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EXPEDITED REVIEWS

Antianginal Efficacy of Ranolazine When Added to Treatment With Amlodipine

The ERICA (Efficacy of Ranolazine in Chronic Angina) Trial

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OBJECTIVES The purpose of this study was to determine if ranolazine improves angina in stable coronary patients with persisting symptoms despite maximum recommended dose of amlodipine.

BACKGROUND Ranolazine is a unique antianginal agent that has been effective in stable angina, but it has not been studied in the setting of maximum recommended doses of conventional antianginal agents.

METHODS Stable patients with coronary disease and ≥3 anginal attacks per week despite maximum recommended dosage of amlodipine (10 mg/day) were randomized to 1,000 mg ranolazine or placebo twice a day for 6 weeks. Primary end point was the frequency of angina episodes per week during the double-blind treatment phase. Efficacy was also assessed by nitroglycerin consumption per week and the Seattle Angina Questionnaire (SAQ). Adjustment for multiple testing of secondary end points used a hierarchic closed testing procedure. Efficacy was assessed in subgroups based on baseline angina frequency, concomitant long-acting nitrate use, gender, and age. Safety was assessed by adverse events and electrocardiogram evaluations.

RESULTS A total of 565 patients were randomized: 281 patients to ranolazine and 284 patients to placebo. Baseline characteristics were similar between treatment groups. At baseline, angina frequency averaged 5.63 ± 0.18 episodes/week, and nitroglycerin consumption averaged 4.72 ± 0.21 tablets/week. Compared with placebo, ranolazine significantly reduced frequency of angina episodes (2.88 ± 0.19 on ranolazine vs. 3.31 ± 0.22 on placebo; $p = 0.028$) and nitroglycerin consumption (2.03 ± 0.20 on ranolazine vs. 2.68 ± 0.22; $p = 0.014$), with treatment effect that appeared consistent across subgroups. The median angina weekly episode rate at baseline was 4.5 per week. Subgroup analysis showed statistically significant reductions of angina frequency, nitroglycerin use, and SAQ angina frequency for patients with a baseline frequency >4.5 per week but only of angina frequency for those with baseline frequency ≤4.5 per week. Patients with more frequent angina appeared to have a more pronounced treatment effect. No hemodynamic changes were observed. Ranolazine was well tolerated.

CONCLUSIONS Ranolazine significantly reduced frequency of angina and nitroglycerin consumption compared with placebo and was well tolerated. (The ERICA [Efficacy of Ranolazine In Chronic Angina] Trial; http://clinicaltrials.gov; NCT00091429) (J Am Coll Cardiol 2006;48: 566–75) © 2006 by the American College of Cardiology Foundation

Angina affects approximately 6.4 million Americans with stable coronary disease (CAD) (1). Currently available antianginal agents in the U.S. include beta-blockers, calcium-channel blockers, and long-acting nitrates (LANs) (2,3). Despite treatment with conventional agents and/or revascularization, many patients remain symptomatic. One year after coronary artery bypass grafting or percutaneous coronary intervention, 25% to 60% of patients continue to have angina and require antianginal medication (4,5). Conventional pharmacologic therapies exert an anti-ischemic effect by lowering determinants of myocardial O_2 demand

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(heart rate, myocardial contractility, or wall stress). Although combination regimens of conventional antianginal therapies may provide incremental efficacy (6–9), such combination regimens may lead to excessive side effects (10–12) or to a decrease in anti-ischemic efficacy (13).

Availability of a new agent that could be used in concert with other antianginal therapies without causing excessive reductions in myocardial O_2 demand determinants would be

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
AE = adverse event
CAD = coronary artery disease
ERICA = Efficacy of Ranolazine In Chronic Angina trial
LAN = long-acting nitrate
SAQ = Seattle Angina Questionnaire

of enormous value. Ranolazine is a new antianginal agent with a novel mechanism of action that involves selective inhibition of the late sodium current. This action reduces the magnitude of ischemia-induced sodium and calcium overload and thereby improves myocardial function as well as myocardial perfusion (14–16).

In stable CAD patients, ranolazine has demonstrated anti-ischemic efficacy alone (17–19) and as part of a combination regimen with submaximal doses of other antianginal agents (20) without significantly affecting heart rate or wall stress (17–21). However, ranolazine has not been studied in a combination regimen with a maximum recommended dosage of a conventional antianginal agent. The goal of the ERICA (Efficacy of Ranolazine In Chronic Angina) trial was to determine if ranolazine could reduce angina in patients with persisting angina despite treatment with maximum recommended daily dosage of amlodipine (10 mg/day) over a 6-week period. Amlodipine was selected as the conventional antianginal agent to be studied at maximum recommended dosage (10 mg/day) in a combination regimen, because the maximum recommended dosages of other conventional agents, such as atenolol (200 mg/day), diltiazem (540 mg/day), or verapamil (480 mg/day), were less feasible for routine use.

METHODS

Patients. INCLUSION CRITERIA. Entry criteria included age ≥18 years, documented history of CAD (angiographic evidence of ≥60% stenosis of at least 1 major coronary artery, history of previous myocardial infarction, and/or a stress-induced reversible perfusion defect identified by radionuclide or echocardiographic imaging), chronic stable angina ≥3 months, and ≥3 episodes of angina per week during a ≥2-week qualification period despite treatment with 10 mg/day amlodipine. Patients were required to have begun 10 mg/day amlodipine at least 2 weeks before entering the 2-week qualification period. All other antianginal medications were proscribed except LANs and sublingual nitroglycerin as required. Long-acting nitrates were permitted if they had been taken at a constant dosage for ≥2 weeks before study entry.

