Journal of the American College of Cardiology Vol. 49, No. 10, 2007

Published by Elsevier Inc.
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2006.10.067

Long-Term Safety of a Novel Antianginal Agent in Patients With Severe Chronic Stable Angina

The Ranolazine Open Label Experience (ROLE)

Michael J. Koren, MD, FACC,* Michael R. Crager, PHD,† Michael Sweeney, MD†

Jacksonville, Florida

Objectives This report describes safety and tolerability data from 746 chronic angina patients treated in the ROLE (Ranolazine Open Label Experience) program.

Background Ranolazine treats angina without depressing hemodynamic status. The long-term safety and tolerability of ranolazine have not been previously reported.

Methods Patients with severe functional impairment from angina (mean Duke Treadmill Score [DTS] of −14.4) who completed 1 of 2 randomized treadmill trials entered the ROLE program. Ranolazine was titrated to optimal dosages between 500 and 1,000 mg twice daily. Physical examination, laboratory tests, and adverse event reporting were performed periodically. We conducted analyses to evaluate possible predictors of ranolazine intolerance, such as advanced age, diabetes, poor exercise tolerance, or history of myocardial infarctions or congestive heart failure (CHF). The ROLE program's mortality was compared against the DTS predictive model and other contemporary cohorts of high-risk CHD patients.

Results Mean follow-up was 2.82 years. Two years after initial dosing, 571 patients (76.7%) remained on therapy and 72 patients (9.7%) discontinued ranolazine due to adverse events. Among 6 factors evaluated, only age ≥64 years predicted for higher withdrawal rates. Patients with a history of CHF had lower withdrawal rates. Mean QTc interval was prolonged by 2.4 ms. No treatment discontinuations occurred due to QTc prolongation, and no Torsades de Pointes was reported. Sixty-four deaths occurred during a total of 2,102 patient-years (3.0% annually) during the ROLE program. When extending observations to all patients exposed to ranolazine during the double-blind trials (n = 972) preceding the ROLE program, annual mortality was 2.8% compared with >5% as predicted by DTS.

Conclusions Long-term therapy with ranolazine seems well tolerated in high-risk CHD patients. Survival analyses suggest that symptomatic improvements attributable to ranolazine are not offset by increased mortality. (J Am Coll Cardiol 2007;49:1027–34) © 2007 by the American College of Cardiology Foundation

Ranolazine is a novel antianginal agent. Although its mechanism of action has not been fully elucidated, ranolazine seems to inhibit the late sodium current in the cardiac myocyte, reducing calcium and sodium overload and thereby increasing the efficiency of oxygen use. Its therapeutic effects do not depend on reductions in heart rate, blood pressure, or vascular resistance (1–4) Three multicenter placebo-controlled trials of extended-release (SR) ranolazine have demonstrated angina symptom improvements as assessed either by treadmill performance or patient diaries (1,2,5).

The MARISA (Monotherapy Assessment of Ranolazine In Stable Angina) trial (1) was a 4-group crossover study in which 191 patients received ranolazine SR at dosages of 500, 1,000, and 1,500 mg twice daily (b.i.d.) and placebo in randomly ordered 1-week phases. All active treatment dosages were associated with improvements in total and angina-free treadmill exercise duration. The CARISA (Combination Assessment of Ranolazine in Stable Angina) trial (2) was a 12-week, 3-group parallel study of 823 patients (receiving background therapy with once-daily diltiazem 180 mg, atenolol 50 mg, or amlodipine 5 mg) randomly assigned to receive ranolazine SR 750 or 1,000 mg b.i.d. or placebo. Both ranolazine dosages improved total and angina-free treadmill exercise duration and reduced angina frequency and nitroglycerin consumption.

The ROLE (Ranolazine Open Label Experience) program involved patients who completed the MARISA or CARISA trial and were willing to participate in an open-label extension program. Because of the entry requirements

From the *Jacksonville Center for Clinical Research, Jacksonville, Florida; and †CV Therapeutics, Inc., Palo Alto, California. This work was supported by CV Therapeutics, Inc.

Manuscript received August 14, 2006; revised manuscript received October 26, 2006, accepted October 30, 2006.

