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Efficacy of Ranolazine in Patients With Chronic Angina

Observations From the Randomized, Double-Blind, Placebo-Controlled MERLIN–TIMI (Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Segment Elevation Acute Coronary Syndromes) 36 Trial

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Objectives We aimed to evaluate the efficacy and safety of ranolazine in a larger and more diverse group of patients with angina than previously studied.

Background Ranolazine is an antianginal shown to reduce angina and improve exercise performance in selected patients with early-positive exercise testing and those with frequent angina.

Methods We investigated the antianginal effects of ranolazine in the subgroup of patients with prior chronic angina (n = 3,565, 54%) enrolled in the randomized, double-blind, placebo-controlled MERLIN–TIMI (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndromes) 36 trial of patients with acute coronary syndrome. Follow-up was a median of 350 days.

Results Patients with prior angina received evidence-based therapy (95% aspirin, 78% statins, 89% beta-blockers, average 2.9 antianginal agents). The primary end point (cardiovascular death, myocardial infarction, recurrent ischemia) was less frequent with ranolazine (hazard ratio [HR]: 0.86; 95% confidence interval [CI]: 0.75 to 0.97; p = 0.017), due entirely to a significant reduction in recurrent ischemia (HR: 0.78; 95% CI: 0.67 to 0.91; p = 0.002). Ranolazine also reduced worsening angina (HR: 0.77; 95% CI: 0.59 to 1.00; p = 0.048) and intensification of antianginal therapy (HR: 0.77; 95% CI: 0.64 to 0.92, p = 0.005). Exercise duration at 8 months was greater with ranolazine (514 s vs. 482 s, p = 0.002). Cardiovascular death or myocardial infarction did not differ between treatment groups (HR: 0.97; 95% CI: 0.80 to 1.16; p = 0.71). Symptomatic documented arrhythmias (2.9% vs. 2.9%, p = 0.92) and total mortality (6.2% vs. 6.4%, p = 0.96) were similar with ranolazine or placebo.

Conclusions In this largest study of ranolazine in patients with established coronary artery disease, ranolazine was effective in reducing angina with favorable safety in a substantially broader group of patients with angina than previously studied. (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndromes; NCT00099788) (J Am Coll Cardiol 2009;53:1510–6) © 2009 by the American College of Cardiology Foundation

Chronic angina impairs functional capacity and quality of life and is associated with decreased economic productivity (1–4). Despite the aggressive use of medical therapies and myocardial revascularization procedures, angina remains highly prevalent, affecting an estimated 9.1 million individuals in the U.S. alone (5,6). This high prevalence is due in part to the increasing burden of atherosclerosis in industrialized regions and in part to limitations of available antianginal agents. Moreover, the

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incidence and prevalence of patients with angina is anticipated to increase in the coming decade as a result of the aging of the population, the worsening epidemic of obesity, and the greater use of life-prolonging therapies (5,7).

Ranolazine, the first member of a new class of medications approved in the U.S. in 2006 for the treatment of angina, is a piperazine derivative that seems to exert its anti-ischemic effects through antagonism of the late phase of the inward sodium current that is increased in myocardial ischemia and contributes to detrimental cellular sodium and calcium overload (8–12). Ranolazine was studied as monotherapy in 175 patients with exercise-limiting angina and significant ST-segment depression between 3 and 9 min on an exercise tolerance test (ETT) using the modified Bruce protocol (13). Ranolazine was also tested in combination with other antianginal agents in 791 patients meeting the same ETT criteria (14) and in 565 patients with at least 3 episodes of angina/week on the maximum dose of amlodipine (15). Together, this experience in approximately 1,500 selected patients with chronic angina showed that ranolazine improved exercise performance and reduced angina frequency and the use of sublingual nitroglycerin. Ranolazine had not yet been studied in a more diverse population of patients with chronic angina.

Therefore, we performed a pre-specified analysis of the antianginal efficacy and safety of ranolazine in the subgroup of 3,565 patients with a history of chronic angina who presented with an acute coronary syndrome (ACS) and were enrolled in the MERLIN–TIMI (Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-Segment Elevation Acute Coronary Syndromes) 36 trial (16).