EXCLUSION CRITERIA. Patients were excluded if they had New York Heart Association functional class IV congestive heart failure, a history of myocardial infarction or unstable angina within the previous 2 months, active acute myocarditis, pericarditis, hypertrophic cardiomyopathy, or uncontrolled hypertension. Patients with a history of torsades de pointes, those receiving agents known to prolong the QTc interval, or who had a QTc interval measurement >500 ms at study entry were excluded. In addition, patients could not be receiving inhibitors of cytochrome P450-3A4, or have clinically significant hepatic disease, creatinine clearance <30 ml/min, or chronic illness likely to interfere with protocol compliance. Patients taking any digitalis preparation, perhexiline, trimetazidine, beta-blockers, or calcium-channel blockers other than amlodipine were excluded. Patients treated with proscribed antianginal medications had to be withdrawn from these agents for ≥4 weeks before initiation of the study drug. Patients could not have participated in another investigative trial within 30 days before study start.

The study was approved by the institutional review board at each hospital, and each patient provided written informed consent.

Study design. The study design is illustrated in Figure 1. Following qualification, patients were randomized to receive either ranolazine or placebo in a 1:1 ratio. Randomization was centralized and not stratified by center. Patients were evaluated at 2 and 6 weeks after initiation of full-dose study drug to assess efficacy and the presence of adverse events (AEs). There were 48 clinical sites (45 in eastern Europe, 2 in the U.S., and 1 in Canada) that enrolled patients from July 30, 2004, through February 16, 2005.

Extended-release ranolazine (CV Therapeutics, Palo Alto, California) was supplied as 500 mg tablets and was administered double-blind initially at 500 mg twice a day during the 1-week run-in phase, and then at 1,000 mg twice a day for the full-dose treatment phase. Amlodipine (Pfizer, New York, New York) was supplied as 10 mg tablets and administered at the same time each day.

Efficacy assessments. The primary efficacy variable was the weekly average frequency of self-reported angina episodes during the 6-week double-blind full-dose treatment phase. The study staff at each clinical site reviewed the angina and nitroglycerin use diaries with the patient at each study visit

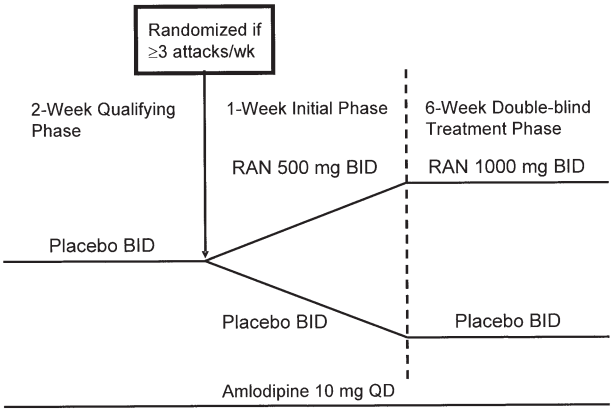

Figure 1. Study design. BID = twice a day; QD = once per day; RAN = ranolazine.

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to ensure accuracy. The secondary efficacy variables were average weekly nitroglycerin consumption rate during the 6-week double-blind full-dose treatment phase and the change from baseline of the 5 dimensions of the Seattle Angina Questionnaire (SAQ). Each SAQ dimension (anginal frequency, physical limitation, anginal stability, disease perception, and treatment satisfaction) was scored on a scale of 0 to 100. Efficacy analyses were conducted in subgroups, including analyses according to angina severity, concomitant LAN users, gender, and age.

Treatment compliance was monitored through patient-recorded anginal diary data and number of tablets dispensed and returned.

Safety and tolerability assessments. Safety and tolerability were assessed by evaluating reported AEs, hemodynamics, routine clinical laboratory measures, and 12-lead electrocardiograms.

Statistical analyses. Efficacy data were analyzed using the full analysis set, which included all patients who received at least 1 dose of study medication during the 6-week treatment phase and had any angina diary data during this period.

The average weekly rates of angina attacks and nitroglycerin consumption over the 6-week treatment phase were analyzed using the Cochran-Mantel-Haenzsel mean scores test, summarizing over strata determined by investigational sites pooled within geographic regions (1: North America; 2: Bulgaria/Romania; 3: Georgia; 4: Moscow, Russia; 5: St. Petersburg, Russia; and 6: other cities in Russia), and using scores proportional to the sample ranks to reduce the influence of outlying data. Several data points were identified as extreme outliers (ranging from 47 to 160 angina attacks per week) before unblinding. In addition to the mean, median, 25th percentile, and 75th percentile rates were summarized as trimmed means (22), averaging all observations except for the top 2% and the bottom 2% to reduce the influence of these outliers.

Primary and secondary efficacy assessment analyses were conducted in a hierarchic manner; each hypothesis was formally tested only if the preceding test was significant at $p < 0.05$. The order of testing for the secondary efficacy variables was average weekly rate of nitroglycerin use followed by dimensions of the SAQ in order from 1 through 5. Subgroup analyses were performed according to baseline symptom frequency, concomitant LAN use, age, and gender. Between-group comparison for each dimension of the SAQ was conducted using an analysis of covariance model with effects for treatment, pooled center, and baseline score.

