more marked in a dose-response manner, all in the absence of a substantial effect on any determinant of myocardial oxygen demand.

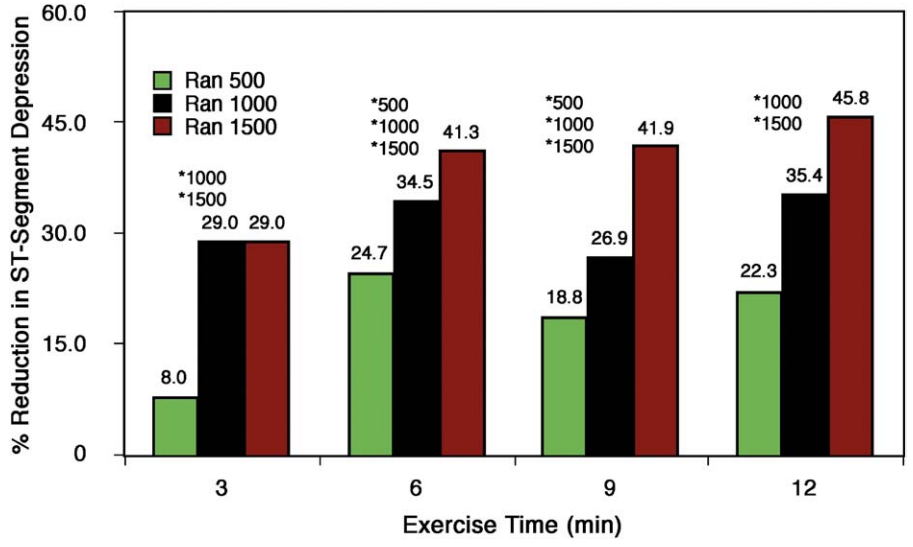

Figure 4 Reduction in Ischemic ST-Segment Depression Compared With Placebo, Adjusted for RPP

Percent magnitude of reduction in ischemic ST-segment depression compared with placebo, adjusted for RPP. The p values for change compared with placebo are noted in Table 3. *$p < 0.05$ versus placebo. Specific p values for each comparison are presented in Table 3. **Green bars** = ranolazine 500 mg; **black bars** = ranolazine 1,000 mg; **red bars** = ranolazine 1,500 mg. Figure by Craig Skaggs. Abbreviations as in Figure 3.

Although determinants of myocardial oxygen demand are modestly reduced by ranolazine, it appears that the most likely mechanism by which this anti-ischemic effect occurs is primarily due to preservation of myocardial blood flow during exercise-induced ischemia.

Study limitations. This study is limited because there were no direct measurements of myocardial blood flow to support the hypothesis that ranolazine indeed increased local blood flow to ischemic areas during exercise. Pre-clinical data from animal models, however, indicate that ranolazine preserves myocardial blood flow during ischemic insults (20,21). Recent studies in humans also support the concept that ranolazine may be beneficial by improving coronary blood flow by either reducing compressive effects of ischemic contracture or by improving endothelial function, or both (22). A recent study of 27 patients with stable ischemic heart disease found that ranolazine 1,000 mg bid improves endothelial dysfunction compared with placebo, as assessed using reactive hyperemia peripheral arterial tonometry of the index finger (23). Furthermore, Venkataraman et al. (24) observed that ranolazine, at a median dose of 1,000 mg bid in patients with stable ischemic heart disease, significantly improved myocardial perfusion in zones of myocardial ischemia during treadmill exercise using technetium-99m sestamibi single-positron emission computed tomography imaging without affecting heart rate or blood pressure at rest or at peak exercise, in an open-label nonrandomized pilot study.

It is also possible that ranolazine reduces myocardial oxygen demand through mechanisms other than reduction of heart rate or blood pressure. Ranolazine has no effect, however, on reducing myocardial contractility or ventricular pre-load (25), the other 2 determinants of myocardial oxygen demand. Ranolazine may also have exerted a beneficial metabolic effect by partially inhibiting free fatty acid substrate oxidation during ischemia, but at therapeutic concentrations, ranolazine has little or no effect in this regard (16,26). The study was not designed to capture RPP and magnitude of ST-segment deviation data in a continuous manner throughout the exercise protocol; values of heart rate, systolic blood pressure, and ST-segment deviation were obtained only at the end of each 3-min exercise stage or at peak exercise with the sample sizes having attrition at the later stages.

To most accurately address the hypothesis that ranolazine reduced myocardial ischemia for any given RPP value, it would be necessary to have continuous measurements of both RPP and ST-segment deviation throughout the exercise protocol. The explanatory analysis for this hypothesis provided a comprehensive description of the relationship between ST-segment change and RPP through its expanded mixed model, additionally including 14 separate and connected RPP slopes per 1,000 for RPP values from 10,000 to 23,000 (8). The results for ST-segment change adjusted for RPP appear in Table 3 and Figures 3 and 4, and they indicate preservation of noteworthy differences from placebo, particularly for the 1,000 and 1,500 mg doses at the 9- and 12-min stages of exercise, although some caution is necessary for interpretation at the 12-min stage of exercise because of the relatively small sample size there. Lastly, the 1,500 mg bid dose of ranolazine, which was most effective in improving regional myocardial perfusion during ischemia, is not available for routine clinical use because of excessive side effects (2).