Abbreviations and Acronyms

AE = adverse event
CHD = coronary heart disease
CHF = congestive heart failure
DTS = Duke Treadmill Score
ECG = electrocardiogram/electrocardiographic
EECP = enhanced external counterpulsation
MI = myocardial infarction
SR = extended-release

of the treadmill studies, all ROLE program participants were well characterized as having severe functional limitations due to angina and were assigned a Duke Treadmill Score (DTS). The DTS (6), a widely accepted prognostic scoring system, provides a measurement by which outcomes for the ROLE program participants can be compared with expected survival rates. Although the open-label methodology of the ROLE program is unsuitable for strictly attributing safety and efficacy outcomes to ranolazine, our analysis is intended to help clinicians identify factors more or less likely related to drug intolerance. In addition, the ROLE cohort is large enough to benchmark outcomes against other similar groups of patients reported in published medical reports.

Methods

Study design. Institutional review board approval and informed consent were obtained for all patients. Upon successful completion of the MARISA or CARISA trials, ROLE program subjects were enrolled at 123 outpatient investigative sites in 12 nations: Australia (<1%), Canada (16%), Czech Republic (22%), Georgia (3%), Greece (<1%), Israel (4%), New Zealand (2%), Poland (11%), Russia (21%), Spain (2%), United Kingdom (<1%), and the U.S. (17%). Investigators could titrate to optimal ranolazine dosages between 500 and 1,000 mg b.i.d. on the basis of clinical responses at up to 6 initial weekly visits. Maintenance-phase visits were scheduled 1 month after completion of titration and every 3 months thereafter. Patients who experienced recurrent angina or adverse events (AEs) during the maintenance phase could be titrated to higher or lower drug doses.

For MARISA patients, ranolazine was initiated at 750 mg b.i.d. and increased to a maximum dose of 1,000 mg b.i.d. as guided by clinical effects. The optional addition of other antianginal agents was permitted. For CARISA patients, ranolazine titration was initiated at 500 mg b.i.d. and could be increased to 1,000 mg b.i.d. Background antianginal therapy was maintained through the period of ranolazine titration, with the options of increasing or decreasing the dose, substituting another background antianginal agent, or discontinuing background antianginal therapy left to investigators. Open-label ranolazine was not immediately available for some of the patients who entered the ROLE program from the CARISA trial. Among 406 patients who entered the ROLE program after receiving ranolazine in the CARISA trial, the resulting interruption in ranolazine dosing averaged 4 months.

Outcome measures. Safety and tolerability assessments included vital signs, electrocardiograms (ECGs), and AE evaluations. Physical examination and laboratory analyses (hematology, chemistry, and plasma ranolazine concentrations) were conducted at baseline and all maintenance-phase visits. Urinalysis and serum lipids were assessed at baseline and every 6 months during maintenance. Reasons for study drug discontinuation were recorded.

Statistical analyses. Adverse events, study drug discontinuations, and ECG intervals were summarized, beginning with first exposure to open-label ranolazine and continuing through April 1, 2005. Exploratory analyses were conducted with Cox proportional hazards regression to assess whether age, gender, history of myocardial infarction (MI), history of congestive heart failure (CHF), diabetes mellitus, or baseline exercise tolerance predicted discontinuation of therapy due to AEs. The ECG intervals were averaged within patients over the follow-up period and compared with pretreatment baseline with the paired Student *t* test.

To avoid selection biases, analyses of survival incorporated all available follow-up of patients who were exposed to ranolazine in the MARISA or CARISA trials or the ROLE program, including patients who participated only in the randomized studies. Survival time was assessed, beginning with first exposure to ranolazine. The ROLE program did not require ongoing follow-up for survival beyond 14 days after treatment discontinuation. When patient deaths more than 14 days after discontinuation were nonetheless reported, they were included in the analysis. Mortality per patient-year was estimated assuming a constant hazard rate, and expected survival rates at 1 and 2 years were computed. Survival over the entire follow-up period was described with Kaplan-Meier methods.

Comparator studies. We searched the PubMed database with the following combination of medical subject heading terms: "coronary disease" OR "myocardial ischemia" OR "angina pectoris" AND "prospective studies" OR "survival

Table 1 Demographic and Clinical Characteristics at Baseline (n = 746)

Characteristic	n (%)
Men	580 (77.7)
White	722 (96.8)
Age <65 yrs	388 (52.0)
Hypertension	476 (63.8)
Previous MI	429 (57.5)
Previous revascularization	257 (34.5)
CHF	215 (28.8)
Unstable angina	172 (23.1)
Diabetes	170 (22.8)
Ventricular arrhythmias	75 (10.1)
Valvular heart disease	47 (6.3)
Stroke	35 (4.7)
Cardiac arrest	14 (1.9)

CHF = congestive heart failure; MI = myocardial infarction.