Comparisons of vital signs between treatment groups were conducted at each visit using analysis of variance with effects for treatment and pooled center. Supine and standing vital sign measurements were summarized descriptively within treatment groups. The incidence of AEs and reason for early withdrawal were summarized by treatment group.

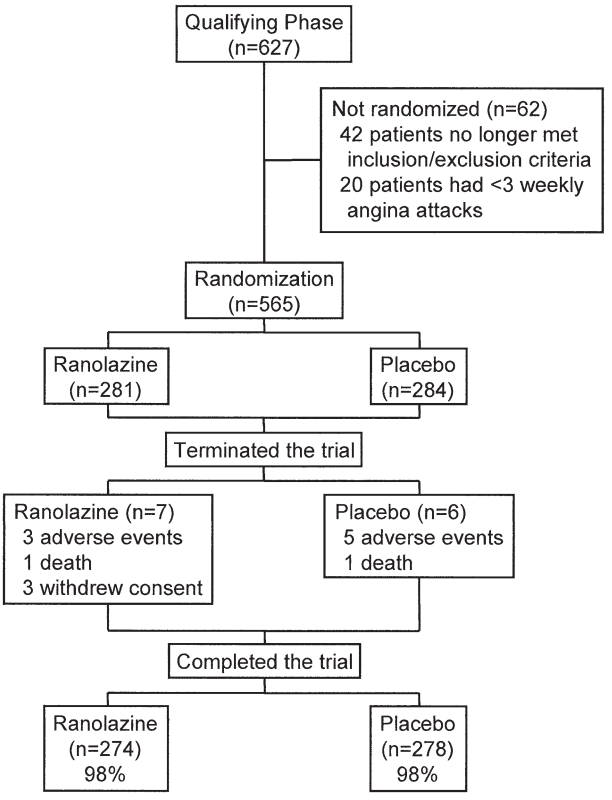

Figure 2. Patient disposition throughout the trial.

RESULTS

The disposition of patients throughout the trial is illustrated in Figure 2. Among the 565 patients randomized, 1 withdrew during the day on which she was randomized and never received double-blind study drug. Among the 564 who began treatment on ranolazine or placebo in the initial phase of the study (1 week on double-blind 500 mg ranolazine or placebo), 3 placebo patients were excluded from the full analysis set because they did not receive any dose in the 6-week double-blind treatment phase and also had no diary data during this phase; 4 ranolazine patients were similarly excluded from the full analysis set, none of the 4 having any diary data in the 6-week double-blind treatment phase and 1 of the 4 also not having received a dose during this phase.

Patient demographics and baseline characteristics including medical history are presented in Table 1. Concomitant medications are listed in Table 2. The baseline characteristics and concomitant medication use appeared similar between treatment groups.

Primary efficacy results. The average weekly rate of angina attacks in ranolazine- versus placebo-treated patients during the 6-week double-blind treatment phase is shown in Table 3 and Figure 3A. Patients receiving ranolazine had a significantly lower weekly rate of angina episodes compared with patients receiving placebo (trimmed mean 2.88 ± 0.19 vs. 3.31 ± 0.22, respectively; $p = 0.028$). As shown in Table 3, the conventional means were strongly influenced by the

Table 1. Demographics, Baseline Characteristics, and Medical History

	Placebo + Amlodipine (n = 283)	Ranolazine + Amlodipine (n = 281)	p Value
Demographics			
Age (yrs), mean ± SD	61.3 ± 9.0	62.0 ± 8.7	0.36*
Gender (M/W), %	73/27	72/28	0.66†
Race, %			0.22†
White	99	98	
Black	1	1	
Asian	0	<1	
Geographic region, %			NC
Eastern Europe	97	97	
North America	3	3	
Concomitant use of LANs, %	43	46	0.72†
Baseline characteristics			
Weekly rate of angina attacks, trimmed mean ± SE	5.68 ± 0.26 (n = 281)	5.59 ± 0.21 (n = 277)	0.48‡
Weekly rate of NTG consumption, trimmed mean ± SE	5.02 ± 0.33 (n = 281)	4.43 ± 0.26 (n = 277)	0.18‡
SAQ score, mean ± SD			
Angina frequency	40.0 ± 14.9 (n = 281)	40.6 ± 13.2 (n = 277)	0.67*
Physical limitation	48.9 ± 17.3 (n = 276)	49.2 ± 17.4 (n = 271)	0.93*
Anginal stability	57.2 ± 17.7 (n = 281)	54.7 ± 18.0 (n = 277)	0.10*
Disease perception	41.5 ± 17.8 (n = 281)	41.6 ± 17.2 (n = 277)	0.89*
Treatment satisfaction	75.4 ± 14.0 (n = 281)	74.6 ± 14.3 (n = 277)	0.46*
Medical history, n (%)			
History of unstable angina	98 (35)	100 (36)	0.87†
History of congestive heart failure	145 (51)	146 (52)	0.58†
NYHA functional class I	38 (13)	32 (11)	0.69†
NYHA functional class II	86 (30)	99 (35)	
NYHA functional class III	21 (7)	15 (5)	
NYHA functional class IV	0	0	
Diabetes mellitus	54 (19)	52 19)	0.82†
Insulin-dependent	2 (1)	11 (4)	
Previous myocardial infarction	233 (82)	218 (78)	0.16†
Previous coronary artery bypass grafting	34 (12)	28 (10)	0.52†
Previous percutaneous coronary intervention	25 (9)	34 (12)	0.095†
Intermittent claudication	32 (11)	39 (14)	0.48†
Hypertension	257 (91)	246 (88)	0.33†

*Analysis of variance with effects for treatment and pooled site. †Cochran-Mantel-Haenszel test, stratifying by pooled site. ‡Cochran-Mantel-Haenszel mean scores test, using rank scores, stratifying by pooled site.

