Journal of the American College of Cardiology Vol. 61, No. 20, 2013

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.02.011

Evaluation of Ranolazine in Patients With Type 2 Diabetes Mellitus and Chronic Stable Angina

Results From the TERISA Randomized Clinical Trial (Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina)

Mikhail Kosiborod, MD,*† Suzanne V. Arnold, MD, MHA,*† John A. Spertus, MD, MPH,*† Darren K. McGuire, MD, MHSC,‡ Yan Li, PHD,* Patrick Yue, MD,§ Ori Ben-Yehuda, MD,§ Amos Katz, MD,‖ Philip G. Jones, MS,* Ann Olmsted, PHD,§ Luiz Belardinelli, MD,§ Bernard R. Chaitman, MD¶

Kansas City and St. Louis, Missouri; Dallas, Texas; Foster City, California; and Ashkelon, Israel

Objectives This study sought to examine the efficacy of ranolazine versus placebo on weekly angina frequency and sublingual nitroglycerin use in subjects with type 2 diabetes mellitus, coronary artery disease (CAD), and chronic stable angina who remain symptomatic despite treatment with up to 2 antianginal agents.

Background Patients with diabetes have more extensive CAD than those without diabetes, and a high burden of angina. Ranolazine is not only effective in treating angina but also may improve glycemic control, thus providing several potential benefits in this high-risk group. We conducted a randomized trial to test the antianginal benefit of ranolazine in patients with diabetes and stable angina.

Methods TERISA (Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina) was an international, randomized, double-blind trial of ranolazine versus placebo in patients with diabetes, CAD, and stable angina treated with 1 to 2 antianginals. After a single-blind, 4-week placebo run-in, patients were randomized to 8 weeks of double-blind ranolazine (target dose 1000 mg bid) or placebo. Anginal episodes and nitroglycerin use were recorded with daily entry into a novel electronic diary. Primary outcome was the average weekly number of anginal episodes over the last 6 weeks of the study.

Results A total of 949 patients were randomized across 104 centers in 14 countries. Mean age was 64 years, 61% were men, mean diabetes duration was 7.5 years, and mean baseline HbA1c was 7.3%. Electronic diary data capture was 98% in both groups. Weekly angina frequency was significantly lower with ranolazine versus placebo (3.8 [95% confidence interval (CI): 3.6 to 4.1] episodes vs. 4.3 [95% CI: 4.0 to 4.5] episodes, $p = 0.008$), as was the weekly sublingual nitroglycerin use (1.7 [95% CI: 1.6 to 1.9] doses vs. 2.1 [95% CI: 1.9 to 2.3] doses, $p = 0.003$). There was no difference in the incidence of serious adverse events between groups.

Conclusions Among patients with diabetes and chronic angina despite treatment with up to 2 agents, ranolazine reduced angina and sublingual nitroglycerin use and was well tolerated. (Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina [TERISA]; NCT01425359) (J Am Coll Cardiol 2013;61:2038–45) © 2013 by the American College of Cardiology Foundation

Despite multiple medical and interventional technologies to reduce myocardial ischemia, chronic angina still affects nearly 8 million people in the United States (1). Although it is associated with worse health-related quality of life (2,3), repeat hospitalizations, and increased healthcare costs (4), angina remains frequently undertreated (5,6). Patients with angina and concomitant type 2 diabetes mellitus (T2DM)

See page 2046

From the *Department of Cardiovascular Research, Saint Luke's Mid America Heart Institute, Kansas City, Missouri; †Department of Medicine, University of Missouri-Kansas City, Kansas City, Missouri; ‡Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas; §Gilead Sciences, Foster City, California; ‖Department of Cardiology, Barzilai Medical Center, Ashkelon and Faculty of health Sciences, Ben Gurion University, Ashkelon, Israel; and the ¶Department of Internal Medicine, Division of Cardiology, St. Louis University, St. Louis, Missouri. The study was sponsored by Gilead Sciences (Foster City, California). Saint Luke's Mid America Heart Institute received funding for the independent statistical analysis of the TERISA trial from Gilead Sciences. Saint Luke's Mid America Heart Institute received research funding from Gilead Sciences, unrelated to the TERISA trial. Dr. Kosiborod has received research support from Gilead Sciences, unrelated to

represent a particularly challenging group, as they often have more diffuse and extensive coronary artery disease (CAD) as compared with those without T2DM (7,8). Furthermore, patients with CAD and T2DM may also have a greater burden of angina than those without diabetes (9,10). Targeted approaches to reduce the burden of angina specifically among patients with T2DM could have a substantial impact on quality of life.

Ranolazine, a selective inhibitor of the late sodium current (late I_{Na}) (11), has been proven effective in treating chronic angina both as a monotherapy (12,13) and in combination with other commonly prescribed antianginal medications (14,15). Furthermore, among patients with poorly controlled T2DM, ranolazine may lower fasting glucose and HbA1c (10,16,17). Although post hoc analyses of prior trials have suggested an antianginal benefit among patients with T2DM (10,17), this hypothesis has not been prospectively tested. Accordingly, we sought to test the efficacy of ranolazine in reducing angina among patients with T2DM, CAD, and chronic angina who remain symptomatic despite treatment with other agents.

