Effects of Ranolazine With Atenolol, Amlodipine, or Diltiazem on Exercise Tolerance and Angina Frequency in Patients With Severe Chronic Angina
A Randomized Controlled Trial

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Chronic angina is a debilitating illness affecting at least 6.6 million US residents. Patients report limitation of their work and other activities 2 to 3 times more frequently than what is reported by the general population. Despite the continued explosive growth in myocardial revascularization, largely to prevent angina attacks, most patients continue to require antianginal drugs; furthermore, despite both revascularization and pharmacotherapy, up to 26% of patients still experience attacks.

Currently available antianginal drugs (β-blockers, calcium channel blockers, and nitrates) all work to reduce myocardial oxygen demand by decreasing 1 or more indices of cardiac work (although the latter 2 classes may also affect myocardial oxygen demand).

Context Many patients with chronic angina experience anginal episodes despite revascularization and antianginal medications. In a previous trial, antianginal monotherapy with ranolazine, a drug believed to partially inhibit fatty acid oxidation, increased treadmill exercise performance; however, its long-term efficacy and safety have not been studied in combination with β-blockers or calcium antagonists in a large patient population with severe chronic angina.

Objectives To determine whether, at trough levels, ranolazine improves the total exercise time of patients who have symptoms of chronic angina and who experience angina and ischemia at low workloads despite taking standard doses of atenolol, amiodipine, or diltiazem and to determine times to angina onset and to electrocardiographic evidence of myocardial ischemia, effect on angina attacks and nitroglycerin use, and effect on long-term survival in an open-label observational study extension.

Design, Setting, and Patients A randomized, 3-group parallel, double-blind, placebo-controlled trial of 823 eligible adults with symptomatic chronic angina who were randomly assigned to receive placebo or 1 of 2 doses of ranolazine. Patients treated at the 118 participating ambulatory outpatient settings in several countries were enrolled in the Combination Assessment of Ranolazine In Stable Angina (CARISA) trial from July 1999 to August 2001 and followed up through October 31, 2002.

Intervention Patients received twice-daily placebo or 750 mg or 1000 mg of ranolazine. Treadmill exercise 12 hours (trough) and 4 hours (peak) after dosing was assessed after 2, 6 (trough only), and 12 weeks of treatment.

Main Outcome Measures Change in exercise duration, time to onset of angina, time to onset of ischemia, nitroglycerin use, and number of angina attacks.

Results Trough exercise duration increased by 115.6 seconds from baseline in both ranolazine groups (pooled) vs 91.7 seconds in the placebo group (P = .01). The times to angina and to electrocardiographic ischemia also increased in the ranolazine groups, at peak more than at trough. The increases did not depend on changes in blood pressure, heart rate, or background antianginal therapy and persisted throughout 12 weeks. Ranolazine reduced angina attacks and nitroglycerin use by about 1 per week vs placebo (P < .02). Survival of 750 patients taking ranolazine during the CARISA trial or its associated long-term open-label study was 98.4% in the first year and 95.9% in the second year.

Conclusion Twice-daily doses of ranolazine increased exercise capacity and provided additional antianginal relief to symptomatic patients with severe chronic angina taking standard doses of atenolol, amiodipine, or diltiazem, without evident adverse, long-term survival consequences over 1 to 2 years of therapy.

JAMA. 2004;291:309-316
www.jama.com

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improve oxygen supply). However, for many patients receiving treatment, angina persists, illustrating the need for a drug with an anti-ischemic mechanism complementary and therefore potentially additive to those of the existing agents.

The antianginal action of ranolazine may be related to partial inhibition of fatty acid oxidation, which can produce anti-ischemic effects without depressing hemodynamic function. Inhibition of fatty acid oxidation reciprocally increases glucose oxidation, which generates more adenosine triphosphate for each molecule of oxygen consumed. This shift in substrate selection may reduce myocardial oxygen supply needed to support a given level of cardiac work so that for any level of coronary flow, ischemia should be less likely.