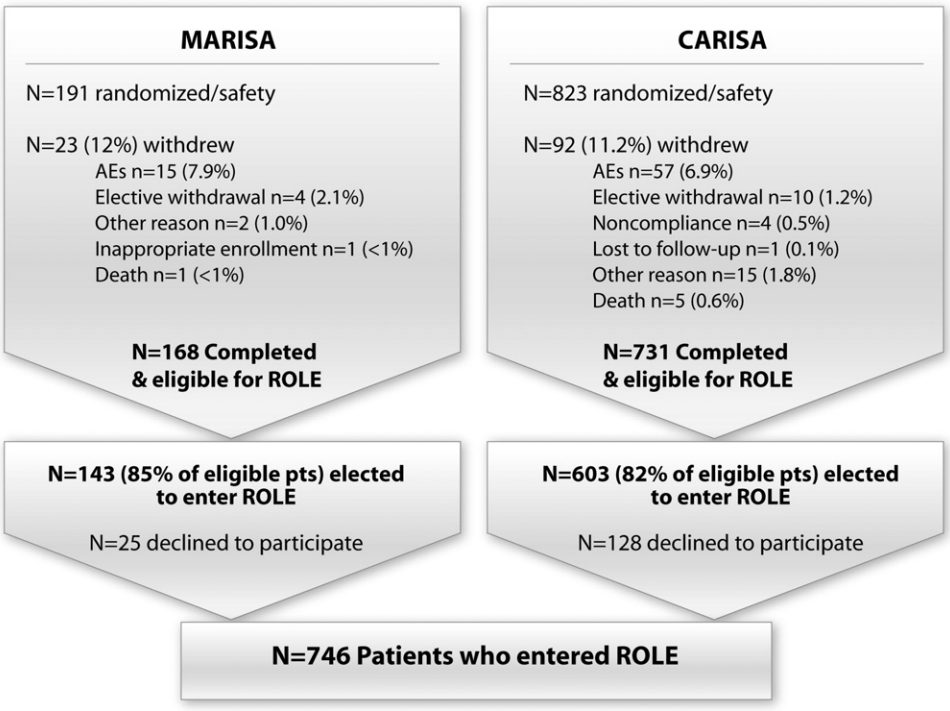

Figure 1 The ROLE Program Schematic

Disposition of subjects in preceding double-blind trials leading to the ROLE (Ranolazine Open Label Experience) program. AE = adverse event; CARISA = Assessment of Ranolazine in Stable Angina trial; MARISA = Monotherapy Assessment of Ranolazine In Stable Angina trial; pts = patients.

analysis" OR "treatment outcome." PubMed search limits were "middle aged: 45 to 64 years," "aged: 65+ years," "English," "publication date from 1996 to 2005," "clinical trial," and "core clinical journals." We limited comparator studies to those of at least 2 years' duration and 500 patients except for one that represented the largest published experience with surgical transmyocardial laser revascularization.

Results

A total of 746 patients entered the ROLE program (143 of the 168 patients who completed the MARISA trial plus 603 of the 731 patients who completed the CARISA trial). Patient characteristics are summarized in Table 1, and the flow of patients through the studies is presented in Figure 1. The population was largely male and white. Average exposure time to ranolazine was 2.82 years (range 6 days to 6.5 years). Twenty-three percent of the population was diabetic, and 58% had a previous MI. Four hundred thirty-two (58%) subjects were titrated at some point to the highest ranolazine dose of 1,000 mg b.i.d., 209 subjects (28%) received a maximum dose of 750 mg b.i.d., and 14% received 500 mg b.i.d.