Methods

Study overview. TERISA (Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina) was a randomized, double-blind, placebo-controlled trial in which subjects with stable angina and T2DM were randomized to twice daily placebo or ranolazine for 8 weeks (Fig. 1). The study was conducted in 14 countries across Asia, Europe, and North America, and was approved by the national regulatory authority in each participating country and by the institutional review board or local ethics committee for each site. All participating subjects gave written informed consent. The full study protocol and the list of participating sites and investigators can be found in the Online Appendix (Online Exhibit A, Online Table 1). The primary aim of the trial was to examine the efficacy of ranolazine versus placebo on weekly angina frequency in subjects with T2DM, CAD, and chronic stable angina who remain symptomatic despite treatment with 1 or 2 antianginal agents.

Abbreviations and Acronyms

CAD = coronary artery disease

late I_{Na} = late sodium current

SF-36 = Medical Outcomes Short Form-36

SL NTG = sublingual nitroglycerin

T2DM = type 2 diabetes mellitus

Patient selection. Full inclusion and exclusion criteria may be found in the Online Appendix (Online Exhibit A). Briefly, to be eligible for randomization in TERISA, subjects had to have a documented history of both T2DM and CAD, and at least a 3-month history of chronic stable angina. Subjects were further required to be treated with 1 or 2 antianginal therapies (beta-blockers, calcium-channel blockers, long-acting nitrates) at a stable dose for at least 2 weeks prior to study entry. Key exclusion criteria were New York Heart Association functional class III to IV heart failure symptoms, acute coronary syndrome in the prior 2 months, planned coronary revascularization during the study period, stroke or transient ischemic attack within 6 months prior to screening, uncontrolled hypertension, clinically significant hepatic impairment, prior treatment with ranolazine, and dialysis.

Study design. Eligible subjects entered a 4-week, single-blind placebo run-in period and were provided a novel, handheld electronic diary (LogPad LV diary, PHT Corporation, Boston, Massachusetts) (Online Fig. 1), with built-in electronic prompts for daily entry. Subjects were instructed to record and transmit the data to the coordinating center every evening, including the number of angina episodes and number of sublingual nitroglycerin (SL NTG) doses taken since the previous evening. Subjects taking >2 antianginal medications at screening were allowed to washout additional antianginal therapies 2 weeks prior to the run-in period. To be randomized at the end of the run-in period, subjects were required to meet the following criteria: 1) ≥85% adherence to daily electronic diary data entry (including angina frequency and SL NTG use) with no week with <5 days of diary use; 2) an average weekly angina frequency between 1 and 28 and at least 1 angina episode during each week; and 3) ≥80% adherence with single-blind placebo. Subjects were then randomized in a double-blind fashion to either ranolazine or placebo for 8 weeks (Online Fig. 2). Ranolazine (Gilead Sciences, Foster City, California) or matching placebo was initiated at 500 mg twice daily (bid) for 1 week and, if tolerated, increased to 1,000 mg bid (subjects taking verapamil or diltiazem were maintained on 500 mg bid of ranolazine or matching placebo). Randomization was stratified by the following: 1) average number of weekly angina episodes during trial run-in (≥1 and <3 vs. ≥3 and ≤28); 2) number of concom-

the TERISA trial; as well as research support from the American Heart Association, Medtronic Minimed, Genentech, Sanofi-Aventis and Glumetrics; and is a consultant for Gilead Sciences, Genentech, F Hoffmann-La Roche, Boehringer-Ingelheim, Medtronic Minimed, and CardioMEMS. Dr. Arnold has received research support from Gilead Sciences, unrelated to the TERISA trial; as well as research support from Genentech, Sanofi-Aventis, and Eli Lilly; and has served on the advisory board for Gilead Sciences. Dr. Spertus has received research support from Gilead Sciences, unrelated to the TERISA trial; as well as research support from NHLBI, ACCF, AHA, PCORI, Amorcyte, Genentech, and Eli Lilly; is a consultant for Gilead Sciences, Genentech, Amgen, United Healthcare (Scientific Advisory Group), and St. Jude Medical; is a board member for Health Outcomes Sciences; and holds patent for SAQ, KCCQ, PAQ, and Prism tool. Dr. McGuire is a consultant for Janssen Pharmaceuticals, Daiichi Sankyo, Pfizer, Boehringer-Ingelheim, Regeneron, Genentech, F Hoffmann-La Roche, Merck, Bristol-Myers Squibb, Tethys Biosciences, AstraZeneca, Orexigen, Eli Lilly, and Takeda. Dr. Yue, Dr. Ben Yehuda, Dr. Belardinelli, and Dr. Olmsted are employees of and own stock and stock options in Gilead Sciences. Dr. Katz has received funding support from Gilead Sciences for the conduct of the TERISA trial. Dr. Chaitman has received research support from Gilead Sciences, unrelated to the TERISA trial; as well as research support from NHLBI; serves as consultant for Gilead Sciences, Merck, Pfizer, Forest Pharmaceuticals, Takeda, Eli Lilly, Sanofi-Aventis, and Roche; is on the speaker's bureau for Gilead Sciences; and has received lecture honoraria from Gilead Sciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received February 10, 2013; revised manuscript received February 18, 2013, accepted February 19, 2013.