Methods

Patient population. The MERLIN–TIMI 36 trial was a multinational, randomized, double-blind, placebo-controlled parallel group trial of ranolazine in patients with a non–ST-segment elevation ACS. The design and primary results of the trial have been published previously (16,17). Study patients had a clinical presentation consistent with an ACS with at least 1 indicator of moderate to high risk of death or recurrent ischemic events. All patients were assessed for a history of prior stable angina before and separate from the presenting ACS, and the information was collected on the case report form. In addition, the severity of angina at 1 month before randomization was classified with the Canadian Cardiovascular Society classification (CCSC) system. Timing of the most recent revascularization procedure and history of known stenosis >50% were also recorded. Exclusion criteria included clinically significant hepatic disease, end-stage renal disease requiring dialysis, treatment with agents known to prolong the QT interval, cardiogenic shock, persistent ST-segment elevation, or a life-expectancy <12 months.

Abbreviations and Acronyms

ACS = acute coronary syndrome
CAD = coronary artery disease
CCSC = Canadian Cardiovascular Society classification
CI = confidence interval
ETT = exercise tolerance test
HR = hazard ratio
MI = myocardial infarction
PCI = percutaneous coronary intervention

Study protocol. Patients were randomized in a 1:1 ratio to receive intravenous ranolazine followed by oral ranolazine or matching placebo. After 12 to 96 h of the intravenous formulation, study medication (ranolazine extended-release or placebo) was to be continued orally at a dose of 1,000 mg twice daily until the end of the study. Individuals with renal insufficiency (estimated creatinine clearance <30 ml/min) received 500 mg twice daily. In addition, protocol-defined dose reductions were made for subjects with persistent and profound prolongation of the QT interval or specific adverse events potentially related to study drug, including nausea, dizziness, or orthostatic hypotension. Individuals received standard medical and interventional therapy as dictated by local practice guidelines.

End points. The primary efficacy end point of the trial was the first occurrence of any element of the composite of cardiovascular death, myocardial infarction (MI), or recurrent ischemia. The definition of MI has been reported in detail (17). Recurrent ischemia was pre-specified as any of the following: 1) recurrent ischemia with electrocardiographic changes; 2) recurrent ischemia leading to hospital stay; 3) recurrent ischemia prompting revascularization; and 4) worsening angina/ischemia requiring additional therapy as defined by an increase in angina to a higher CCSC requiring new or increasing doses of antianginal medications in response to the symptom change. End points specifically designed to assess the efficacy of ranolazine as antianginal therapy included worsening angina as defined in the preceding text, the need for an increase or addition of any antianginal therapy, and exercise duration on treadmill or bicycle ETT performed at 8 months (or final visit, whichever was sooner). All elements of the primary efficacy end point as well as symptomatic documented arrhythmia were adjudicated by a blinded clinical events committee. The ETT results were interpreted by a core laboratory (St. Louis, Missouri) blinded to treatment allocation and outcomes. As part of an efficacy and safety analysis, all patients had a continuous electrocardiographic recording (Lifecard CF, DelMar Reynolds/Spacelabs, Issaquah, Washington) performed during the first 7 days after randomization. Holter recordings were interpretable in 97% of subjects with a median duration of 6.8 days (17). Recordings were evaluated in the Thrombolysis In Myocardial Infarction Core Laboratory by reviewers blinded to treatment assignment and clinical outcome. The incidence of clinically significant arrhythmias detected on Holter monitoring was pre-specified as an episode of ventricular tachycardia of at least 100 beats/min for 3 or more beats, supraventricular

tachycardia of at least 120 beats/min for 4 or more beats, bradycardia of <45 beats/min for 4 or more beats, pauses of more than 2.5 s, or third-degree heart block (17).

Statistical analysis. These analyses were planned exploratory analyses of efficacy and safety included in the statistical analysis plan that was finalized before locking the trial database. Baseline characteristics were compared with the chi-square test for categorical variables and the *t* test for continuous variables. All comparisons of elements of the primary efficacy end point were performed with the log-rank test conducted according to the intention-to-treat principle. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated with a Cox proportional-hazards regression model. Event rates are presented as Kaplan-Meier failure rates at 12 months. A landmark analysis was also conducted to evaluate the effect of ranolazine starting from 30 days to end of study. Analyses of safety were conducted in the safety cohort defined as those who received at least 1 dose of study drug.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the paper as written.