Discontinuations. Patient disposition over time is shown in Table 2. Of the original 746 patients enrolled, all but 2 have follow-up data through 2 years or discontinued prior to that point owing to adverse effects, death, or choice. Five hundred seventy-one patients (76.7%) completed 2 years of

Table 2 Patient Disposition by Time on Open-Label Treatment

Time on Open-Label Treatment	1 Yr	2 Yrs	All Follow-Up to Date (Mean 2.8 yrs, Max 6.5 yrs)
Patients with at least this much time on treatment	746	744*	
Patients terminating participation	115 (15.4%)	173 (23.3%)	290 (38.9%)
Unacceptable adverse event	53 (7.1%)	72 (9.7%)	94 (12.6%)
Elective withdrawal	31 (4.2%)	46 (6.2%)	95 (12.7%)
Death	25 (3.4%)	36 (4.8%)	56 (7.5%)†
Patients who completed 2 yrs of ranolazine therapy		571 (76.7%)	

*Two patients had not yet reached 2 years on open-label treatment at the time of this analysis. †Eight additional patients died after terminating participation in the ROLE (Ranolazine Open Label Experience) program.

Table 3 Summary of All Adverse Events ≥4% Incidence Reported During the ROLE Program

Preferred Term	Number of Patients (%) (n = 746)
Angina pectoris	111 (14.9)
Dizziness	88 (11.8)
Constipation	81 (10.9)
Peripheral edema	62 (8.3)
Angina, unstable	53 (7.1)
Fatigue	52 (7.0)
Hypertension	48 (6.4)
Cough	45 (6.0)
Chest pain	44 (5.9)
Nausea	42 (5.6)
Headache	41 (5.5)
Myocardial infarction	37 (5.0)
Diabetes mellitus	37 (5.0)
Back pain	36 (4.8)
Anemia	34 (4.6)
Arthralgia	33 (4.4)
Asthenia	33 (4.4)
Dyspnea	32 (4.3)
Vertigo	32 (4.3)
Influenza	31 (4.2)
Acute MI	28 (3.8)
Diarrhea	28 (3.8)

MI = myocardial infarction; ROLE = Ranolazine Open Label Experience.

open-label ranolazine therapy, and 173 patients (23.3%) had discontinued therapy. Adverse events were the most common reason for discontinuation in the first 2 years of open-label treatment, accounting for slightly less than one-half of all discontinuations (n = 72 [9.7% of total cohort]). The next most common reasons for discontinuation were elective withdrawal at the discretion of patients and/or investigators (n = 46 [6.0%]) and death (n = 34 [4.6%]). Adverse events are summarized by preferred term in the MedDRA dictionary (Version 8) in Table 3. Aside from angina, the symptom under study, the most common AEs recorded were dizziness (11.8%) and constipation (10.9%). These complaints, solely or in combination with other AEs, led to discontinuation in 7 (0.9%) and 5 (0.6%) patients, respectively. Adverse event profiles did not differ between the 197 subjects who received ranolazine for the first time in the ROLE program (randomized to placebo in MARISA or CARISA trials) and 549 patients who had previously received ranolazine.

Table 4 shows the results of predictive modeling to analyze possible correlations between baseline demographic and clinical variables and the likelihood of AE-related discontinuation. Older age (≥64 years) was the only factor that showed a statistically significant correlation with increased AE-related discontinuation (relative risk 2.32, $p < 0.001$). History of CHF was the only factor that showed a significant correlation with reduced AE-related discontinuation (relative risk 0.55, $p = 0.030$). There was a trend toward decreased risk of AE-related discontinuations among patients with a history of MI (relative risk 0.74, $p = 0.14$) and those with baseline exercise duration shorter than the median (relative risk 0.75, $p = 0.16$).

ECG findings. Durations of the PR, QRS, and QTc (Fridericia correction) intervals at baseline and the within-patient average values during open-label ranolazine treatment are presented in Table 5. There were no significant changes from baseline in either the PR or QRS interval. The QTc interval showed a mean prolongation of approximately 2.4 ms compared with baseline ($p < 0.001$). Sixteen ECG tracings showed QTc interval prolongation exceeding 500 ms occurring in 10 patients (1.2%). Ten occurrences of QTc intervals >500 ms were recorded while patients received the 1,000 mg b.i.d. dosage, and 6 occurrences were recorded at the 750 mg b.i.d. dosage. No subject was withdrawn from the ROLE program for QTc interval prolongation. Serum electrolyte levels obtained proximate to the time of QTc interval

Table 4 Influence of Demographic and Clinical Categorical Variables on Risk of Discontinuations Due to AEs