LAN = long-acting nitrate; NC = not calculated; NTG = nitroglycerin; NYHA = New York Heart Association; SAQ = Seattle Angina Questionnaire; SD = standard deviation; SE = standard error.

Table 2. Concomitant Medications

Drug, n (%)	Placebo + Amlodipine (n = 283)	Ranolazine + Amlodipine (n = 281)
Aspirin	244 (86)	245 (87)
ACE inhibitors	144 (51)	152 (54)
LAN	123 (43)	130 (46)
Statins	93 (33)	109 (39)
Diuretics	77 (27)	89 (32)
Antidiabetics (including insulin)	29 (10)	33 (12)

ACE = angiotensin-converting enzyme; LAN = long-acting nitrate.

few outliers in the data and may not be representative of the true treatment effect. The difference in angina frequency between the 75th percentiles was larger than the difference between the 25th percentiles, which suggests that the magnitude of the treatment effect was higher among the more symptomatic patients.

Secondary efficacy results. As shown in Table 3 and Figure 3B, the average weekly rate of nitroglycerin consumption was significantly lower in patients receiving ranolazine versus those receiving placebo during the 6-week double-blind treatment phase ($p = 0.014$). The nonsignificant ($p = 0.18$) differences in baseline nitroglycerin consumption between treatment groups were noted. A non-

Table 3. Weekly Angina Frequency and Nitroglycerin Consumption

	Placebo (n = 281)	Ranolazine (n = 277)	p Value*
Weekly angina frequency			
Trimmed mean ± SE	3.31 ± 0.22	2.88 ± 0.19	0.028
Arithmetic mean ± SE	4.30 ± 0.64	3.29 ± 0.26	
25th percentile	1.47	1.24	
Median	2.43	2.18	
75th percentile	4.17	3.66	
Weekly nitroglycerin consumption			
Trimmed mean ± SE	2.68 ± 0.22	2.03 ± 0.20	0.014
Arithmetic mean ± SE	3.57 ± 0.54	2.72 ± 0.38	
25th percentile	0.50	0.47	
Median	1.67	1.34	
75th percentile	4.00	2.48	

*Cochran-Mantel-Haenszel mean scores test using rank scores, stratifying by pooled site.
SE = standard error.

parametric analysis based on the technique described by Koch et al. (23) that adjusted for baseline values yielded a treatment effect p value of 0.033. This confirmed the result of the main analysis of nitroglycerin consumption, because the treatment effect was still significant when a baseline adjustment was made.

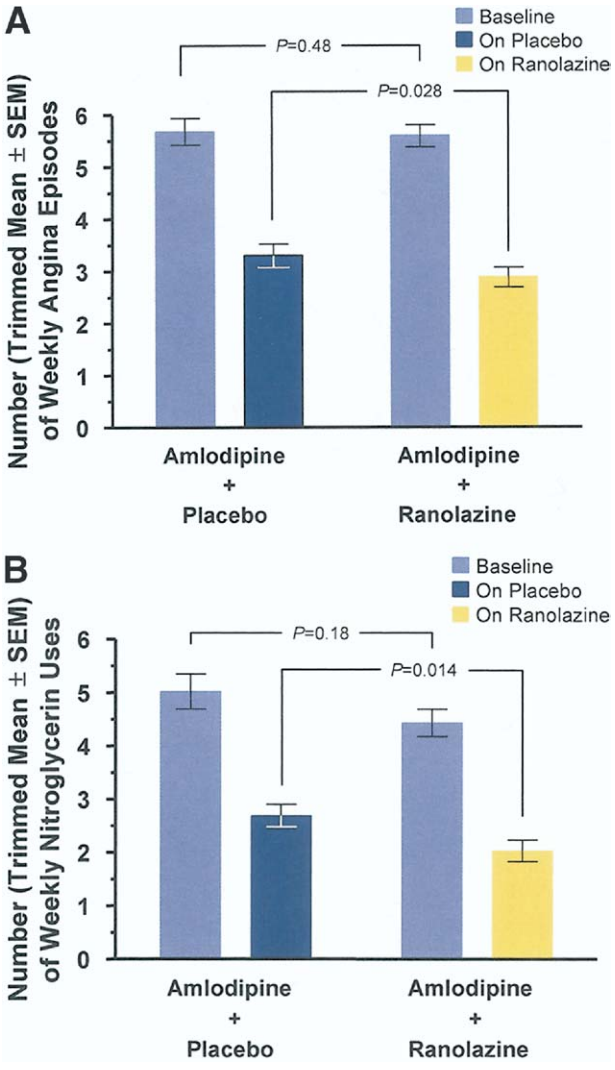

Figure 3. Number of weekly angina attacks **(A)** and number of weekly nitroglycerin uses **(B)**, excluding patients with weekly angina rate in the top 2% and bottom 2% of each treatment group (trimmed mean). SE = standard error of the trimmed mean.