JACC Vol. 61, No. 20, 2013
May 21, 2013:2038–45

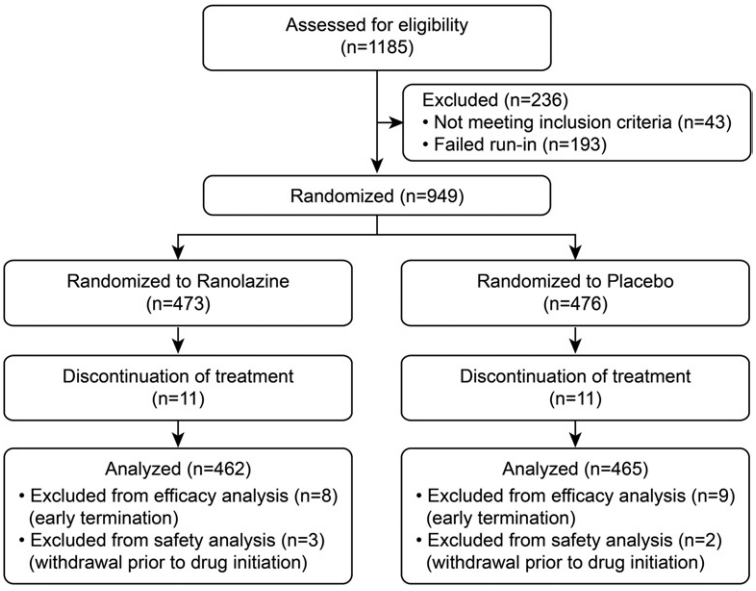

Figure 1 **Enrollment and Randomization of Patients With Type 2 Diabetes Mellitus and Stable Angina in the TERISA Trial**

Eligible subjects entered a 4-week, single-blind placebo run-in period. To be randomized, subjects were required to meet the following criteria: 1) ≥85% adherence to daily electronic diary data entry with no week with <5 days of diary use; 2) an average weekly angina frequency between 1 and 28 and at least 1 angina episode during each week; and 3) ≥80% adherence with single-blind placebo. Randomized patients who took at least 1 dose of the study drug (ranolazine or placebo) were included in the safety analyses. The efficacy analyses included all randomized subjects who took at least 14 days of the study drug, completed at least 1 diary entry, and met all major eligibility criteria.

itant antianginal agents (1 vs. 2); 3) geographic region (Russia, Ukraine, and Belarus vs. Other). The proportion of subjects being treated with 2 concomitant antianginal medications was capped at 50%, and the proportion of subjects with baseline average weekly angina frequency <3 was capped at 30%. Number and doses of concomitant antianginal medications were kept stable during the study per protocol.

Study endpoints. The primary outcome was the average number of angina episodes per week from weeks 2 to 8 of treatment. Pre-specified secondary endpoints included average weekly frequency of SL NTG use, number of angina-free days, proportion of subjects with ≥50% reduction in average weekly angina frequency, and health-related quality of life, as assessed by the Medical Outcomes Short Form-36 (SF-36) (18) and the Patient's Global Impression of Change scale score (19).

Statistical analysis. Full details of the statistical analysis plan may be found in the Online Appendix (Online Exhibit B). Assuming an average weekly angina frequency of 2.0 episodes on placebo, we estimated that a sample size of 900 subjects, randomized in a 1:1 ratio to ranolazine and placebo, would provide 90% power to show a relative reduction of 20% in weekly angina frequency with ranolazine as compared with placebo.

The pre-specified efficacy analyses included all randomized subjects who took at least 14 days of the study drug, completed at least 1 diary entry, and met all major eligibility criteria. The primary efficacy analysis comparing weekly angina frequency was performed by fitting a generalized linear model with negative binomial distribution, as was the analysis of average weekly SL NTG use. Pre-specified subset analyses included the following: 1) average number of weekly angina episodes at baseline (<3 vs. ≥3); 2) number of concomitant antianginal agents (1 vs. 2); 3) geographic region (Russia, Ukraine, and Belarus vs. Other); 4) age (<65 vs. ≥65 years); and 5) sex (male vs. female). In addition, a number of exploratory stratified analyses were performed, including history of percutaneous coronary intervention (yes vs. no); history of coronary artery bypass graft surgery (yes vs. no); and HbA1c at various thresholds.

All analyses were conducted using SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina), and statistical significance was determined by a 2-sided p value of <0.05. A pre-specified testing sequence incorporating Hochberg adjustments was used to preserve the type I error rate.

Study oversight. The study was sponsored by Gilead Sciences (Foster City, California). Statistical analysis was performed by Saint Luke's Mid America Heart Institute independent of the sponsor. The decision to submit the manuscript for publication was made by the publication committee (Online Table 2).

Results

Study population. From October 5, 2011, to July 20, 2012, 1,185 patients were screened (Fig. 1). Of these, 1,142

Table 1 Baseline Characteristics of the Patients, According to the Study Group

	Ranolazine (n = 462)	Placebo (n = 465)
Age, yrs	63.2 ± 8.5	64.2 ± 8.4
Men	283 (61.3%)	286 (61.5%)
White	456 (98.7%)	462 (99.4%)
Hypertension	438 (95.0%)	445 (95.9%)
Dyslipidemia	350 (79.4%)	355 (80.3%)
Current smoking	71 (15.4%)	77 (16.6%)
Prior myocardial infarction	346 (75.4%)	336 (72.7%)
Prior angioplasty	197 (42.7%)	180 (38.8%)
Prior bypass graft surgery	84 (18.2%)	88 (18.9%)
Duration of diabetes, yrs	7.2 ± 6.7	7.7 ± 7.0
HbA1c, %	7.3 ± 1.5	7.3 ± 1.5
Antidiabetic medication	431 (93.3%)	431 (92.7%)
Insulin	81 (17.5%)	96 (20.6%)
Antianginal medications		
On 1	259 (56.1%)	259 (55.7%)
On 2	203 (43.9%)	206 (44.3%)
Beta-blockers	418 (90.5%)	418 (89.9%)
Calcium-channel blockers	124 (26.8%)	143 (30.8%)
Long-acting nitrates	161 (34.8%)	151 (32.5%)
Statins	381 (82.5%)	383 (82.4%)
Antiplatelet agents	415 (89.8%)	402 (86.5%)
ACE-I/ARBs	407 (88.1%)	407 (87.5%)
Baseline heart rate (beats/min)	69.0 ± 8.0	70.0 ± 9.8
Baseline systolic blood pressure (mm Hg)	131.0 ± 11.0	131.0 ± 11.3
Baseline diastolic blood pressure (mm Hg)	79.0 ± 7.7	79.0 ± 7.8