Predictor	Group 1 Group 2	Breakdown: 746 Patients	Breakdown: 94 DCs Due to AEs	Relative Risk* (95% Confidence Interval)	p Value
Gender	Men	580	72	0.931 (0.577–1.501)	0.77
	Women	166	22		
Age	>64 yrs	389	66	2.32 (1.49–3.61)	<0.001
	<64 yrs	357	28		
History of MI	Present	429	47	0.74 (0.492–1.104)	0.14
	Absent	317	47		
History of CHF	Present	215	16	0.55 (0.320–0.943)	0.030
	Absent	531	78		
History of diabetes	Present	170	22	1.04 (0.65–1.68)	0.87
	Absent	576	72		
Baseline exercise duration	≥Median	373	42	0.745 (0.50–1.12)	0.16
	<Median	373	52		

*Cox proportional hazards regression analysis relative risk estimate is expressed as the ratio of group 1 to group 2.
AE = adverse event; DC = discontinuation; other abbreviations as in Table 1.

Table 5 Electrocardiographic Findings at Baseline and Average Values on Treatment

Interval	Number of Patients Assessed	Milliseconds (Mean ± SE)	
		Baseline	On Treatment
PR	739	167.1 ± 1.0	167.2 ± 0.9
QRS	745	94.6 ± 0.5	93.5 ± 0.4
QTc (Fridericia correction)	739	419.9 ± 0.8	422.3 ± 0.7

prolongation did not indicate any significant abnormalities. No case of Torsades de Pointes was reported.

Mortality. Data were available and analyzed from a total of 2,372 patient-years of follow-up of the 942 patients exposed to ranolazine through randomization in the MARISA or CARISA trials or in the ROLE program, incorporating 2,233 patient-years of ranolazine treatment exposure. The difference between the patient-years of follow-up and patient-years of treatment is due primarily to the delay in availability of the ROLE program for some CARISA trial patients. There were 4 deaths during ranolazine treatment in the MARISA and CARISA trials (vs. 3 deaths during placebo treatment) and 64 deaths during 2,102 patient-years in the ROLE program (3.0% annual incidence). In all, there were 68 deaths during the 2,372 patient-years of follow-up (2.8% annual incidence). The estimated 1- and 2-year survival from this incidence is 97.2% and 94.4%, respectively. A Kaplan-Meier survival plot is shown in Figure 2. Among the 68 deaths reported, the most common causes—not unexpected in this population—were cardiovascular including MI and ventricular tachyarrhythmia. The most common noncardiac causes of death were cancer and pulmonary embolism (Table 6).

Table 7 compares the ROLE program mortality rates with those predicted by the DTS model and contemporary treatment trials (6–12). Comparison cohorts were selected in which patients had either refractory chronic angina or coronary heart disease (CHD) with increased risk. With the exception of the younger population reflected in the DTS model, comparative cohorts were of similar age as ROLE program participants.

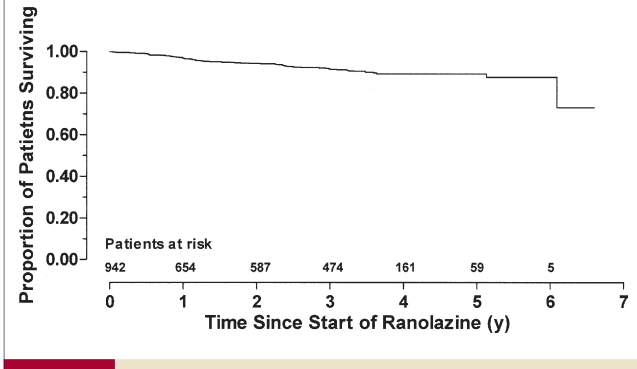

Figure 2 Survival Time During the ROLE Program and the Original, Randomized Trials MARISA and CARISA

Kaplan-Meier estimate. Abbreviations as in Figure 1.

Table 6 Cumulative Mortality to Date

Cause of Death	Number of Deaths (%)
Any cause (total deaths)	68 (100.0)
CV deaths	54 (79.4)
Acute MI	23 (33.8)
MI, cardiogenic shock, acute coronary syndrome	3 (4.4)
Sudden death	15 (22.0)
Ventricular tachyarrhythmia	4 (5.9)
CHF, low-output syndrome, cardiac insufficiency	3 (4.4)
Cerebrovascular event	2 (2.9)
Pulmonary embolism	2 (2.9)
Cardiac arrest	1 (1.5)
Hemopericardium	1 (1.5)
Non-CV deaths (cancer, infection, respiratory failure, bowel obstruction, accident, trauma unknown)	14 (20.6)

CV = cardiovascular; other abbreviations as in Table 1.