The scores on the angina frequency dimension of the SAQ (dimension 1) were significantly improved in patients receiving ranolazine treatment compared with those receiving placebo (22.5 ± 19.0 vs. 18.5 ± 18.8; p = 0.008). None of the other dimensions of the SAQ was significantly different between treatment groups.

Subgroup analyses results. BASELINE SYMPTOM SEVERITY. The median angina weekly episode rate at baseline was 4.5 per week. Subgroup analysis showed statistically significant reductions of angina frequency, nitroglycerin use, and SAQ angina frequency for patients with a baseline frequency >4.5 per week, but only of angina frequency for those with baseline frequency ≤4.5 per week (Fig. 4).

LANS, GENDER, AND AGE. These data include the first reported experience of ranolazine in combination with LANs. The LANs were used by 253 (45%) of the 564 patients assessed (123 patients in the placebo group and 130 patients in the ranolazine group). The mean daily dosage of LANs (isosorbide mononitrate) was 45.4 mg/day and was similar between groups.

The efficacy analyses by subgroup for the primary efficacy end point are shown in Table 4. The differences between treatment groups observed in the subgroups of concomitant LAN users, gender, and age were numerically similar for the population as a whole. The study was not powered for testing treatment effects within subgroups. Statistical testing for the presence of treatment by subgroup interaction using an analysis of variance of rank scores did not provide any evidence that the treatment effect differed between subgroups. However, the power of such interaction tests is low.

Effect on heart rate and blood pressure. Vital signs remained relatively constant over the course of treatment in both treatment groups, and there were no significant differences between groups (Table 5). The impact of ranolazine treatment on postural changes (supine to standing) was not clinically significant and was similar to that of placebo.

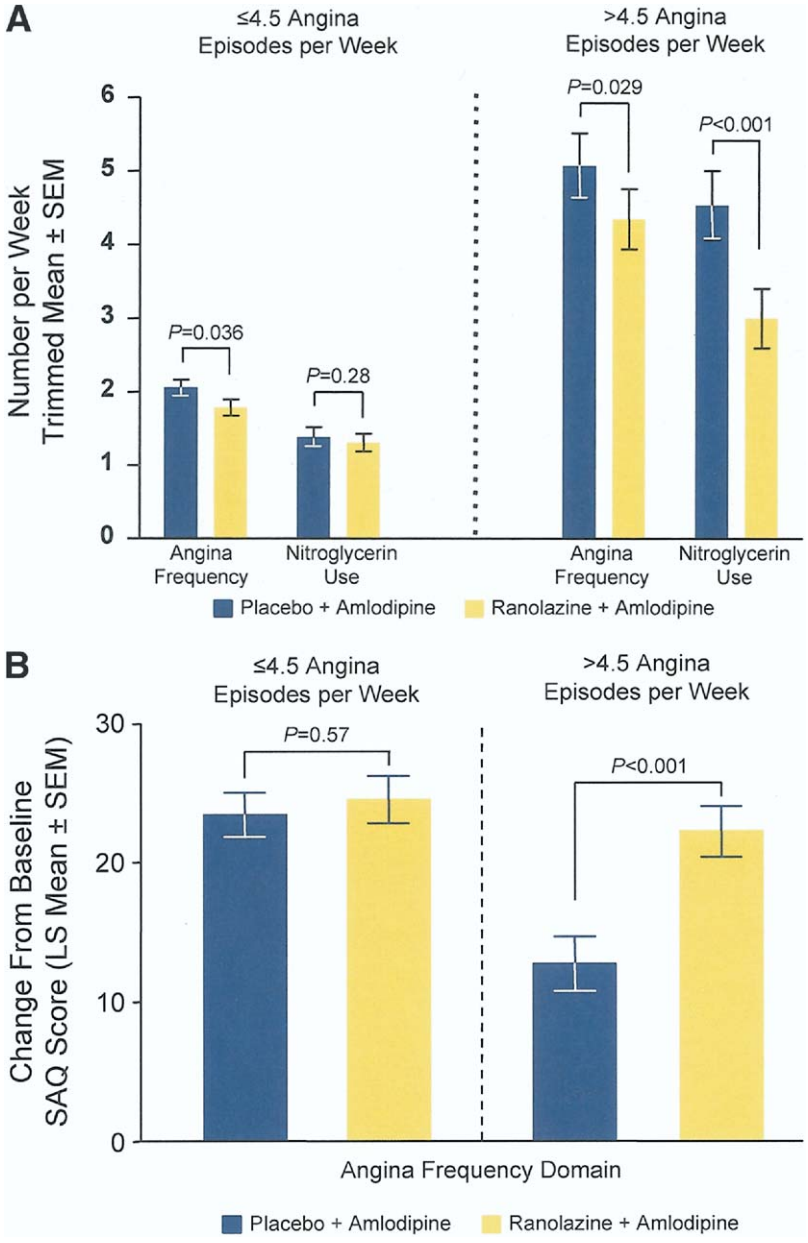

Figure 4. Number of weekly angina attacks **(A)** and change from baseline in Seattle Angina Questionnaire (SAQ) angina frequency domain scores **(B)** for patients with baseline median angina attack rates of ≤4.5 and >4.5 per week within each treatment group (trimmed mean).