Values are n mean ± SD or (%).
ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.

patients were considered trial-eligible, signed informed consent, and entered into a 4-week single-blind placebo run-in period. A total of 193 patients failed the run-in period and were excluded prior to randomization; 949 patients were randomized (473 to ranolazine, 476 to placebo). Twenty-two patients that either never initiated or discontinued the study drug during the first 2 weeks (11 in the ranolazine arm, 11 in the placebo arm) were excluded from the analysis, leaving the final analytic sample size of 927 patients (462 in the ranolazine arm, 465 in the placebo arm). The target dose of ranolazine or matching placebo (1,000 mg bid or 500 mg bid in the presence of diltiazem or verapamil) was achieved in >95% of patients.

Baseline characteristics of the randomized patients are listed in Table 1, and were well matched between groups. The mean age was 64 ± 8.5 years, 61% were male, and 99% were white. Seventy percent of subjects were enrolled in Russia, Ukraine, and Belarus, and 30% were enrolled in other countries (enrollment by country, Online Table 3). CAD risk factors were common, including hypertension (96%), dyslipidemia (80%), and smoking (16%); and the majority of patients had a previous myocardial infarction (74%) and prior revascularization (51%). Average diabetes duration was 7.5 ± 6.8 years, mean HbA1c was 7.3 ± 1.5%, and 93% of patients were treated with glucose-lowering medications, including 19% treated with insulin.

A total of 56% of patients were treated with 1 antianginal agent, with the remainder receiving 2 agents at baseline. Most patients were treated with beta-blockers (90%), with lower rates of calcium channel blocker (29%) and long-acting nitrate use (34%). The use of concomitant cardiovascular medications was high, including statins (82%), antiplatelet agents (88%), and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (88%).

Primary outcome. Compliance with electronic diary submission of patient-reported angina frequency and SL NTG was high (98% of all patient-days during weeks 2 to 8 of treatment had a diary entry, both in ranolazine and placebo arms). During the 4-week run-in phase, average weekly angina frequency was similar between the ranolazine and placebo groups (6.6 [95% confidence interval (CI): 6.27 to 7.02] episodes vs. 6.8 [95% CI: 6.42 to 7.19] episodes, p = 0.54). Though patients treated with placebo had a substantial decrease in angina frequency, weekly angina frequency was significantly lower in the ranolazine group than in the placebo group during weeks 2 to 8 after randomization (3.8 [95% CI: 3.57 to 4.05] episodes vs. 4.3 [95% CI: 4.01 to 4.52] episodes, p = 0.008) (Fig. 2A, Table 2).

Secondary outcomes. At baseline, there was no statistical difference in average weekly SL NTG use between the ranolazine and placebo groups (4.1 [3.74 to 4.60] vs. 4.5 [4.05 to 4.98] doses, p = 0.27). During weeks 2 to 8 after randomization, the average weekly number of SL NTG doses was significantly lower in the ranolazine group (Fig. 2B), and was significantly lower in the ranolazine group than in the placebo group (1.7 [95% CI: 1.58 to 1.92] vs. 2.1 [95% CI: 1.92 to 2.31] doses, p = 0.003) (Fig. 2B, Table 2).

During weeks 2 to 8 after randomization, the proportion of angina-free days did not differ between the ranolazine and placebo groups (67% vs. 64%, p = 0.068) (Table 2). The proportion of patients achieving at least 50% reduction in weekly angina frequency was higher in the ranolazine than placebo group (47% vs. 42%, p = 0.034), and the increase from baseline to end of treatment in SF-36 Physical Component Summary Score was also greater in the ranolazine than placebo group (2.9 [95% CI: 2.3 to 3.5] points vs. 1.9 [95% CI: 1.3 to 2.5] points, p = 0.005). However, these latter 2 differences were not considered statistically significant (despite p values <0.05) based on the pre-specified multiple testing procedure. There was no difference between the ranolazine and placebo groups in the change in SF-36 Mental Component Score (1.0 [95% CI: 0.18 to 1.82] points vs. 1.1 [95% CI: 0.28 to 1.92] points, p = 0.77) or in the Patient's Global Impression of Change scale score at end of treatment (4.0 [95% CI: 3.82 to 4.19] vs. 3.9 [95% CI: 3.74 to 4.10], p = 0.41).