Discussion

The market availability of novel pharmaceutical products inevitably generates both excitement and concern among clinicians. Although physicians might welcome ranolazine as an agent that addresses the unmet need of treating CHD symptoms without altering hemodynamic status, safety concerns are understandable. These concerns are particularly germane to cardiovascular therapeutics, recently including drugs such as flosequinone, mibefradil, and nesiritide—all agents that received regulatory approval on the basis of symptom relief only to be subsequently withdrawn or highly scrutinized after the release of safety data that were unavailable at the time of initial approvals.

Ranolazine was well tolerated during long-term treatment, which is consistent with the findings of randomized, double-blind studies (1,2,5). The most common side effects were dizziness and constipation, but these symptoms were usually not severe enough to cause treatment discontinuation. Overall, 76.7% of patients completed 2 years of open-label therapy. Of the 23.3% of patients who did not complete 2 years of therapy, less than one-half (9.7%) stopped study participation owing to AEs. Predictive modeling showed a significantly increased likelihood of AE-related discontinuation associated with only 1 categorical variable, age ≥64 years. Increased susceptibility to untoward effects with advancing age is common for many therapeutic interventions and is not an unexpected finding (13–15). Curiously, there was a decreased probability of AE-related discontinuation in patients with a history of CHF. Although this finding should be interpreted with caution, it is intriguing that improvements in ventricular function related to ranolazine were observed in animal models (15,16).

The open-label methodology of the ROLE program does not allow for a rigorous analysis of mortality. Because of the absence of a comparator group, it is difficult to fully

Table 7 Patient Survival in ROLE and Other Published Patient Cohorts

Publication	Study Type	Follow-Up Duration, yrs	Study Population	Age, yrs	Number of Subjects	Survival
Mark et al. (6,12)	Historical observational	5 (median)	Patients with heart catheterizations and stress tests at Duke University Medical Center Nov 1969–Jan 1981	49 (median)	2,842 (M: 70%)	4-yr rate by risk, Low (DTS >5): 99%; Moderate (DTS −10 to 4): 95%; High (DTS <−10): 79%
Morrison et al. (8)	Contemporary treatment in high-risk population	3	16 VA centers enrolling patients with medically refractory myocardial ischemia undergoing high-risk CABG or PCI	Approx 40% of patients >70 yrs	760	3 yrs (reported by subsets) 65% to 86%
Allen et al. (9)	Contemporary treatment in high-risk population	1	Medically refractory class IV angina not amenable to revascularization	TMR: 60 ± 10 Med Rx: 60 ± 11 (mean ± SD)	TMR: 132 (M: 74%) Med Rx: 143 (M: 76%)	1-yr TMR: 84%; Med Rx: 89%
Michaels et al. (7)	Contemporary treatment in high-risk population	2	Patients undergoing EECP for chronic angina	65.8 ± 10.9 (mean ± SD)	1,097 (M: 74%)	2 yrs 91.5%
Poole-Wilson et al. (11)	Contemporary treatment in lower-risk population	4.9 ± 1.1 (mean ± SD)	Patients with stable angina. Abnormal treadmill study not required.	Nifedipine: 63.5 ± 9.3 Placebo: 63.4 ± 9.3 (mean ± SD)	Nifedipine: 3,825 (M: 80%) Placebo: 3,840 (M: 79%)	Nifedipine GITS: 91.9% Placebo: 92.4%
Pepine et al. (10)	Contemporary treatment	2.7 (mean)	Patients with CAD and hypertension	66 ± 9.7 (mean ± SD)	22,576 (M: 48%)	CCB strategy: 92.2% Non-CCB strategy: 92.1%
The ROLE program	Current study	2.8	Patients with severe functional impairment due to CAD who completed 1 of 2 randomized treadmill tests	63.6 ± 9.0 (mean ± SD)	746 (M: 78%)	2 yrs 94.4%

CABG = coronary artery bypass grafting; CAD = coronary artery disease; CCB = calcium channel blocker; DTS = Duke Treadmill Score; EECP = enhanced external counterpulsation; GITS = gastrointestinal therapeutic system; M = men; PCI = percutaneous coronary intervention; TMR = transmyocardial revascularization; VA = Veterans Administration.

characterize implications of the 68 deaths reported. However, the mortality rate of 5.6% over 2 years can be placed into context by comparing this result with predictions based on DTS and cohorts treated with other antianginal modalities.