Safety analyses. There were no clinically significant laboratory or physical examination abnormalities. The AEs occurred in 35.3% of placebo- and 39.9% of ranolazine-treated patients, and most were mild to moderate in severity. Constipation was the most frequently reported AE (8.9% ranolazine patients vs. 1.8% placebo patients) followed by peripheral edema (5.7% ranolazine patients vs. 2.8% placebo patients), dizziness (3.9% ranolazine patients vs. 2.5% placebo patients), nausea (2.8% ranolazine patients vs. 0.7% placebo patients), and headache (2.8% ranolazine patients vs. 2.5% placebo patients).

Among ranolazine-treated patients, the overall incidence, type, and frequency of AEs between LAN versus non-LAN was similar. Overall, more women than men in both ranolazine and placebo groups reported an AE. Constipation was reported by more women (15.0%) than men (6.5%) in the ranolazine group. Peripheral edema was reported by more women than men in both ranolazine (7.5% vs. 5.0%) and placebo (5.2% vs. 1.9%) groups. As might be expected, AEs were more frequently reported by older patients (≥65 years) receiving ranolazine than by younger patients (<65 years), with constipation more prevalent among older patients.

Seven patients (3 ranolazine treated; 4 placebo treated) discontinued the study because of AEs. One patient from each treatment group died during the study. The ranolazine-treated patient died as a result of pneumonia and

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Table 4. Primary Efficacy End Point Stratified by Subgroup (LAN Use, Gender, and Age)

	Placebo + Amlodipine		Ranolazine + Amlodipine	
Parameter	**LAN Users**	**LAN Nonusers**	**LAN Users**	**LAN Nonusers**
Weekly angina attacks, trimmed mean ± SE	3.70 ± 0.41 (n = 122)	2.99 ± 0.26 (n = 159)	3.26 ± 0.39 (n = 129)	2.64 ± 0.21 (n = 148)
Comparison to placebo			p = 0.15*	p = 0.16*
	Women	**Men**	**Women**	**Men**
Weekly angina attacks, trimmed mean ± SE	3.48 ± 0.45 (n = 76)	3.19 ± 0.24 (n = 205)	2.86 ± 0.41 (n = 79)	2.91 ± 0.23 (n = 198)
Comparison to placebo			p = 0.33*	p = 0.026*
	Age <65 yrs	**Age ≥65 yrs**	**Age <65 yrs**	**Age ≥65 yrs**
Weekly angina attacks, trimmed mean ± SE	3.30 ± 0.27 (n = 166)	3.25 ± 0.38 (n = 115)	2.83 ± 0.25 (n = 162)	2.91 ± 0.34 (n = 115)
Comparison to placebo			p = 0.074*	p = 0.15*

*Cochran-Mantel-Haenszel mean scores test using rank scores, stratifying by pooled site.
LAN = long-acting nitrate; SE = standard error.

subsequent cardiopulmonary arrest 10 days after starting ranolazine treatment; however, this death was determined to be unrelated to the study medication. The placebo-treated patient died of an acute myocardial infarction 28 days after beginning the double-blind treatment phase. No cases of torsades de pointes were reported.

Cardiovascular events were collected only if they were reported as an AE. The incidence of cardiac AEs was 5.7% in ranolazine- versus 7.8% in placebo-treated patients. There were no reports of unstable angina or stroke in either treatment group. Myocardial infarction and congestive heart failure were each reported in 0.4% of ranolazine- versus 0.7% of placebo-treated patients. Other cardiovascular events that occurred with an incidence of ≥1% in either treatment group included: ventricular extrasystoles (1.1% of ranolazine vs. 1.1% of placebo patients), sinus bradycardia (0.7% of ranolazine vs. 1.1% of placebo patients), sinus tachycardia (0% of ranolazine vs. 1.4% of placebo patients), tachycardia (1.1% of ranolazine vs. 0.4% of placebo patients), and first-degree AV block (0% of ranolazine vs. 1.1% of placebo patients).

DISCUSSION

Ranolazine has shown efficacy as an antianginal agent when used alone (17–19) and when used as part of a combination therapy regimen with conventional doses of other agents (20). The ERICA trial expands on the findings of previous studies (Table 6) by demonstrating that ranolazine provided additional antianginal benefit in patients who remained symptomatic despite treatment with a maximum recommended dosage of the calcium-channel blocker amlodipine. The present results are also the first to demonstrate incremental antianginal effects with ranolazine in patients treated with amlodipine in combination with LANs.

As monotherapy, ranolazine has been effective to reduce angina frequency and improve exercise performance in patients with stable CAD (17,18). In the Monotherapy Assessment of Ranolazine in Stable Angina (17) study, 191 patients with chronic stable angina demonstrated significant increases in exercise parameters with ranolazine 500 mg, 1,000 mg, or 1,500 mg twice a day compared with placebo, without clinically meaningful changes in heart rate or blood pressure. Ranolazine was as effective as 100 mg/day atenolol in reducing angina frequency and nitroglycerin consumption and improving exercise time to the onset of 1 mm ST-segment depression and was more effective than atenolol in prolonging the total exercise duration (18).

