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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**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, amlodipine, 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, amlodipine, or diltiazem, without evident adverse, long-term survival consequences over 1 to 2 years of therapy.

**Author Affiliations, Financial Disclosures, and CARISA Investigators**
are listed at the end of this article.

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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 antiangiinal 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 phosphate for each molecule of oxygen consumed.9 This shift in substrate

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 antiangiinal 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 amiodipine 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 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 antiangiinal 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 antiangiinal treatment with the most commonly used agents and doses in clinical practice (atenolol 50 mg, amiodipine 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-

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, amiodipine, or diltiazem.

Figure 1. Patient Study Flow Diagram

Safety data are presented for all 823 patients who received at least 1 dose of study medication. Efficacy data are available from 791 patients (737 patients completed the full 12-week protocol and 54 patients had the last observation carried forward).
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, amlo-
dipine, 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 enve-
lopes. 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 random-
ized 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 modi-
fied Bruce exercise treadmill tests conducted 1 week apart. A supine stand-
dard 12-lead ECG was obtained before each exercise treadmill test, and stand-
ing torso ECGs were monitored throughout the exercise testing. A core ECG laboratory (St Louis University; St Louis, Mo) blinded to treatment assign-
ment interpreted all rest and exercise ECGs. All rest ECGs were classi-
ﬁed using the Minnesota code. All exercise ECGs were analyzed using cus-
tomized software as previously described. The longest QT interval in each 12-lead ECG was reported, cor-
rected using Bazett’s formula. QT dis-
persion measurements, deﬁned as the difference in milliseconds between the longest and shortest QT interval ob-
served in the ECG tracing, were re-
corded.

Exercise-induced ECG ischemia was deﬁned as the new development of hori-
zontal or down-sloping ST-segment de-
pression (≥1 mm at 80 milliseconds af-
ter the J point) vs baseline tracing. For patients with permitted baseline ST-
depression at rest (<1 mm), qualifi-
ing ST-segment depression was de-
ﬁned as additional ST depression of at
least 1 mm below the resting value. Pa-
tients were randomized into the double-
blind phase of the study if they devel-
oped exercise-limiting angina and ECG ischemia between 3 and 9 minutes dur-
ing both qualifying exercise treadmill tests, and the difference in exercise du-
ration between the 2 tests did not ex-
ceed 20% of the longer test or 1 minute.

Subsequent exercise tests were per-
fomed at trough drug levels 2, 6, and
12 weeks after randomization. At 2 and
12 weeks after randomization, a peak exercise test was performed approxi-
mately 4 hours after dosing, and on the
same day, after the 12-hour postdos-
ning trough exercise test had been com-
pleted.

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

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<th>Table 1. Baseline Characteristics*</th>
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<td>Variables</td>
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<tr>
<td><strong>Background antianginal drug</strong></td>
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<tr>
<td>Atenolol, 50 mg</td>
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<td>Amiodipine, 5 mg</td>
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<td>Diltiazem, 180 mg</td>
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<td><strong>Age, mean(SD), y</strong></td>
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<td>≥65</td>
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<td>&lt;65</td>
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<td><strong>Male, No. (%)</strong></td>
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<td><strong>Baseline electrocardiographic results, No. (%)</strong></td>
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<td>Pathologic Q waves</td>
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<td>Major ST-T wave abnormalities†</td>
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<tr>
<td>Minor ST-T wave abnormalities†</td>
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<tr>
<td>No pathologic Q or ST-T waves</td>
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<td><strong>Prior medical history, No. (%)</strong></td>
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<tr>
<td>Hypertension</td>
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<td>Unstable angina</td>
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<td>Myocardial infarction</td>
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<td>Congestive heart failure</td>
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</table>
| Coronary artery bypass graft sur-
  gery                            | 36 (13.4)     | 53 (19.0)      | 56 (20.4) | .07      |
| Percutaneous coronary interven-
  tion                           | 53 (19.7)     | 46 (16.5)      | 53 (19.3) | .57      |
| Diabetes mellitus                | 57 (21.2)     | 68 (24.4)      | 64 (23.3) | .67      |
| Angina frequency, mean (SD), at-
  tacks/wk                        | 4.6 (5.7)     | 4.3 (5.3)      | 4.5 (5.4) | .86      |
| Nitroglycerin use, mean (SD), tab-
  lets/wk                         | 4.0 (6.7)     | 4.0 (7.7)      | 3.7 (6.9) | .81      |