The Monotherapy Assessment of Ranolazine In Stable Angina (MARISA) trial was the first placebo-controlled trial to establish the antianginal and anti-ischemic effects of ranolazine monotherapy, demonstrating increased exercise tolerance and prolonged times to exercise-induced angina and ischemic ST-segment depression with twice-daily ranolazine doses ranging from 500 mg to 1500 mg. The Combination Assessment of Ranolazine In Stable Angina (CARISA) trial assessed the antianginal and anti-ischemic effects of ranolazine in symptomatic chronic angina patients with severe coronary disease, evidenced by exercise-induced myocardial ischemia at low workloads despite treatment with standard doses of atenolol, amlodipine, or diltiazem.

**METHODS**

**Study Overview**

CARISA was a double-blind, 3-group parallel trial in which patients were randomly assigned to receive twice-daily placebo or 750 mg or 1000 mg of sustained-release ranolazine for 12 weeks (CV Therapeutics, Palo Alto, Calif) (FIGURE 1). Patients were stratified according to the antianginal therapy they were taking at the time of enrollment (50 mg of atenolol, 180 mg of diltiazem in a once-a-day formulation, or 5 mg of amlodipine once a day). The choice of background therapy was at the discretion of the investigator and the doses were fixed throughout the study. One patient interrupted background therapy (atenolol) for 1 day prior to performing the week 12 exercise treadmill test. The protocol was approved by the appropriate institutional review board governing each participating center, and all participants signed a written informed consent form that explained the risks and benefits of study participation.

The primary aim of the study was to compare the effects of ranolazine vs placebo on treadmill exercise duration at trough ranolazine levels (ie, 12 hours after dosing). Secondary efficacy end points included exercise duration at the approximate time of peak drug levels (ie, 4 hours after dosing), times to angina and to 1 mm ST-segment depression at peak and trough, and the angina attacks and sublingual nitroglycerin uses reported in the patients’ daily diaries. Vital signs were measured and recorded, and drug tolerability and safety were assessed.

**Patient Selection**

All patients had coronary artery disease (confirmed by angiography, documented prior myocardial infarction, or a diagnostic stress myocardial imaging study) and a minimum 3-month history of exertional angina. Patients were withdrawn from antianginal drugs (other than the required background therapy) for at least 5 days before the first qualifying exercise test and for the remainder of the trial. At the screening visit, which was at the start of the washout phase, a medical history, physical examination, resting electrocardiogram (ECG), blood pressure and heart rate measurements, and clinical laboratory tests were performed. Eligible patients had reproducible angina, ischemic ST-segment depression of at least 1 mm and limited exercise capacity on treadmill testing (3-9 minutes on a modified Bruce protocol) while receiving required background antianginal treatment with the most commonly used agents and doses in clinical practice (atenolol 50 mg, amlodipine 5 mg, or diltiazem 180 mg once daily). Factors that precluded satisfactory interpretation of the ECG (eg, resting ST-segment depression ≥1 mm in any lead, left bundle-branch block, digoxin therapy), class III or IV heart failure, or an acute coronary syndrome or coronary revascularization procedure within the prior 2 months were exclu-
sion criteria. Voltage criteria for left ventricular hypertrophy in the absence of repolarization abnormalities were not an exclusion criterion.

Randomization
Quintiles (UK) Limited (Bracknell, England) generated separate randomization schedules using a random number generator in SAS version 6.12 (SAS Institute, Cary, NC). Randomization was stratified by the 3 background antianginal therapies (atenolol, amiodipine, and diltiazem), using a block size of 6. The schedules were sent to Brecon Pharmaceuticals Ltd (Hay-on-Wye, England), for drug packaging and preparation of the code break envelopes. A second paper copy and a disk-based electronic backup were filed securely in a sealed envelope at Quintiles Limited. Brecon provided the sealed medication assignment envelope to the clinical units for each patient randomized in the study. Depending on expected enrollment, each site received study medication in either single or multiple sets of mini blocks. The medication assignment was provided to the principal investigator in a sealed envelope to be used only if knowledge of the therapeutic assignment was required to treat a medical emergency.

Exercise Protocol
Eligible patients entered a single-blind, placebo-treatment qualifying phase during which they had 2 modified Bruce exercise treadmill tests 11 conducted 1 week apart. A supine standard 12-lead ECG was obtained before each exercise treadmill test, and standing torso ECGs were monitored throughout the exercise testing. A core ECG laboratory (St Louis University; St Louis, Mo) blinded to treatment assignment interpreted all rest and exercise ECGs. All rest ECGs were classified using the Minnesota code. All exercise ECGs were analyzed using customized software as previously described. 12 The longest QT interval in each 12-lead ECG was reported, corrected using Bazett's formula. QT dispersion measurements, defined as the difference in milliseconds between the longest and shortest QT interval observed in the ECG tracing, were recorded.