High-risk DTS (<−10) has been associated with a 4-year survival rate of <79%, intermediate-risk scores (−10 to +4) with a 4-year survival risk of 75% to 95%, and low-risk scores (≥+5) with a 4-year survival rate of ≥99% (6,12). The mean baseline DTS for ROLE patients, −14.4, implies a poor prognosis and a yearly mortality estimate above 5%. The finding of an actual 2-year mortality of 5.6% and a yearly mortality of approximately one-half the DTS predicted rate is reassuring prognostic information about ranolazine. Although prognosis on the basis of the DTS might not reflect recent invasive and noninvasive advances in cardiovascular care (e.g., stents and statin use) and might overestimate contemporary CHD mortality, the DTS cohort was significantly younger than ROLE program participants—an offsetting factor that could lead to underestimation of DTS-predicted mortality for the ROLE program patients.

Benchmarking outcomes in patients exposed to ranolazine with the prognosis reported in recent high-risk CHD treatment trials is another useful comparison. In 1998, a registry was set up to assess treatment with enhanced external counterpulsation (EECP) in patients with refractory angina (17). In 2001, Michaels et al. (7) described the experience of 978 patients at 43 centers, of whom 81% had previously undergone revascularization and 69% were considered unsuited for either percutaneous coronary intervention or coronary artery bypass graft surgery at the start of treatment with EECP. Although EECP registry patients might have had more severe CHD, on average, in that they could be angina treatment failures despite multiple drugs, these patients might not be dissimilar prognostically to ROLE program participants who were required to have angina limiting exercise at low work levels (≤ end of Bruce protocol stage 1). Cumulative mortality among EECP registry patients was 8.5% at 2 years (7) versus 5.6% in ROLE program participants. Data from cohorts undergoing other treatments for medically refractory angina such as high-risk coronary revascularization or surgical laser transmyocardial revascularization also show mortality rates greater than the ROLE program cohort (8,9). By contrast, studies of lower-risk CHD populations have shown similar (10) or lower mortality risk (11).

The finding of mortality rates in the ROLE program at or below expectations should help address concerns about whether or not the QTc interval prolongation previously reported in association with ranolazine use is of clinical significance. Previous work with ranolazine demonstrated a prolongation of the Bazett's corrected QTc interval by <10 ms (2). Although prolongation of QTc interval is associated with Torsades de Pointes, investigators (18) have shown that QTc interval prolongation alone is not sufficient to cause Torsades de Pointes. Induction of early after depolarizations (EADs) and an increase in transmural dispersion are also required. Electrophysiologically, ranolazine does not induce EADs in animal models and reduces transmural dispersion (19). In the ROLE program, there were no investigator-ordered discontinuations related to QTc interval prolongation or cases of Torsades de Pointes.

Although the safety results of the ROLE experience are encouraging, clinicians should maintain their vigilance for untoward effects. While the relatively large ROLE cohort safety dataset should be predictive of patient experiences as ranolazine makes it way into routine clinical use, limitations of the present study should be acknowledged. Some patients in the original randomized studies terminated early from the randomized studies because of AEs (7.9% of ranolazine patients vs. 4.8% of placebo patients in the CARISA trial, and 1.1%, 0.6%, 0.6%, and 5.9% of patients treated with placebo, ranolazine 500 mg b.i.d., ranolazine 1,000 mg b.i.d., and ranolazine 1,500 mg b.i.d., respectively, in the MARISA trial). Because completion of a blinded study was required to participate in the ROLE program we might have eliminated patients who were more intolerant of ranolazine and reduced the incidence of AEs in the ROLE program. There was also no requirement for long-term systematic follow-up after patients discontinued medication in the ROLE program. Although these discontinued patients are not expected to have any untoward long-term complications attributable to their use of the drug, this possibility cannot be entirely excluded.