Subgroup analyses. The results of subgroup analyses are presented in Figures 3A and 3B. The superior efficacy of ranolazine versus placebo on the primary endpoint was consistent in the pre-specified subgroups of baseline average

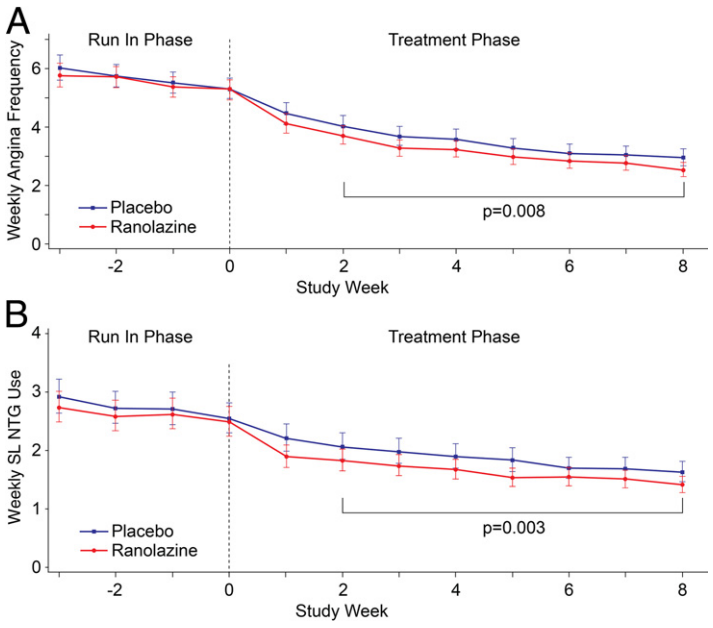

Figure 2 **Weekly Angina Frequency and Use of SL NTG, by Study Group**

Average weekly angina frequency **(A)** and sublingual nitroglycerin (SL NTG) use **(B)** by study group, as recorded in the electronic diary. The run-in phase refers to the 4-week, single-blind, placebo phase. Randomization occurred at week 4 **(dashed line)**, after which subjects entered a double-blind treatment phase. Ranolazine or matching placebo was initiated at 500 mg bid for 1 week and, if tolerated, increased to a 1,000 mg bid with ranolazine or matching placebo. The primary outcome was weekly angina frequency during weeks 2 to 8 of the treatment phase. Weekly SL NTG use during weeks 2 to 8 was the key secondary outcome. The geometric means and 95% confidence intervals are plotted due to skewed distributions.

weekly angina episodes (<3 vs. ≥3; $p_{interaction}$ = 0.85), number of concomitant antianginal medications (1 vs. 2; $p_{interaction}$ = 0.89), age (<65 vs. ≥65; $p_{interaction}$ = 0.97), and sex ($p_{interaction}$ = 0.46). There was a significant interaction in the effect of ranolazine versus placebo on the primary endpoint by the geographic region of enrollment (Russia, Ukraine and Belarus vs. Other; $p_{interaction}$ = 0.016). Baseline characteristics by enrollment region stratified by randomized treatment assignment are presented in Online Table 4. The average number of weekly angina episodes during the treatment phase decreased significantly in both treatment groups (Online Fig. 3), but was not statistically different between the ranolazine and placebo arms among patients enrolled in Russia, Ukraine, and Belarus (4.1 [95% CI: 3.9 to 4.4] vs. 4.3 [95% CI: 4.1 to 4.6], p = 0.31). However, among patients enrolled in other countries, those treated with ranolazine experienced a significant reduction in average weekly angina episodes as compared with placebo-treated patients (3.1 [95% CI: 2.8 to 3.5] vs. 4.1 [95% CI: 3.7 to 4.6], p = 0.002) (Online Fig. 3).

In exploratory analyses, the greater therapeutic benefit of ranolazine versus placebo was consistent across revascularization subgroups (Fig. 3A). However, the therapeutic superiority of ranolazine versus placebo on reducing weekly angina frequency was more pronounced in patients with higher baseline HbA1c, regardless of the HbA1c threshold used ($p_{interaction}$ = 0.027) (Fig. 3B).

Safety. There was no difference in the incidence of serious adverse events between groups (Table 2). Of the 20 subjects discontinued from the study due to adverse events, 9 were in the ranolazine group and 11 were in the placebo group. Five subjects died during the study, 3 in the ranolazine group (2 myocardial infarctions and 1 sudden cardiac death) and 2 in the placebo group (1 acute cardiac failure and 1 pulmonary embolism). Nonserious adverse events of nausea, dizziness, and constipation occurred more frequently with ranolazine compared with placebo.

Discussion

In this trial of patients with T2DM, established CAD, and stable angina, ranolazine was more effective than placebo in reducing the primary outcome of average weekly angina episodes, as well as average weekly sublingual nitroglycerin use. These results were consistent across the subgroups of baseline average weekly angina episodes, number of concomitant antianginal medications, age, and sex. The therapeutic benefit of ranolazine versus placebo was greater among patients enrolled outside of Russia, Ukraine, and Belarus, and among those with higher baseline HbA1c. In addition, ranolazine was safe and well tolerated in this patient population.

While patients with T2DM and CAD have more extensive disease (7,8) and worse outcomes (20,21) than those