Exercise-induced ECG ischemia was defined as the new development of horizontal or down-sloping ST-segment depression (≥1 mm at 80 milliseconds after the J point) vs baseline tracing. For patients with permitted baseline ST-depression at rest (<1 mm), qualifying ST-segment depression was defined as additional ST depression of at least 1 mm below the resting value. Patients were randomized into the double-blind phase of the study if they developed exercise-limiting angina and ECG ischemia between 3 and 9 minutes during both qualifying exercise treadmill tests, and the difference in exercise duration between the 2 tests did not exceed 20% of the longer test or 1 minute. Subsequent exercise tests were performed at trough drug levels 2, 6, and 12 weeks after randomization. At 2 and 12 weeks after randomization, a peak exercise test was performed approximately 4 hours after dosing, and on the same day, after the 12-hour postdosing trough exercise test had been completed.

Statistical Analyses
Under the assumptions of normally distributed data and an SD of 80 seconds, a sample size of 462 evaluable patients was projected to have 90% power to detect a difference of 30 seconds in the primary end point (exercise duration at trough) between 750 mg of ranolazine and placebo and between 1000 mg of ranolazine and placebo. After considering a potential 20% dropout rate, it was estimated that 577 patients would need

<table>
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<tr>
<th>Variables</th>
<th>Placebo (n = 269)</th>
<th>750 (n = 279)</th>
<th>1000 (n = 275)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Background antiangial drug once daily, No. (%)</td>
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<td></td>
</tr>
<tr>
<td>Atenolol, 50 mg</td>
<td>118 (43.9)</td>
<td>119 (42.7)</td>
<td>117 (42.6)</td>
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<td>Amlodipine, 5 mg</td>
<td>81 (30.1)</td>
<td>86 (30.8)</td>
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<td>Diltiazem, 180 mg</td>
<td>70 (26.0)</td>
<td>74 (26.5)</td>
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<td>.70</td>
</tr>
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<td>Age, mean (SD), y</td>
<td>63.7 (8.9)</td>
<td>64.3 (9.3)</td>
<td>63.9 (9.3)</td>
<td>.73</td>
</tr>
<tr>
<td>Age, No. (%), y ≥65</td>
<td>140 (52.0)</td>
<td>138 (49.5)</td>
<td>137 (49.8)</td>
<td>.80</td>
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<tr>
<td>≤65</td>
<td>129 (48.0)</td>
<td>141 (50.5)</td>
<td>138 (50.2)</td>
<td>.80</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>202 (75.1)</td>
<td>217 (77.8)</td>
<td>219 (79.6)</td>
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<td>Baseline electrocardiographic results, No. (%)</td>
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<td>Pathologic Q waves</td>
<td>45 (16.7)</td>
<td>59 (21.1)</td>
<td>55 (20.0)</td>
<td>.57</td>
</tr>
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<td>Major ST-T wave abnormalities†</td>
<td>39 (14.5)</td>
<td>41 (14.7)</td>
<td>35 (12.7)</td>
<td>.57</td>
</tr>
<tr>
<td>Minor ST-T wave abnormalities†</td>
<td>71 (26.4)</td>
<td>68 (24.4)</td>
<td>82 (29.8)</td>
<td>.57</td>
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<tr>
<td>No pathologic Q or ST waves</td>
<td>114 (42.4)</td>
<td>111 (39.8)</td>
<td>103 (37.5)</td>
<td>.57</td>
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<td>Prior medical history, No. (%)</td>
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<td>Hypertension</td>
<td>173 (64.3)</td>
<td>177 (63.4)</td>
<td>177 (64.4)</td>
<td>.97</td>
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<td>Unstable angina</td>
<td>54 (20.1)</td>
<td>58 (20.8)</td>
<td>65 (23.6)</td>
<td>.54</td>
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<td>Myocardial infarction</td>
<td>150 (55.8)</td>
<td>166 (59.5)</td>
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<td>Congestive heart failure</td>
<td>77 (28.6)</td>
<td>87 (31.2)</td>
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<td>Coronary artery bypass graft surgery</td>
<td>36 (13.4)</td>
<td>53 (19.0)</td>
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<td>Percutaneous coronary intervention</td>
<td>53 (19.7)</td>
<td>46 (16.5)</td>
<td>53 (19.3)</td>
<td>.57</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>57 (21.2)</td>
<td>68 (24.4)</td>
<td>64 (23.3)</td>
<td>.67</td>
</tr>
<tr>
<td>Angina frequency, mean (SD), attacks/wk</td>
<td>4.6 (5.7)</td>
<td>4.3 (5.3)</td>
<td>4.5 (5.4)</td>
<td>.84</td>
</tr>
<tr>
<td>Nitroglycerin use, mean (SD), tablets/wk</td>
<td>4.0 (6.7)</td>
<td>4.0 (7.7)</td>
<td>3.7 (6.9)</td>
<td>.86</td>
</tr>
</tbody>
</table>