Results

Of the 6,560 patients enrolled in the trial, 3,565 (54%) had a history of prior chronic angina. The presenting characteristics of those with and without prior angina are provided in Online Table 1A. The presenting characteristics of those with prior angina, who comprised the cohort for this analysis, were well-balanced between the randomized treatment groups (Table 1). The mean duration of chronic angina was 5.2 years. The majority of patients were in CCSC class 2 (41%), with 32% reporting more severe anginal symptoms (CCSC score ≥3) at 1 month before study entry (Table 1). Evidence-based therapies for secondary prevention were used in a high proportion of the population, including aspirin in 95%, beta-blockers in 89%, and statins in 78%, and were similarly balanced between the ranolazine and placebo groups. More than one-third of patients had a history of prior revascularization (Table 1). Of those in whom the timing of prior revascularization was known (n = 866), 448 underwent percutaneous coronary intervention (PCI) in the prior 24 months, of which 315 had PCI performed in the past 12 months before study

Table 1 Baseline Characteristics of Patients With Prior Chronic Angina by Randomized Treatment Group

Characteristics	Ranolazine (n = 1,789)	Placebo (n = 1,776)	p Value
Age, yrs, median (25th, 75th)	65 (57, 73)	66 (56, 73)	0.98
Age ≥75 yrs	334/1,789 (18.7)	346/1,776 (19.5)	0.54
Female sex	640/1,789 (35.8)	693/1,776 (39.0)	0.045
White race	1,689/1,789 (94.4)	1,697/1,776 (95.6)	0.12
Weight, kg, median (25th, 75th)	80 (72, 91)	80 (71, 91)	0.40
Risk factors for atherosclerosis			
Diabetes mellitus	660/1,789 (36.9)	689/1,776 (38.8)	0.24
Hypertension	1,469/1,781 (82.5)	1,461/1,764 (82.8)	0.79
Hyperlipidemia	1,209/1,630 (74.2)	1,199/1,601 (74.9)	0.64
Current smoker	384/1,788 (21.5)	367/1,776 (20.7)	0.55
Cardiac history			
Prior MI	801/1,769 (45.3)	756/1,756 (43.1)	0.18
Prior heart failure	460/1,789 (25.7)	464/1,776 (26.1)	0.78
Prior coronary revascularization (PCI or CABG)	624/1,789 (34.9)	566/1,775 (31.9)	0.058
Prior known stenosis >50%	672/768 (87.5)	667/744 (89.7)	0.19
CCSC at 1 month before enrollment			
0–I	491/1,766 (27.8)	431/1,750 (24.6)	0.011
II	743/1,766 (42.1)	715/1,750 (40.9)	
III–IV	532/1,766 (30.1)	604/1,750 (34.5)	
Estimated creatinine clearance <60 ml/min*	425/1,784 (23.8)	436/1,769 (24.6)	0.57
Coronary angiography during the index hospital stay	893/1,789 (49.9)	853/1,776 (48.0)	0.26
Cardiac medications during index hospital stay and/or discharge			
Aspirin	1,707/1,789 (95.4)	1,691/1,776 (95.2)	0.77
Thienopyridine	988/1,789 (55.2)	984/1,776 (55.4)	0.91
Beta-blocker	1,575/1,789 (88.0)	1,598/1,776 (90.0)	0.064
Calcium-channel blocker†	544/1,789 (30.4)	570/1,776 (32.1)	0.28
Long acting nitrate†	728/1,789 (40.7)	747/1,776 (42.1)	0.41
ACE inhibitor or angiotensin II receptor blocker	1,426/1,789 (79.7)	1,462/1,776 (82.3)	0.047
Statin	1,403/1,789 (78.4)	1,362/1,776 (76.7)	0.21

Data are expressed as n/total (%) unless otherwise specified. Systeme International unit conversion: to convert creatinine clearance to ml/s, multiply by 0.0167. *Estimated with Cockroft-Gault equation; †at discharge.