Table 2 Clinical Outcomes

	Ranolazine	Placebo	p Value
Efficacy endpoints*	n = 462	n = 465	
Primary endpoint			
Angina frequency, baseline, n/week	6.6 (6.3–7.0)	6.8 (6.4–7.2)	0.54
Angina frequency, on treatment, n/week	3.8 (3.6–4.1)	4.3 (4.0–4.5)	0.008
Secondary endpoints			
SL NTG use, baseline, n/week	4.1 (3.7–4.6)	4.5 (4.1–5.0)	0.27
SL NTG use, on treatment, n/week	1.7 (1.6–1.9)	2.1 (1.9–2.3)	0.003
Percentage of angina-free days, %	67 (65–70)	64 (61–67)	0.068
Subjects with ≥50% reduction in angina episodes, %	47 (43–51)	42 (38–46)	0.034
SF-36 mental component score, change from baseline	1.0 (0.2–1.8)	1.1 (0.3–1.9)	0.77
SF-36 physical component score, change from baseline	2.9 (2.3–3.5)	1.9 (1.3–2.5)	0.005
PGIC scale score	4.0 (3.8–4.2)	3.9 (3.7–4.1)	0.41
Diary compliance, %	98 (95–98)	98 (95–98)	0.46
Safety endpoints*	n = 470	n = 474	
Serious adverse events			
Serious adverse event	16 (3.4)	20 (4.2)	0.51
Death	3 (0.6)	2 (0.4)	0.69
Nonfatal myocardial infarction	1 (0.2)	3 (0.6)	0.62
Stroke/transient ischemic attack	1 (0.2)	4 (0.8)	0.37
Unstable angina or coronary revascularization	6 (1.3)	7 (1.5)	0.79
Notable nonserious adverse events			
Dizziness	17 (3.6)	6 (1.3)	0.019
Nausea	17 (3.6)	2 (0.4)	<0.001
Headache	7 (1.5)	9 (1.9)	0.63
Constipation	8 (1.7)	2 (0.4)	0.063
Hypoglycemia	3 (0.6)	0 (0.0)	0.12
Any adverse event	126 (26.8)	105 (22.2)	0.096

Values are least-squares mean (95% confidence interval), n (%), or median (interquartile range) (arithmetic means for angina frequency and SL NTG use are presented in Online Table 5). *Analytic sample for the safety dataset includes patients who took any dose of the study drug whereas analytic sample for the efficacy dataset includes patients who completed 14 days of the study drug.

PGIC = Patient's Global Impression of Change; SF-36 = Medical Outcomes Short Form-36; SL NTG = sublingual nitroglycerin.

without DM, the data on whether they experience more angina are conflicting. Several older studies suggested that patients with DM have less angina than their non-DM counterparts due to an increased likelihood of "silent" ischemia related to diabetic autonomic neuropathy (22–24). However, both a recent observational study and a multinational clinical trial demonstrated that patients with DM experienced a higher burden of angina compared with patients without DM after an acute coronary syndrome (9,10). Given the high prevalence of angina in patients with DM, as well as its relationship with worse health-related quality of life (2,3), greater risk of repeat hospitalizations, and increased healthcare costs (4), effective therapeutic strategies for angina management in this patient group are clinically important.

To our knowledge, the TERISA trial is the first randomized clinical trial to study antianginal medical therapy (ranolazine or otherwise) specifically in patients with T2DM—a high-risk and therapeutically challenging group. A post hoc analysis of the CARISA (Combination Assessment of Ranolazine in Stable Angina) randomized trial that evaluated ranolazine versus placebo among patients with stable angina showed that ranolazine decreased angina frequency to a similar degree in patients with and without T2DM (17). Moreover, a subgroup analysis of the MERLIN−TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndromes−Thrombolysis In Myocardial Infarction 36) study of subjects following acute coronary syndromes suggested a trend toward greater therapeutic benefit of ranolazine versus placebo in reducing recurrent ischemia among patients with T2DM than those without T2DM (10). Although these observational analyses suggested an antianginal benefit of ranolazine in patients with T2DM, this hypothesis has not been prospectively tested until now. By specifically focusing on patients with T2DM in a prospective, randomized clinical trial, the TERISA trial establishes, for the first time, the therapeutic effectiveness of ranolazine in this patient population.

The subgroup analyses of the TERISA trial produced intriguing findings, particularly the greater efficacy of ranolazine versus placebo among patients with higher HbA1c. The mechanisms underlying this finding remain to be determined. There is, however, evidence that cardiomyocytes exposed ex vivo to high glucose, or isolated from hearts of diabetic animals have up-regulated phosphorylated CaMKII (25), a kinase known to phosphorylate the cardiac sodium channel resulting in an increased late I_{Na} (26),

JACC Vol. 61, No. 20, 2013
May 21, 2013:2038–45

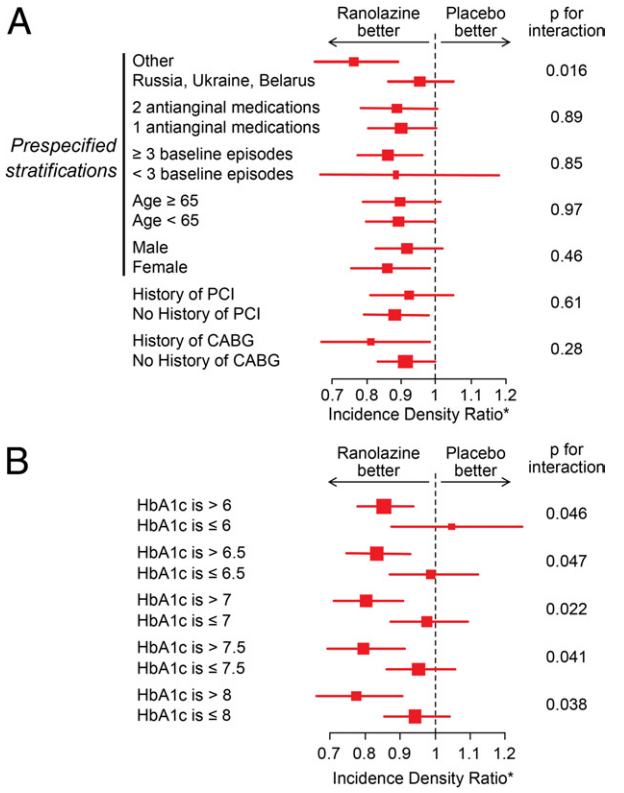

Figure 3 **Subgroup Analyses of the Primary Endpoint of Weekly Angina Frequency**