*Treatment comparison P values for continuous variables are from an analysis of variance with effects fitted for treatment and background therapy. Treatment comparison P values for categorial variables are based on a Cochran Mantel-Haenszel test, stratified by background therapy. †Without pathologic Q waves.
to be enrolled. To reassess the sample size estimate, the protocol specified that a treatment-blinded interim assessment of the SD about the primary end point (change from baseline in total exercise treadmill test duration at trough) would be performed when 231 or one half of the planned completed study patients had been randomized and followed up for 12 weeks. The recalculation of sample size, using only blinded data, was adjusted based on the estimated SD of the primary efficacy parameter (exercise duration at trough) from the aggregate data and yielded a revised SD estimate that increased the sample size to at least 810 patients (adjusted for dropouts).13-15

The primary efficacy parameter was the change from baseline in exercise treadmill time at trough, analyzed using an analysis of variance model with terms for treatment, pooled site, background therapy, and baseline exercise treadmill time, using the last observation carried forward after randomization on an intent-to-treat basis. For the primary efficacy parameter, a 2-stage, step-down procedure, based on closed testing and union intersection principles, maintained the experiment-wise type I error rate at .05.16,17 The first step compared the 2 ranolazine treatment doses with placebo. When statistical significance was achieved, the individual doses were compared with placebo. All comparisons were carried out using 2-sided α of .05.

Angina frequency and nitroglycerin consumption per week of double-blind treatment were descriptively summarized. Because the data were not normally distributed, treatment comparisons between ranolazine and placebo were obtained from a nonparametric analysis of variance model using ranked data with effects of treatment, baseline covariate, pooled site, and background therapy.18 A survival curve was prepared using Kaplan-Meier estimates for 750 patients, including 554 who received ranolazine in the CARISA trial and 196 patients who began open-label ranolazine after receiving double-blind placebo during the CARISA trial. Patients were censored 1 day after their last treatment with ranolazine. Data are given as least square means (SE unless otherwise noted).

### RESULTS

The CARISA trial began in July 1999 and ended in August 2001. Long-term follow-up is reported through October 31, 2002. Patients (n=823) were randomized at 118 investigational sites in 15 countries, received at least 1 dose of the double-blind study medication, and contributed safety data. At enrollment, 354 patients (43%) were taking atenolol; 256 (31.1%), amlodipine; and 213 (25.9%), diltiazem. Baseline characteristics, including the distribution of the background antianginal drugs, angina frequency, and nitroglycerin use,
were similar across the 3 treatment groups at baseline, although marginally fewer patients in the placebo group had undergone bypass surgery (TABLE 1). Two hundred sixty-nine patients were assigned to receive placebo, and 279 were assigned to receive 750 mg, and 275 to receive 1000 mg of ranolazine (Figure 1). Each medication dosage was prescribed to be taken twice a day.

Treadmill Exercise Testing
The primary end point of the study was met. Exercise duration for those taking either ranolazine dose (pooled) was increased compared with placebo \((P = .01)\). Each individual ranolazine dose increased treadmill exercise duration at both trough \((P = .03)\) and peak \((P < .02)\) (TABLE 2). This effect was sustained throughout 12 weeks of therapy at both dosage levels (FIGURE 2). Similar results were observed for times to angina and to ECG ischemia. Effects at peak were generally greater than at trough. Antianginal background therapy did not significantly modify the response to ranolazine (FIGURE 3).