Conclusions

Ranolazine over the dose range of 500 to 1,500 mg twice daily clearly improves exercise-induced ischemic ST-segment depression during submaximal and maximal exercise without inducing a substantial change in the determinants of myocardial oxygen demand. Thus, the anti-ischemic effects of ranolazine in stable ischemic heart disease appear primarily to be due to an improvement in regional coronary perfusion in areas of myocardial ischemia.

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REFERENCES

1. Abrams J. Clinical practice. Chronic stable angina. N Engl J Med 2005;352:2524–33.
2. Chaitman BR, Skettino SL, Parker JO, et al. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. J Am Coll Cardiol 2004;43:1375–82.
3. Rousseau MF, Pouleur H, Cocco G, Wolff AA. Comparative efficacy of ranolazine versus atenolol for chronic angina pectoris. Am J Cardiol 2005;95:311–6.
4. Pepine CJ, Wolff AA. A controlled trial with a novel anti-ischemic agent, ranolazine, in chronic stable angina pectoris that is responsive to conventional antianginal agents. Ranolazine Study Group. Am J Cardiol 1999;84:46–50.
5. Chaitman BR, Pepine CJ, Parker JO, et al. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. JAMA 2004;291:309–16.
6. Belardinelli L, Shyrock JC, Fraser H. The mechanism of ranolazine action to reduce ischemia-induced diastolic dysfunction. Eur Heart J Suppl 2006;8 Suppl:A10–3.
7. Caralis DG, Shaw L, Bilgere B, et al. Application of computerized exercise ECG digitization. Interpretation in large clinical trials. J Electrocardiol 1992;25:101–10.
8. Malllinckrodt CHLP, Schnell D, Peng Y, Mancuso JP. Recommendations for the primary analysis of continuous end points in longitudinal clinical trials. Drug Info J 2008;42:303–19.
9. Stone PH, Gratsiansky NA, Blokhin A, Huang IZ, Meng L. Antianginal efficacy of ranolazine when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine in Chronic Angina) trial. J Am Coll Cardiol 2006;48:566–75.
10. Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, et al. Effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes: the MERLIN-TIMI 36 randomized trial. JAMA 2007;297:1775–83.
11. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503–16.
12. Katritsis DG, Ioannidis JP. Percutaneous coronary intervention versus conservative therapy in nonacute coronary artery disease: a meta-analysis. Circulation 2005;111:2906–12.

13. Holubkov R, Laskey WK, Haviland A, et al. Angina 1 year after percutaneous coronary intervention: a report from the NHLBI Dynamic Registry. Am Heart J 2002;144:826–33.
14. Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). J Am Coll Cardiol 2003;41:159–68.
15. Epstein S, Redwood DR, Goldstein RE, et al. Angina pectoris: pathophysiology, evaluation, and treatment. Ann Intern Med 1971; 75:263–96.
16. Wang P, Fraser H, Lloyd SG, McVeigh JJ, Belardinelli L, Chatham JC. A comparison between ranolazine and CVT-4325, a novel inhibitor of fatty acid oxidation, on cardiac metabolism and left ventricular function in rat isolated perfused heart during ischemia and reperfusion. J Pharmacol Exp Ther 2007;321:213–20.
17. Antzelevitch C, Belardinelli L, Zygmunt AC, et al. Electrophysiological effects of ranolazine, a novel antianginal agent with antiarrhythmic properties. Circulation 2004;110:904–10.
18. Song Y, Shryock JC, Wu L, Belardinelli L. Antagonism by ranolazine of the pro-arrhythmic effects of increasing late INa in guinea pig ventricular myocytes. J Cardiovasc Pharmacol 2004;44:192–9.
19. Chaitman BR. Ranolazine for the treatment of chronic angina and potential use in other cardiovascular conditions. Circulation 2006;113: 2462–72.
20. Chandler MP, Stanley WC, Morita H, et al. Short-term treatment with ranolazine improves mechanical efficiency in dogs with chronic heart failure. Circ Res 2002;91:278–80.
21. Fraser H, Belardinelli L, Wang L, Light PE, McVeigh JJ, Clanachan AS. Ranolazine decreases diastolic calcium accumulation caused by ATX-II or ischemia in rat hearts. J Mol Cell Cardiol 2006;41:1031–8.
22. Klocke FJ. Ranolazine and the myocardial demand-supply balance. J Am Coll Cardiol Img 2009;2:1310–2.
23. Deshmukh SH, Patel SR, Pinassi E, et al. Ranolazine improves endothelial function in patients with stable coronary artery disease. Coron Artery Dis 2009;20:343–7.
24. Venkataraman R, Belardinelli L, Blackburn B, Heo J, Iskandrian AE. A study of the effects of ranolazine using automated quantitative analysis of serial myocardial perfusion images. J Am Coll Cardiol Img 2009;2:1301–9.
25. Hale SL, Leeka JA, Kloner RA. Improved left ventricular function and reduced necrosis after myocardial ischemia/reperfusion in rabbits treated with ranolazine, an inhibitor of the late sodium channel. J Pharmacol Exp Ther 2006;318:418–23.
26. MacInnes A, Fairman DA, Binding P, et al. The antianginal agent trimetazidine does not exert its functional benefit via inhibition of mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. Circ Res 2003;93:e26–32.

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