Incidence density ratio (*) (or the relative difference in the incidence rates) of weekly angina frequency, according to the generalized linear model with negative binomial distribution, within pre-specified stratifications and categorical subgroups **(A)**. **B** shows the exploratory analysis of subgroups of HbA1c by various thresholds. CABG = coronary artery bypass graft surgery; PCI = percutaneous coronary intervention.

thereby leading to increases in intracellular sodium and calcium (27). Ranolazine, an inhibitor of late I_{Na} (11), would then be expected to have a greater therapeutic effect in patients with poor glycemic control. Alternative explanations for this observation may also exist. Beyond its antianginal benefit, ranolazine may also lower HbA1c, particularly among patients with suboptimal glucose control (16,17). Hyperglycemia may worsen myocardial perfusion through microvascular and endothelial dysfunction, enhanced platelet aggregation and prothrombotic state, and increased oxidative stress—detrimental effects that may be reduced with better glucose control (28). Ranolazine's antianginal effect mediated through inhibition of late I_{Na} may, therefore, be potentiated by its glucose-lowering properties through some of these mechanisms. However, because glucose-lowering per se has never been shown to improve angina, this mechanism is a less plausible one. Regardless of the underlying physiology, these findings, if confirmed in future clinical trials, would suggest that T2DM patients with angina and suboptimal glucose control may receive greater benefit from ranolazine therapy—both in terms of its antianginal and glucose-lowering effects.

We also observed a difference in the therapeutic effectiveness of ranolazine among patients enrolled in Russia, Ukraine, and Belarus versus other countries. Preliminary analyses have determined that this observation was driven primarily by several sites located in Russia and was not explained by differences in baseline characteristics between geographic regions. The underlying reasons behind this finding remain uncertain and will be investigated in future detailed analyses.

The TERISA study has several strengths. The design of the study, including the single-blind placebo run-in period, ensured high angina frequency at baseline and compliance with the study medication and self-reporting of outcomes among the study patients. It also allowed appropriate accounting for the marked placebo effect, which is of critical importance in clinical trials of antianginal agents. Prior antianginal trials often compared on-treatment angina frequency to a baseline value without a parallel placebo group (29–31). The primary endpoint of the TERISA trial (patient-reported angina frequency) was both patient-centered and clinically meaningful. Other studies, even when showing a reduction in intermediate measures of angina (e.g., time to limiting angina on exercise testing), failed to demonstrate a reduction in angina frequency (32,33). Additionally, we used a novel electronic diary instrument (Online Fig. 2) to record patient-reported angina and SL NTG use, with outstanding compliance. Studies using traditional paper diaries are often limited by inappropriate input of multiple entries in a single sitting (so-called "hoarding") and low subject compliance (as low as 11% in 1 study) (34). Our successful use of the electronic diary should inform the design of future clinical studies that evaluate patient-reported outcomes. Finally, the use of concomitant medical therapy for CAD, such as antiplatelet agents, antihypertensive medications, and statins, was high in both treatment groups.

Study limitations. The results of this study should be interpreted in the context of several potential limitations. Most of the subjects were enrolled in European centers, thereby limiting inclusion of a racially diverse study population. More data are needed on the effect of ranolazine among blacks, Hispanics, and Asians. In addition, several of the subgroup analyses were not pre-specified and should be regarded as exploratory and hypothesis-generating. Specifically, while the findings of greater ranolazine efficacy in patients with higher HbA1c were adjusted for several key factors (including geographic region), a possibility of residual confounding cannot be definitively ruled out. Finally, the relatively short duration of treatment in the TERISA trial limits our ability to know the durability of the observed antianginal effect of ranolazine; however, prior studies have demonstrated this effect to persist for at least 12 months (35).

Conclusions

Among patients with T2DM, CAD, and persistent chronic angina, despite treatment with up to 2 antianginal agents, ranolazine significantly reduced angina frequency and SL NTG use and was safe and well tolerated.

Reprint requests and correspondence: Dr. Mikhail Kosiborod, Saint Luke's Mid America Heart Institute, 4401 Wornall Road, Kansas City, Missouri 64111. E-mail: mkosiborod@saint-lukes.org.