In addition to testing differences between placebo and ranolazine using last observation carried forward analysis, a sensitivity analysis of the primary efficacy variable was found to support the conclusions obtained. We found that the study would have failed to demonstrate efficacy if the 11 patients with missing data in the placebo group had an increase from baseline in exercise duration of 91.7 seconds while the 21 patients taking ranolazine with missing data had a decrease from baseline of 40 seconds or more, which is unlikely. Finally, differences between treatment groups were tested in all patients after 12 weeks of treatment. The results were not appreciably different from results obtained using the last observation carried forward method.

Angina Frequency and Nitroglycerin Consumption
At baseline, patients were very symptomatic, experiencing an average of 4.5 angina attacks per week, prompting nearly as many nitroglycerin uses. Ranolazine reduced the mean (SE) angina attacks per week from 3.3 (0.3) for placebo to 2.5 (0.2) for 750 mg \((P = .006)\) to 2.1 (0.2) for 1000 mg \((P < .001)\) ranolazine. Ranolazine also significantly reduced nitroglycerin consumption with a similar dose response (FIGURE 4).

Hemodynamic Data
There were no clinically meaningful changes in standing or end-exercise blood pressures or heart rates. The following least square means (SEs) change from baseline reached statistical significance vs placebo: For the 1000-mg ranolazine group, standing systolic blood pressure decreased by 2.8 (1.1) mm Hg at trough and 2.8 (1.2) mm Hg at peak \((P = .02)\), end-exercise systolic blood pressure decreased by 3.3 (1.5) mm Hg at trough \((P = .04)\) but did not change at peak, and end-exercise heart rate at trough was reduced by 2.8/min \((1.2 / \text{min}; P = .02)\) and decreased by 2/min at peak \((P = .09)\). For the 750-mg ranolazine group, the end-exercise heart rate decreased by 3.1/min \((1.2 / \text{min}; P = .01)\) at trough and by 2.3/min at peak \((1.2 / \text{min}; P = .05)\).

Adverse Events
Adverse events were reported in 26.4% of patients in the placebo group and 31.2% in the 750-mg and 32.7% in the 1000-mg ranolazine groups. The most common dose-related adverse effects were constipation, dizziness, nausea, and asthenia \((= 7.3\% \text{ in both ranolazine groups}; = 0.7\% \text{ in the placebo group})\). Mortality during the 12-week randomization trial (including the 14-day safety follow-up) in the placebo group was 1.1% \((3/269)\) and was 0.7% \((2/279)\) in the 750-mg and 0.4% \((1/275)\) in the 1000-mg ranolazine groups. Five patients in the 1000-mg ranolazine group reported experiencing syncope. None were injured during their events; all recovered spontaneously, and no symptoms, signs, or ECG evidence of ventricular tachyarrhythmias were recorded.

ECG Findings
Small, dose-related increases in Bazett’s QTc interval occurred with ranolazine vs placebo. At week 12, the mean (SE) QTc were 421.5 (1.0) milliseconds for the placebo group and 427.6 (1.0) milliseconds for the 750-mg and 430.7 (1.0) milliseconds for the 1000-mg ranolazine groups. The mean (SE) increases over placebo were 6.1 (1.3) milliseconds for the 750-mg and 9.2 (1.4) milliseconds for the 1000-mg ranolazine groups \((P < .001)\). Ranolazine did not affect QT
We report the first evidence that ranolazine can reduce both angina frequency and nitroglycerin consumption when added to a standard dose of 1 of 3 frequently prescribed antianginal drugs: atenolol, amlodipine or diltiazem. The decrease in angina attacks vs placebo was slightly less than 1 per week for those in the 750-mg and somewhat more than 1 per week for those in the 1000-mg ranolazine groups (Figure 4). Exercise duration after 12 weeks of ranolazine therapy increased by 113.6 seconds at trough for those taking ranolazine compared with 91.7 seconds for those taking placebo. This net increase is similar to that observed with ranolazine as monotherapy in an earlier placebo-controlled randomized trial10 and to improvements observed in some trials of current therapies added to one another 20,21 Of note, however, in several earlier studies, current antianginal drugs in combination have not always improved exercise capacity compared with monotherapy. 22-24 Exercise testing also confirmed continuous antianginal and anti-ischemic effects throughout the 12-hour dosing interval, maintained from 2 through 12 weeks of treatment. The absence of an evident dose response in exercise parameters between 750-mg and 1000-mg ranolazine groups in the CARISA trial contrasts to the dose effects observed for angina frequency and nitroglycerin use in this study. In the MARISA trial,10 a broader dose range (500-1500 mg of ranolazine twice daily) likely facilitated the demonstration of a clear dose effect on exercise parameters.