*Treatment comparison P values for continuous variables are from an analysis of variance with effects fitted for treat-
ment and background therapy. Treatment comparison P values for categorical 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 recalcula-
tion 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 re-
vised SD estimate that increased the sample size to at least 810 patients (ad-
justed 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, back-
ground therapy, and baseline exercise treadmill time, using the last observa-
tion 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 treat-
ment doses with placebo. When statistical significance was achieved, the in-
dividual doses were compared with placebo. All comparisons were carried
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 compa-

<table>
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<th>Table 2. Treadmill Exercise Data, Intent-to-Treat Population*</th>
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<tr>
<td>Variables</td>
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<tr>
<td>Trough Ranolazine Levels</td>
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<tr>
<td>Background antianginal drug once daily, No. (%)</td>
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<tr>
<td>Atenolol, 50 mg</td>
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<td>Amlodipine, 5 mg</td>
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<td>Diltiazem, 180 mg</td>
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<td>Exercise duration, mean (SE), s</td>
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<td>Baseline</td>
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<td>Change from baseline</td>
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<td>Difference from placebo</td>
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<td>P value vs placebo</td>
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<td>Time to onset of angina, mean (SE), s</td>
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<td>Baseline</td>
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<td>Change from baseline</td>
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<td>Difference from placebo</td>
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<td>P value vs placebo</td>
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<td>Time to ECG ischemia, mean (SE), s</td>
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<td>Baseline</td>
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<td>Change from baseline</td>
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<td>Mean difference from placebo</td>
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<td>P value vs placebo</td>
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<tr>
<td>Peak Ranolazine Levels</td>
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<td>(n = 256)</td>
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<tr>
<td>Exercise duration, mean (SE), s</td>
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<tr>
<td>Baseline</td>
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<td>Change from baseline</td>
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<td>Mean difference from placebo</td>
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<td>P value vs placebo</td>
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Abbreviation: ECG, electrocardiogram.

*All values (except baselines, which are mean [SE]) are least square means (SEs) based on an analysis of variance model, including effects for baseline, pooled site, background therapy, and treatment. There were no significant dif-
ferences between treatment groups in any baseline exercise time. Times to angina and to ECG ischemia substitute exercise duration when angina or ECG ischemia did not occur. Changes from baseline are to last observation car-
rried forward.
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/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/min; $P = .01$) at trough and by 2.3/min at peak (1.2/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 asthma ($\leq 7.3\%$ in both ranolazine groups; $\leq 0.7\%$ 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 intervals.

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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, amiodipine 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 115.6 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 trial and to improvements observed in some trials of current therapies added to one another. Of note, however, in several earlier studies, current antianginal drugs in combination have not always improved exercise capacity compared with monotherapy.

Long-term Follow-up

As of October 31, 2002, among 750 patients who took ranolazine during the CARISA trial or during the open-label follow-up study, 685 had received their first dose at least 1 year earlier; 292 patients received their first dose at least 2 years earlier. Of these, 480 (70.1%) after year 1 and 173 (59.2%) after year 2 continued taking ranolazine. After 2 years, 128 (74.0%) of 173 patients were still receiving doses of less than 1000 mg of ranolazine twice a day. Survival rates for those taking ranolazine were 98.4% (95% CI, 97.4%-99.5%) at year 1 and 93.9% (95% CI, 94.0%-97.7%) at year 2.

COMMENT

The frequency of angina attacks is the most significant determinant of quality of life for patients with chronic angina, even after adjusting for their many comorbidities. Consequently, an increasing majority of revascularization procedures are done for angina relief rather than for improving survival, especially in the United States. Nevertheless, a year after their procedures, most patients still require antianginal medications and up to 26% of them still have angina attacks.

Figure 4. Angina Frequency and Nitroglycerin Consumption in the Intent-to-Treat Population

Data are presented as means (SE). P values are for comparisons of each ranolazine group vs placebo.

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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%, 27,28.

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, amlopidine, 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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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, Skopal, Chumakova, Kuch, Wang, Skettino, Wolff. Analysis and interpretation of data: Chaitman, Pepine, Wang, Wolff. Drafting of the manuscript: Chaitman, Pepine, Wang, Wolff. Critical revision of the manuscript for important intellectual content: Chaitman, Pepine, Skopal, Parker, Chumakova, Kuch, Wang, Skettino, Wolff. Statistical expertise: Wang. Administrative, technical, or material support: Chaitman, Skettino, Wolff. Study supervision: Skettino, Wolff.

Investigators

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

RANOLAZINE FOR TREATMENT OF CHRONIC ANGINA

REFERENCES


Be able to be alone. Lose not the advantage of solitude, and the society of thyself.
—Sir Thomas Browne (1605-1682)