REFERENCES

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. Circulation 2013;127:e6–245.
2. Brown N, Melville M, Gray D, et al. Quality of life four years after acute myocardial infarction: short form 36 scores compared with a normal population. Heart 1999;81:352–8.
3. Brorsson B, Bernstein SJ, Brook RH, Werko L. Quality of life of patients with chronic stable angina before and four years after coronary revascularisation compared with a normal population. Heart 2002;87:140–5.
4. Arnold SV, Morrow DA, Lei Y, et al. Economic impact of angina after an acute coronary syndrome: insights from the MERLIN-TIMI 36 trial. Circ Cardiovasc Qual Outcomes 2009;2:344–53.
5. Beltrame JF, Weekes AJ, Morgan C, Tavella R, Spertus JA. The prevalence of weekly angina among patients with chronic stable angina in primary care practices: the Coronary Artery Disease in General Practice (CADENCE) study. Arch Intern Med 2009;169:1491–9.
6. Maddox TM, Reid KJ, Spertus JA, et al. Angina at 1 year after myocardial infarction: prevalence and associated findings. Arch Intern Med 2008;168:1310–6.
7. Duarte R, Castela S, Reis RP, et al. Acute coronary syndrome in a diabetic population—risk factors and clinical and angiographic characteristics. Rev Port Cardiol 2003;22:1077–88.
8. Herlitz J, Wognsen GB, Emanuelsson H, et al. Mortality and morbidity in diabetic and nondiabetic patients during a 2-year period after coronary artery bypass grafting. Diabetes Care 1996;19:698–703.
9. Peterson PN, Spertus JA, Magid DJ, et al. The impact of diabetes on one-year health status outcomes following acute coronary syndromes. BMC Cardiovasc Disord 2006;6:41.
10. Morrow DA, Scirica BM, Chaitman BR, et al. Evaluation of the glycometabolic effects of ranolazine in patients with and without diabetes mellitus in the MERLIN-TIMI 36 randomized controlled trial. Circulation 2009;119:2032–9.
11. Antzelevitch C, Belardinelli L, Zygmunt AC, et al. Electrophysiological effects of ranolazine, a novel antianginal agent with antiarrhythmic properties. Circulation 2004;110:904–10.
12. 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.
13. Rousseau MF, Pouleur H, Cocco G, Wolff AA. Comparative efficacy of ranolazine versus atenolol for chronic angina pectoris. Am J Cardiol 2005;95:311–6.
14. 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.
15. Stone PH, Gratsiansky NA, Blokhin A, Huang IZ, Meng L. Antianginal efficacy of ranolazine when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine in Chronic Angina) trial. J Am Coll Cardiol 2006;48:566–75.
16. Chisholm JW, Goldfine AB, Dhalla AK, et al. Effect of ranolazine on A1C and glucose levels in hyperglycemic patients with non-ST elevation acute coronary syndrome. Diabetes Care 2010;33:1163–8.
17. Timmis AD, Chaitman BR, Crager M. Effects of ranolazine on exercise tolerance and HbA1c in patients with chronic angina and diabetes. Eur Heart J 2006;27:42–8.
18. Ware JE Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–83.
19. Guy W. ECDEU Assessment Manual for Psychopharmacology (DHEW Publication No. ADM 76–338). Washington, DC: U.S. Government Printing Office, 1976.
20. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229–34.
21. Donahoe SM, Stewart GC, McCabe CH, et al. Diabetes and mortality following acute coronary syndromes. JAMA 2007;298:765–75.
22. Marchant B, Umachandran V, Stevenson R, Kopelman PG, Timmis AD. Silent myocardial ischemia: role of subclinical neuropathy in patients with and without diabetes. J Am Coll Cardiol 1993;22:1433–7.
23. Murray DP, O'Brien T, Mulrooney R, O'Sullivan DJ. Autonomic dysfunction and silent myocardial ischaemia on exercise testing in diabetes mellitus. Diabet Med 1990;7:580–4.
24. Chiariello M, Indolfi C, Cotecchia MR, Sifola C, Romano M, Condorelli M. Asymptomatic transient ST changes during ambulatory ECG monitoring in diabetic patients. Am Heart J 1985;110:529–34.
25. Nishio S, Teshima Y, Takahashi N, et al. Activation of CaMKII as a key regulator of reactive oxygen species production in diabetic rat heart. J Mol Cell Cardiol 2012;52:1103–11.
26. Koval OM, Snyder JS, Wolf RM, et al. Ca2+/calmodulin-dependent protein kinase II-based regulation of voltage-gated Na+ channel in cardiac disease. Circulation 2012;126:2084–94.
27. Yao L, Fan P, Jiang Z, et al. Nav1.5-dependent persistent Na+ influx activates CaMKII in rat ventricular myocytes and N1325S mice. Am J Physiol Cell Physiol 2011;301:C577–86.
28. Deedwania P, Kosiborod M, Barrett E, et al. Hyperglycemia and acute coronary syndrome: a scientific statement from the American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation 2008;117:1610–9.
29. Jackson G, Schwartz J, Kates RE, Winchester M, Harrison DC. Atenolol: once-daily cardioselective beta blockade for angina pectoris. Circulation 1980;61:555–60.
30. Weiss R, Ferry D, Pickering E, et al. Effectiveness of three different doses of carvedilol for exertional angina. Carvedilol-Angina Study Group. Am J Cardiol 1998;82:927–31.
31. Estrada JN, Saglietti H, Di Marco M, Casabe H, Oliveri R. Antiischemic properties of amlodipine, a new calcium antagonist, in patients with severe coronary artery disease: a prospective trial. Am Heart J 1989;118:1130–2.
32. Tardif JC, Ponikowski P, Kahan T. Efficacy of the I(f) current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial. Eur Heart J 2009;30:540–8.
33. Frishman WH, Heiman M. Usefulness of oral nisoldipine for stable angina pectoris. The Nisoldipine Multicenter Angina Study Group. Am J Cardiol 1991;68:1004–9.
34. Stone AA, Shiffman S, Schwartz JE, Broderick JE, Hufford MR. Patient non-compliance with paper diaries. BMJ 2002;324:1193–4.
35. Arnold SV, Morrow DA, Wang K, et al. Effects of ranolazine on disease-specific health status and quality of life among patients with acute coronary syndromes: results from the MERLIN-TIMI 36 randomized trial. Circ Cardiovasc Qual Outcomes 2008;1:107–15.

Key Words: clinical trial ■ coronary artery disease ■ diabetes ■ ranolazine ■ stable angina.

APPENDIX

For Exhibit A and B and supplemental tables and figures, please see the online version of this article.