Experimental studies with ranolazine suggest that the most likely mechanism of action is mediated through a proposed metabolic mechanism.7,10 Ranolazine may thus be well suited for patients with lower blood pressures or heart rates, in whom the institution or upward titration of antianginal drugs with important hemodynamic effects may not be tolerated.

The most common adverse effects with ranolazine were constipation, nausea, asthenia, and dizziness, no more than 6.2% greater than what the placebo group experienced for each reaction. Five patients taking 1000 mg of ranolazine experienced syncope. Four of the 5 were taking diltiazem, which is known to increase ranolazine plasma levels,25 and all were taking an angiotensin-converting enzyme inhibitor. Although little or no effect of ranolazine on mean blood pressures has been observed over the dose range of 500 mg to 1000 mg twice daily, postural hypotension and syncope have occurred in healthy volunteers given higher doses, up to 2000 mg twice daily. This is likely due to α1-adrenergic receptor blocking activity at higher doses and plasma concentrations. Thus, syncope should be avoidable by the usual clinical practice of initiating antianginal therapy with the lowest available dose and carefully titrating upward based on both efficacy and tolerability. Small QTc increases (<10 milliseconds vs placebo, on average) were not associated with persistent, frank QT prolongation in any patient nor with a mean increase in QT dispersion. Torsade de pointes has not been reported on ranolazine. The ECG effects with ranolazine appear to be balanced between inhibition of the potassium currents, Ik and Ik,s, which lengthens the QT, and inhibition of the late sodium current, late Ina,s, that suppresses early after depolarizations in isolated cardiomyocytes.

One- and 2-year survival rates of 98.4% and 95.9% with ranolazine are not worrisome, considering that these patients had severe chronic angina, with about four angina attacks per week at baseline, and exercise-induced angina.
and ischemic ST segment depression at workloads of less than 5 metabolic equivalents. Annual mortality rates in such patients have been reported ranging from 4% to 13%, 7,28

In conclusion, ranolazine affords additional anti-anginal and anti-ischemic efficacy in patients with severe chronic angina who remain symptomatic while taking standard doses of atenolol, amiodipine, or diltiazem, with minimal hemodynamic effects and without evident adverse long-term survival consequences over 1 to 2 years of therapy. It may be particularly useful in patients who cannot tolerate the initiation or upward titration of currently available antianginal drugs because of their depressive effects on blood pressure and heart rate.

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**Financial Disclosures:** Dr Chaitman has received re- search support from Aventis Pharmaceuticals, Berlex Laboratories, CV Therapeutics, and Pfizer Pharmaceu- ticals and has served as a consultant for CV Thera- peutics, the speaker's bureau for Pfizer Pharma- ceuticals. Dr Parker received research support from and served as a consultant for CV Therapeutics. Dr Pepe has received research support or educational grants from AstraZeneca Pharmaceuticals, Monarch Pharmaceuticals, Pfizer Pharmaceuticals, and Wyeth-Ayerst Laboratories and has served as a con- sultant for Abbott and CV Therapeutics.

Drs Wang, Skettino, and Wolff are employees of CV Therapeutics and hold shares in the company.

**Author Contributions:** Dr Chaitman had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Chaitman, Skettino, Wolff. **Acquisition of data:** Parker, Skopel, Chumakova, Kuch, Wang, Skettino, Wolff. **Statistical expertise:** Wang. **Administrative, technical, or material support:** Chaitman, Skettino, Wolff. **Study supervision:** Skettino, Wolff.

**Institutions**

**Canada:** British Columbia: Vancouver: Hospital and Health Science Centre: V. Bernstein; Victoria: Victo-

**REFERENCES**


Ranolazine for Treatment of Chronic Angina


Be able to be alone. Lose not the advantage of solitude, and the society of thyself.
—Sir Thomas Browne (1603-1682)