Conclusions

Long-term safety and tolerability of ranolazine in patients with chronic stable angina seems favorable without indication of increased long-term cardiac mortality compared with reference populations. Electrophysiological complications were not a major determinant of study drug discontinuation. Ranolazine discontinuation due to adverse experiences was more common in older patients. Because participation in the ROLE program was voluntary, it is reasonable to conclude that the high rate of patients continuing ranolazine open-label treatment reflects a perception of net benefit for a symptomatic condition by study participants and their physicians.

Reprint requests and correspondence: Dr. Michael J. Koren, Jacksonville Center for Clinical Research, 4085 University Boulevard South, Suite 1, Jacksonville, Florida 32216. E-mail: MichaelKoren@jaxresearch.com.

REFERENCES

1. Chaitman BR, Skettino SL, Parker JO, et al. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. J Am Coll Cardiol 2004;43:1375–82.
2. Chaitman BR, Pepine CJ, Parker JO, et al. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. JAMA 2004;291:309–16.
3. Cocco G, Rousseau MF, Bouvy T, et al. Effects of a new metabolic modulator, ranolazine, on exercise tolerance in angina pectoris patients

treated with beta-blocker or diltiazem. J Cardiovasc Pharmacol 1992;20:131–8.
4. Pepine CJ, Wolff AA. A controlled trial with a novel anti-ischemic agent, ranolazine, in chronic stable angina pectoris that is responsive to conventional antianginal agents. Ranolazine Study Group. Am J Cardiol 1999;84:46–50.
5. Stone PH, Gratsiansky NA, Blokhin A, Huang I-Z, Meng L, for the ERICA Investigators. Antianginal efficacy of ranolazine when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine in Chronic Angina) trial. J Am Coll Cardiol 2006:48:566–75.
6. Mark DB, Hlatky MA, Harrell FE Jr., Lee KL, Califf RM, Pryor DB. Exercise treadmill score for predicting prognosis in coronary artery disease. Ann Intern Med 1987;106:793–800.
7. Michaels AD, Linnemeier G, Soran O, Kelsey SF, Kennard ED. Two-year outcomes after enhanced external counterpulsation for stable angina pectoris (from the International EECP Patient Registry [IEPR]). Am J Cardiol 2004;93:461–4.
8. Morrison DA, Sethi G, Sacks J, et al. Percutaneous coronary intervention versus repeat bypass surgery for patients with medically refractory myocardial ischemia: AWESOME randomized trial and registry experience with post-CABG patients. J Am Coll Cardiol 2002;40:1951–4.
9. Allen KB, Dowling RD, Fudge TL, et al. Comparison of transmyocardial revascularization with medical therapy in patients with refractory angina. N Engl J Med 1999;341:1029–36.
10. Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. JAMA 2003;290:2805–16.
11. Poole-Wilson PA, Lubsen J, Kirwan BA, et al. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. Lancet 2004;364:849–57.
12. Mark DB, Shaw L, Harrell FE Jr., et al. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. N Engl J Med. 1991;325:849–53.
13. Thomas EJ, Brennan TA. Incidence and types of preventable adverse events in elderly patients: population based review of medical records. BMJ 2000;320:741–4.
14. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. JAMA 2003;289:1107–16.
15. Sabbah HN, Imai M, Morita H, Stanley WC, Blackburn B. Long-term therapy with ranolazine prevents progressive left ventricular dysfunction and remodeling in dogs with chronic heart failure (abstr). Circulation 2004;110 Suppl III:III679–80.
16. Sabbah HN, Chandler MP, Mishima T, et al. Ranolazine, a partial fatty acid oxidation (pFOX) inhibitor, improves left ventricular function in dogs with chronic heart failure. J Card Fail 2002;8:416–22.
17. Barsness G, Feldman AM, Holmes DR Jr., Holubkov R, Kelsey SF, Kennard ED. The International EECP Patient Registry (IEPR): design, methods, baseline characteristics, and acute results. Clin Cardiol 2001;24:435–42.
18. Belardinelli L, Antzelevitch C, Vos MA. Assessing predictors of drug-induced torsade de pointes. Trends Pharmacol Sci 2003;24:619–25.
19. Antzelevitch C, Belardinelli L, Zygmunt AC, et al. Electrophysiological effects of ranolazine, a novel antianginal agent with antiarrhythmic properties. Circulation 2004;110:904–10.