In combination with conventional daily doses of amlodipine (5 mg), atenolol (50 mg), or diltiazem (180 mg), the addition of ranolazine improved total exercise time, time to

Table 5. Mean Change From Baseline ± SD in Vital Signs at the End of the 6-Week Double-Blind Treatment Phase

Parameter	Placebo + Amlodipine	Ranolazine + Amlodipine	p Value*
Supine measurements			
Heart rate, beats/min	−1.6 ± 9.0	−2.0 ± 9.2	0.66
Systolic BP, mm Hg	−1.7 ± 10.7	−2.0 ± 10.0	0.72
Diastolic BP, mm Hg	−0.6 ± 7.6	−1.0 ± 7.0	0.61
Standing measurements			
Heart rate, beats/min	−1.1 ± 8.7	−1.8 ± 9.7	0.39
Systolic BP, mm Hg	−1.8 ± 11.6	−2.9 ± 10.9	0.24
Diastolic BP, mm Hg	−0.6 ± 7.9	−0.6 ± 7.2	0.99

*Analysis of variance with effects for treatment and pooled site.
BP = blood pressure; SD = standard deviation.

Table 6. Summary of Randomized Clinical Trials With Ranolazine

	MARISA	CARISA	RAN080	ERICA
Design	Double-blind, 4-period crossover, placebo-controlled, n = 191 randomized	Double-blind, parallel group, placebo-controlled, n = 823 randomized	Double-blind, 3-period crossover, placebo-controlled, n = 158 randomized	Double blind, parallel group, placebo-controlled, n = 565 randomized
Treatments and duration	Ranolazine ER 500, 1,000, or 1,500 mg or placebo twice a day as monotherapy for 1 week each	Ranolazine ER at 750 or 1,000 mg or placebo twice a day for 12 weeks. Background treatment with diltiazem 180 mg QD, atenolol 50 mg QD, or amlodipine 5 mg QD	Ranolazine IR 400 mg TID, atenolol 100 mg QD and placebo for 1 week each	Ranolazine ER 1,000 mg twice a day or placebo for 6 weeks, preceded by ranolazine ER 500 mg twice a day or placebo for 1 week. Background therapy with amlodipine 10 mg QD throughout dosing and at least 4 weeks before.
Primary efficacy measure	Exercise duration on treadmill at trough ranolazine concentration	Exercise duration on treadmill at trough ranolazine concentration	Time to onset of angina during treadmill or bicycle exercise testing at peak ranolazine concentration	Average weekly frequency of angina attacks
Secondary efficacy measures	Time to angina onset and time to 1-mm ST-segment depression at trough and peak; exercise duration at peak	Time to angina onset; time to 1-mm ST-segment depression at trough and peak; frequency of angina attacks; exercise duration at peak; frequency of NTG use	Time to 1-mm ST-segment depression and exercise duration at peak ranolazine concentration	Average weekly NTG consumption; scores in 5 dimensions of SAQ (angina frequency, physical limitations, anginal stability, disease perception, and treatment satisfaction)
Summary of efficacy results	Exercise duration at trough increased in dose-dependent fashion relative to placebo (23.8 s, 33.7 s, 45.9 s for 500 mg, 1,000 mg, 1,500 mg dose, respectively, $p < 0.005$).	Exercise duration at trough increased by 23.7 s (750 mg dose) and 24.0 s (1,000 mg dose) relative to placebo ($p = 0.03$ and $p = 0.029$, respectively).	Time to onset of angina inreased by 51.0 s relative to placebo ($p < 0.001$) on ranolazine, 39.5 s on atenolol ($p < 0.001$).	Angina frequency reduced by 0.43 episodes per week relative to placebo ($p = 0.028$).
	Significant, dose-related increases in exercise duration at peak and in time to angina onset and time to 1-mm ST-segment depression at peak and trough.	Significant increases in exercise duration, time to angina onset and time to 1-mm ST-segment depression at peak, and in time to angina onset at trough. Significant reduction in average weekly angina frequency and nitroglycerin consumption.	Exercise duration and time to 1-mm ST-segment depression significantly increased relative to placebo.	NTG consumption significantly reduced. SAQ angina frequency assessment significantly improved. Other SAQ dimensions not significantly changed.

CARISA = Combination Assessment of Ranolazine in Stable Angina; ER = extended release; ERICA = Efficacy of Ranolazine In Chronic Angina trial; MARISA = Monotherapy Assessment of Ranolazine in Stable Angina; NTG = nitroglycerin; QD = once per day; RAN080 = Ranolazine clinical study #080; SAQ = Seattle Angina Questionnaire; TID = three times per day.

onset of angina, and time to onset of 1 mm ST-segment depression in patients with symptomatic chronic stable angina (20). Ranolazine also significantly reduced angina frequency by 1.2 episodes per week and nitroglycerin consumption by 1.3 uses per week (both $p < 0.001$ vs. placebo) (20).

The ERICA trial data reported here expands on findings from previous ranolazine trials by demonstrating that significant additional benefit was achieved with ranolazine in patients who remained symptomatic despite maximum recommended therapy with a calcium-channel blocker. Consistent with other ranolazine studies (17,19–21), the ERICA trial data demonstrates that the antianginal efficacy of ranolazine occurred without clinically significant effects on heart rate or blood pressure. There was consistency of treatment effect irrespective of gender, LAN use, or age. The efficacy of the drug may have been greater in patients who had more frequent episodes of angina, as suggested by the greater difference between groups in angina frequency and nitroglycerin use in the 75th versus 25th percentiles (Table 3) and the significant improvement compared with placebo in nitroglycerin use observed only in those patients with >4.5 angina attacks per week at baseline versus those with ≤4.5 attacks per week at baseline (Fig. 4A). The more

symptomatic group also experienced a significant improvement from baseline in the SAQ angina frequency domain with ranolazine treatment compared with placebo, whereas ranolazine did not alter the change from baseline in SAQ score in the less symptomatic group (Fig. 4B). The greater antianginal efficacy in patients with more frequent angina, without a significant change in heart rate or blood pressure, may reflect the fact that these patients with more frequent angina may have more severe or prolonged ischemia-associated myocardial dysfunction and consequent hypoperfusion, a pathophysiologic state most likely to benefit from the unique mechanism of action of ranolazine.