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; CCSC = Canadian Cardiovascular Society classification; MI = myocardial infarction; PCI = percutaneous coronary intervention.

entry. Coronary angiography was also undertaken in 49% of patients during the index hospital stay. The median duration of follow-up was 350 days (25th, 75th percentiles: 237, 460). Only 5 patients (0.14%) with prior angina were lost to follow-up. The mean number of antianginal agents administered at hospital discharge to patients with prior angina was 1.9 with no difference between treatment groups (p = 0.20). A calcium-channel blocker or nitrate was administered in 58% of patients. Over the entire duration of follow-up, the mean number of antianginals used/patient was 2.9, with 67.5% of patients treated with 2 or more medication classes.

Efficacy of ranolazine as antianginal therapy. Among patients with prior angina, the primary end point (cardiovascular death, MI, or recurrent ischemia) was lower in patients treated with ranolazine compared with placebo (25.2% vs. 29.4%, HR: 0.86; 95% CI: 0.75 to 0.97; p = 0.017); however, this effect was driven entirely by the impact of ranolazine on recurrent ischemia. Ranolazine had no effect on the risk of cardiovascular death or MI in the patients with prior angina (HR: 0.97; 95% CI: 0.80 to 1.16, p = 0.71), consistent with the result in the overall cohort (16). In contrast, ranolazine significantly reduced the incidence of each of the major end points with respect to its antianginal efficacy (Fig. 1). Specifically, compared with placebo, ranolazine reduced the incidence of recurrent ischemia (HR: 0.78; 95% CI: 0.67 to 0.91; p = 0.002), worsening angina (HR: 0.77; 95% CI: 0.59 to 1.00; p = 0.048), and intensification of antianginal therapy (HR: 0.77; 95% CI: 0.64 to 0.92, p = 0.005). Moreover, in those with prior angina, ranolazine also improved severe recurrent ischemia, defined as ischemia associated with new electrocardiographic changes or leading to hospital stay or revascularization (11.9% vs. 14.4%; HR: 0.81; 95% CI: 0.67 to 0.98; p = 0.026) (Table 2). Notably, in patients without prior angina, there was no detectable benefit of ranolazine with respect to recurrent ischemia (HR: 1.03; 95% CI: 0.81 to 1.29, p = 0.83).

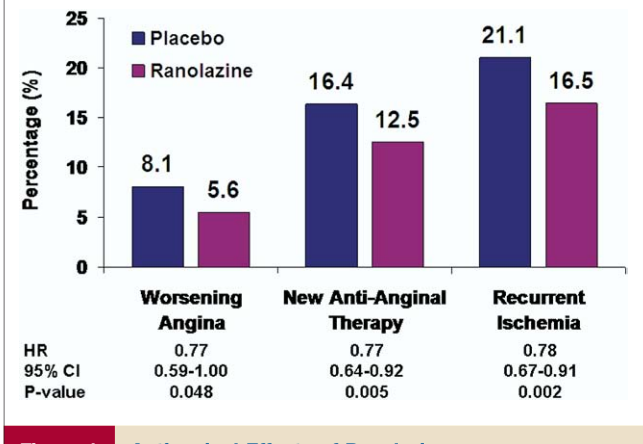

Figure 1 Antianginal Effects of Ranolazine

Effect of ranolazine compared with placebo on angina and recurrent ischemia in patients with a history of chronic angina who have presented with an acute coronary syndrome. CI = confidence interval; HR = hazard ratio.

This effect of ranolazine on the primary end point and recurrent ischemia was consistent in patients with prior angina who were treated with an early invasive management strategy (n = 1,184; HR: 0.75; 95% CI: 0.60 to 0.94; p = 0.013; and HR: 0.71; 95% CI: 0.54 to 0.94; p = 0.015, respectively). Also, when the analysis was restricted to patients with a history of moderate or more severe angina (CCSC 2 to 4) 1 month before enrollment (n = 2,594), the effect of ranolazine remained apparent with respect to the primary composite end point (HR: 0.83; 95% CI: 0.72 to 0.97; p = 0.016) and recurrent ischemia (HR: 0.75; 95% CI: 0.63 to 0.91; p = 0.0026).

The number of classes of traditional antianginal drugs used/subject was shifted slightly toward fewer with ranolazine (p = 0.004) such that 65% of patients assigned to ranolazine received 2 or more classes compared with 70% of those allocated to placebo. The mean number of traditional antianginal agents across all visits was decreased, albeit modestly, in patients treated with ranolazine (2.8 vs. 2.9, p = 0.045).

