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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)

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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)

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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.

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