An important potential value of the unique mechanism of action of ranolazine is that its inclusion in a combination regimen may be more effective than that of other conventional antianginal agents whose anti-ischemic efficacy is based on reduction in determinants of myocardial O_2 demand. Addition of a second conventional antianginal agent to monotherapy with one of the other conventional antianginal agents does not always confer an improvement in efficacy (10,11), and combination regimens with these conventional agents may actually worsen efficacy (12,13). The use of multiple conventional agents must also be carefully monitored to avoid additive AEs (e.g., hypotension, bradycardia, atrioventricular nodal block) (24). Use of a new antianginal agent that uses a complementary mechanism of action to the existing antianginal therapies may provide enhanced benefit.

The magnitude of antianginal benefit observed in the ERICA trial is similar to that observed in other antianginal trials using conventional agents. In a study of patients with minimal or moderate anginal symptoms receiving a maximum recommended therapeutic dose of a beta-blocker (9), an additional reduction of 0.8 anginal episodes per week was observed when the beta-blocker was combined with a calcium-channel blocker titrated to its maximal tolerated dose. These data are comparable to the 0.4 episodes per week reduction we observed. The additional reduction in nitroglycerin use (0.7 uses per week) was also comparable to the reduction of 0.6 uses per week observed in our study. Of note, however, in contrast to the improved benefits from the combination of ranolazine and amlodipine without a change in heart rate or blood pressure, the benefits achieved by combining the beta-blocker and a calcium-channel blocker (9) were associated with significant undesirable changes in hemodynamics. Use of ranolazine may allow for more optimal anti-ischemic effect without excessive adverse effects on heart rate and blood pressure. In the Combination Assessment of Ranolazine in Stable Angina study (20), the reduction in angina and nitroglycerin use when ranolazine was added to a regimen of 5 mg/day amlodipine was greater than that observed in the ERICA trial, where the amlodipine dose was 10 mg/day. The patient populations were different in the 2 studies, but one cannot exclude that the higher dose of amlodipine in these refractory patients may have somewhat limited the potential antianginal efficacy of an additional agent such as ranolazine.

Adverse events reported with ranolazine in the ERICA trial were infrequent and mild and similar to what have been observed in other studies with ranolazine. The peripheral edema observed in both treatment groups was likely related to the use of 10 mg/day amlodipine, because such edema is reported in nearly 11% of patients taking this dose (25). Furthermore, amlodipine is associated with a greater incidence of peripheral edema in women than men (25), a finding confirmed in this study. Ranolazine was well tolerated in this trial; only 1% of patients withdrew because of a treatment-related AE.

Study limitations. A limitation of this study is the use of amlodipine alone at the maximum recommended dose. Possible future studies may investigate the role of ranolazine when added to a more clinically relevant combination regimen such as maximally tolerated beta-blocker plus amlodipine.

The short-term nature of this study (6 weeks) does not necessarily extrapolate to long-term efficacy. The use of patient anginal diaries rather than ambulatory Holter monitors to detect episodes of ischemia adds a subjective component to the design; however, all patients had a documented history of CAD and angina although exercise testing was not conducted in this study. Because most of the patients were white and eastern European and not necessarily receiving optimal medical treatment for CAD (e.g., only 36% were being treated with statins, 10% had prior CABG, and 10% had prior PCI), careful interpretation of the data is warranted.

The lack of consistency in the magnitude of the responses to the SAQ concerning the benefit of ranolazine was likely due to comprehension issues, because the SAQ was not culturally and linguistically validated in the locations where the trial took place. It is also possible that the statistically significant differences in angina frequency and nitroglycerin use may not have been of sufficient importance to the patients to manifest as significant improvements in quality of life.

Per protocol, the patients in this study were not taking beta-blockers, and therefore our data may be especially applicable to the proportion of patients who cannot tolerate beta-blocker therapy (11% for metoprolol [26], 27% for atenolol [6]). A recent meta-analysis has shown that, overall, beta-blockers were equivalent to calcium-channel blockers in reducing angina symptoms and as well tolerated (27); therefore, additional studies are warranted to determine if the present results can be extrapolated to patients refractory to other traditional therapies, including those patients receiving maximally tolerated doses of beta-blockers.

Conclusions. This study demonstrated that ranolazine was an effective antianginal agent in patients with stable CAD and persisting angina despite a maximum recommended dosage of 10 mg/day amlodipine. The addition of 1,000 mg

ranolazine twice a day significantly reduced the frequency of angina episodes and rate of nitroglycerin consumption and had a consistent treatment effect across subgroups including gender, age, and LAN use. Ranolazine was well tolerated; most AEs were mild to moderate, and antianginal efficacy was unrelated to changes in blood pressure or heart rate. Ranolazine is a promising anti-ischemic therapy that may be valuable in a wide variety of subsets of patients with CAD who remain symptomatic despite treatment with other anti-ischemic agents.

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APPENDIX

For a list of the ERICA trial investigators, please see the online version of this article.