In a landmark analysis conducted to evaluate the chronic effect of ranolazine after the first 30 days, ranolazine reduced the incidence of recurrent ischemia (HR: 0.80; 95% CI: 0.67 to 0.96; p = 0.015), worsening angina (HR: 0.76; 95% CI: 0.58 to 0.99; p = 0.044), and intensification of other antianginal therapy (HR: 0.77; 95% CI: 0.64 to 0.93; p = 0.007) (Table 2). In addition, when evaluated at 8 months (or the final visit if sooner), ranolazine significantly improved all metrics of exercise performance on ETT or bicycle exercise testing (Table 3). Exercise duration (least squares mean ± SEM) was 514 ± 7 s with ranolazine, compared with 482 ± 7 s with placebo (p = 0.002). A treatment effect was also observed for the time to onset of angina: 508 ± 7 s in the ranolazine group versus 477 ± 7 s in the placebo group (p = 0.002). In addition, the time to onset of 1-mm ST-segment depression was 509 ± 7 s versus 479 ± 7 s (p = 0.003). Among patients undergoing treadmill testing (n = 1,459), which was the primary study assessment in prior studies of ranolazine, the mean difference in exercise duration compared with placebo was 44 s (589 ± 10 s vs. 545 ± 10 s, p = 0.001). There was no significant impact of ranolazine on exercise duration (p = 0.14) or time to ischemia on exercise testing (p = 0.17) in those without a history of stable angina, consistent with the lack of effect on recurrent ischemia in patients without prior angina.

Safety and tolerability. Ranolazine was generally well-tolerated in patients with prior angina. The most common adverse effects that were more frequent in the ranolazine group compared with placebo were dizziness (12.4% vs. 7.4%), nausea (9.7% vs. 6.1%), and constipation (8.5% vs. 3.3%). Ranolazine was discontinued due to an adverse event in 8.1% of subjects compared with 4.1% receiving placebo (p < 0.001). During oral treatment, the dose of ranolazine was

Table 2 Efficacy Outcomes

	Ranolazine (n = 1,789)	Placebo (n = 1,776)	Hazard Ratio (95% CI)	p Value
Randomization to end of study				
Primary end point*	443 (25.2)	503 (29.4)	0.86 (0.75–0.97)	0.017
Major secondary end point†	379 (21.2)	414 (23.5)	0.89 (0.78–1.03)	0.12
CV death or MI	214 (11.9)	221 (12.5)	0.97 (0.80–1.16)	0.71
Recurrent ischemia	277 (16.5)	344 (21.1)	0.78 (0.67–0.91)	0.002
Worsening angina	96 (5.6)	124 (8.1)	0.77 (0.59–1.00)	0.048
Severe recurrent ischemia	204 (11.9)	245 (14.4)	0.81 (0.67–0.98)	0.026
Intensification of antianginal therapy	205 (12.5)	260 (16.4)	0.77 (0.64–0.92)	0.005
30 days until end of study (Landmark analysis)				
Primary end point	338 (19.8)	386 (23.3)	0.86 (0.74–0.99)	0.039
Recurrent ischemia	226 (13.7)	274 (17.2)	0.80 (0.67–0.96)	0.015
Worsening angina	92 (5.4)	120 (7.9)	0.76 (0.58–0.99)	0.044

Data are reported as n (%). Event rates in parentheses are Kaplan-Meier estimates (%) at 1 year. *Cardiovascular (CV) death, myocardial infarction (MI), or recurrent ischemia. †CV death, MI, or severe recurrent ischemia.
CI = confidence interval.

decreased in 190 (10.6%) patients—18 patients (1.0%) for renal dysfunction, 10 patients (0.6%) for persistent prolongation of the corrected QT interval, 154 patients (8.6%) for adverse events, and 8 patients for unknown reasons.

There was no difference in the incidence of the major safety end points in patients with prior angina treated with ranolazine versus placebo (Table 4). Specifically, death from any cause did not differ between treatment groups (HR: 1.01; 95% CI: 0.78 to 1.30; p = 0.96). Sudden cardiac death also did not differ with ranolazine compared with placebo (HR: 0.81; 95% CI: 0.53 to 1.25, p = 0.35). Similarly, no significant increase in frequency of symptomatic documented arrhythmias was observed with ranolazine (risk ratio: 0.98; 95% CI: 0.67 to 1.43; p = 0.92). Clinically significant arrhythmias on Holter evaluation were significantly lower in the ranolazine group (73.9% vs. 83.1%, p < 0.0001), including ventricular tachycardia ≥8 beats (5.2% vs. 8.7%, p < 0.0001).

Because of the inhibitory effect of diltiazem and verapamil on the clearance of ranolazine, we examined the tolerability in those patients receiving these agents. Of those patients with prior angina, at the time of hospital discharge, 307 were treated with diltiazem (n = 219) and/or verapamil (n = 96) in combination with study drug. The incidence of discontinuation of ranolazine for an adverse event was higher with ranolazine compared with placebo (11.7% vs. 5.1%, p = 0.048), similarly to those treated without these calcium-channel blockers.

Table 3 Performance on ETT at 8 Months (s, mean ± SEM)

	Ranolazine (n = 1,190)	Placebo (n = 1,173)	p Value
Total duration	514 ± 7	482 ± 7	0.002
Time to 1-mm ST-segment depression	509 ± 7	479 ± 7	0.003
Time to onset of angina	508 ± 7	477 ± 7	0.002

ETT = exercise tolerance test.

Discussion

This analysis of more than 3,500 patients with established coronary artery disease (CAD) and chronic angina treated with ranolazine or placebo for approximately 1 year more than doubles the total experience with ranolazine from prior phase 3 trials and extends its evaluation as antianginal therapy to a substantially more heterogeneous population than previously studied. We found that ranolazine was effective as an antianginal, reducing the incidence of recurrent ischemia by 22% with a corresponding 24% reduction in the incidence of worsening angina and improvement in exercise performance on treadmill testing. In addition, there was no excess of all-cause mortality, sudden cardiac death, or symptomatic documented arrhythmia in this high-risk group with ischemic heart disease treated with ranolazine, compared with placebo. Our findings also confirmed that, despite its efficacy as an antianginal, ranolazine did not impact the incidence of cardiovascular death or MI over the duration studied in this trial, nor did ranolazine offer a detectable improvement in outcomes or symptoms in patients with CAD without chronic angina. The results of this analysis therefore offer additional insight that is useful in defining the clinical role for this newer agent for treatment of patients with ischemic heart disease. On the basis of this evidence, ranolazine is an effective antianginal and antiischemic agent but is not useful as a disease-modifying secondary preventive therapy or for prophylaxis of recurrent angina in asymptomatic patients stabilized after an ACS.

Management of angina and clinical implications. Angina is a prevalent and morbid condition with respect to its adverse impact on quality of life. Among patients with a history of angina, the frequency of exacerbations is the most important determinant of quality of life (18). For these reasons, guidelines from the American Heart Association and American College of Cardiology emphasize dual goals for the management of patients with chronic CAD: first, the secondary prevention of cardiovascular death and MI,

Table 4 Safety and Tolerability Outcomes

Major Safety End Points*	Ranolazine (n = 1,785)	Placebo (n = 1,775)	Hazard Ratio (95% CI)	p Value
Death from any cause	111 (6.2)	114 (6.4)	1.01 (0.78–1.30)	0.96
Sudden cardiac death	37 (2.0)	46 (2.4)	0.81 (0.53–1.25)	0.35
Symptomatic documented arrhythmias	52 (2.9)	52 (2.9)	0.98 (0.67–1.43)	0.92
Clinically significant arrhythmias on Holter evaluation†	1,279/1,730 (73.9)	1,448/1,743 (83.1)	NA	<0.001

*Safety population. †Denominators are for those with evaluable Holter data available.
CI = confidence interval.

and second, the amelioration of angina (5). These guidelines also recommend an approach that includes consideration of both pharmacological and invasive therapies in order to achieve optimal results with respect to these dual objectives. The results of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial (19)—which showed no difference between aggressive secondary preventive pharmacotherapy plus PCI compared with optimal medical therapy alone with respect to the incidence of death or MI—confirmed that a strategy of initial optimal medical therapy is reasonable for most patients with stable CAD and that medical therapy and PCI are important complementary options for managing angina.

Notably, even with aggressive pharmacotherapy and revascularization, approximately 25% of patients with chronic angina continue to experience attacks with contemporary therapy (20,21). Moreover, even after treatment for a recognized MI, nearly 1 in 5 patients will have recurrence of angina by 1 year (22). In addition, use of traditional antianginal agents is limited in some patients by side effects (5). Therefore, it is not surprising that population-based studies demonstrate that 65% of patients with chronic stable angina require more than 1 antianginal agent to control their symptoms (23). For these reasons, there has been a sustained interest in newer antianginal agents that might add effectively to traditional options for treatment of angina, particularly those that act without affecting heart rate or blood pressure.

Our findings provide strong evidence that ranolazine can add to contemporary therapy for relief of symptoms in patients with chronic angina. The group of patients with prior chronic angina enrolled in the MERLIN–TIMI 36 trial share many of the clinical features of patients enrolled in the COURAGE trial (19); compared with patients without prior angina, they had a higher prevalence of risk factors for atherosclerosis, more extensive cardiac history and clinical comorbidities, and a greater need for antianginal medications at discharge. These findings identify an important subset of patients with chronic angina who seem to derive clinical benefit (reduced angina and ischemia) with ranolazine. Importantly, the reduction in worsening angina and improvement in exercise capacity that we observed occurred in patients with high-risk ischemic heart disease but without stringent selection criteria based upon early failure during exercise testing or extremely frequent angina. In addition, the beneficial effect of ranolazine with respect to recurrent ischemia occurred on the background of traditional antianginal therapy and evidence-based therapies for secondary prevention. These findings therefore complement the results of prior trials of ranolazine in patients with chronic angina and expand the studied population to one more reflective of the broad population with ischemic heart disease. Notably, ranolazine has not been shown to improve cardiovascular survival, as is the case for calcium-channel blockers and nitrates (5,24). Therefore, given the associated survival benefit in patients with prior MI, there remains a rationale for prioritization of beta-blockers in patients without contraindications. Our findings indicate that ranolazine is among the effective therapeutic options for treatment of angina. Moreover, previous studies have established its unique properties as an antianginal that exerts its anti-ischemic effects without an impact on heart rate and blood pressure (8). Therefore, ranolazine might be particularly useful when treatment is limited by bradycardia or hypotension.

Study limitations. Given the neutral primary efficacy analysis of the MERLIN–TIMI 36 trial of ranolazine for reduction of major cardiovascular events (16), all additional analyses, including this one, must be regarded as inherently exploratory. However, on the basis of pre-existing data from smaller trials in patients with chronic angina, there was a strong a priori basis for evaluation of this pre-defined subgroup. Second, the overall population of patients studied in the MERLIN–TIMI 36 trial was selected on the basis of their presentation with an ACS, and thus they represent a high-risk subset of patients with established ischemic heart disease. Nevertheless, given that the pathophysiology and natural history of chronic angina in patients with a history of ACS is typical of that for patients with stable CAD, our findings are likely to be relevant to patients with established ischemic heart disease in the absence of recent ACS. Moreover, this assertion is supported by the consistent findings with ranolazine in the preceding smaller trials among selected patients with stable CAD (13–15). Lastly, because randomization was not stratified by a history of prior angina, small differences in clinical characteristics between those randomized to ranolazine or placebo exist (Table 1). A supportive analysis adjusting for those covariates with significant or borderline imbalances (sex, prior revascularization, CCSC, and beta-blocker and angiotensin-converting enzyme inhibitor use) showed no qualitative difference in the results (ranolazine vs. placebo for primary end point

HR: 0.83; 95% CI: 0.77 to 0.99, p = 0.039, and recurrent ischemia HR: 0.78; 95% CI: 0.67 to 0.93, p = 0.004). It should also be noted that by design the landmark analysis performed starting at 30 days is limited to the selected subset of survivors to that time point and should be regarded as exploratory.

Conclusions

In this largest study of ranolazine in patients with established CAD, ranolazine was effective in reducing angina and recurrent ischemia in a substantially broader group of patients with angina than previously studied with a favorable overall profile of safety in a high-risk group of patients. Ranolazine is an option to be considered in the optimal medical therapy of patients with chronic angina.

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Key Words: angina ■ exercise tolerance ■ ranolazine ■ recurrent ischemia.

APPENDIX

For a supplementary table on the baseline characteristics of patients with and without prior chronic angina, please see the online version of this article.