Long-Term (3 Years) Outcomes of Ranolazine Therapy for Refractory Angina Pectoris (from the Ranolazine Refractory Registry)

Katelyn M. Storey, BA[a], Julia Wang[a], Ross F. Garberich, MS[a], Noel M. Bennett, MD[a], Jay H. Traverse, MD[a], Theresa L. Arndt, RN[a], Christian W. Schmidt, MS[a], and Timothy D. Henry, MD, FACC, MSCAI[b,*]

Ranolazine is approved for patients with chronic stable angina but has not been formally studied in patients with refractory angina pectoris (RAP). Patients with RAP have limited therapeutic options and significant limitations in their quality of life. The Ranolazine Refractory Angina Registry was designed to evaluate the safety, tolerability, and effectiveness of ranolazine in RAP patients in order to expand treatment options for this challenging patient population. Using an extensive prospective database, we enrolled 158 consecutive patients evaluated in a dedicated RAP clinic. Angina class, medications, major adverse cardiac events including death, myocardial infarction, and revascularization were obtained at 12, 24, and 36 months. At 3 years, 95 (60%) patients remained on ranolazine. A ≥2 class improvement in angina was seen in 48% (38 of 80 patients with known Canadian Cardiovascular Society class) of those who remained on ranolazine. Discontinuation due to side effects, ineffectiveness, cost, and progression of disease were the principle reasons for discontinuation, but primarily occurred within the first year. In conclusion, ranolazine is an effective antianginal therapy at 3-year follow-up in patients with RAP and may reduce cardiac readmission. **(Am J Cardiol 2020;129:1−4)**

As the population ages and the mortality due to coronary artery disease decreases, there are an increasing number of patients with severe myocardial ischemia who are not candidates for percutaneous or surgical revascularization. These patients with refractory angina pectoris (RAP) have limited therapeutic options and significant limitations in their quality of life.[1−4] Although the long-term mortality in RA patients has improved, quality of life continues to be a major challenge, and therapeutic options should focus on angina relief and improved quality of life.[5] Ranolazine was approved in 2006 by the Food and Drug Administration as a firstline antianginal agent for patients with chronic stable angina but its use in RAP has not been well studied.[6] Ranolazine has a novel mechanism of action that involves selective inhibition of the late sodium current, which reduces the magnitude of ischemia-induced sodium and calcium overload, thereby improving myocardial function and perfusion.[6] We previously reported the 1-year results of the first 100 patients enrolled into the Ranolazine Refractory Angina Registry which showed 77% of patients had an improvement in angina class and 43% had a ≥2 class improvement in angina. Additionally, ranolazine treated patients required less revascularization and experienced fewer major adverse cardiac events (MACEs), than those who discontinued the drug.[7] Herein, we report the 3-year results of the Ranolazine Refractory Angina Registry.

Methods

The OPTions in Myocardial Syndrome Therapy (OPTIMIST) program includes a dedicated clinic, a comprehensive prospective database and yearly follow-up for patients with RAP. The goals of the OPTIMIST program are to define the epidemiology of RAP and improve quality of care for a unique and growing subset of patients. We enrolled 158 consecutive RAP seen in the OPTIMIST program and treated with ranolazine. Patients were divided into those already on ranolazine when enrolled in the RAP registry (retrospective) and those who began ranolazine at the time of enrollment (prospective). Patients were started on 500 mg po BID and titrated up to 1,000 mg po BID as necessary, based on their symptoms and as directed by the clinical cardiologist. At the time of initial evaluation, physicians and clinical staff comprehensively reviewed patients' medical records, assessed angina symptoms, determined Canadian Cardiovascular Society (CCS) angina class, medical regimen for angina, and secondary risk factor modification for coronary artery disease. Baseline demographics, cardiovascular risk factors, cardiovascular medical history, cardiovascular medications, and clinical tests (including left ventricular function, stress testing, and coronary angiography) are also included in the OPTIMIST database. At 12, 24, and 36 months, patients' CCS class, medications and MACEs including revascularization, myocardial infarction (MI), and death were obtained.

[a]Minneapolis Heart Institute Foundation, Minneapolis, Minnesota; and [b]The Carl and Edyth Lindner Center for Research and Education, The Christ Hospital, Cincinnati, Ohio. Manuscript received October 17, 2019; revised manuscript received and accepted May 12, 2020.

See page 3 for disclosure information.

*Corresponding author: Tel: 513-585-2017; fax: 513-585-4857.
E-mail address: Tim.Henry@thechristhospital.com (T.D. Henry).

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Table 1
Patient characteristics at baseline

Variable	All patients (n = 158)	Discontinued within 1 year (n = 48)	Continued past 1 year (n = 110)	p Value	Discontinued between 1-3 years (n = 15)	Continued to 3 years (n = 95)	p Value
Age (years), mean (SD)	64.4 ± 10.4	63.5 ± 10.8	64.8 ± 10.2	0.47	61.3 ± 11.0	65.4 ± 10.0	0.15
Men	116 (73%)	33 (69%)	83 (75%)	0.38	14 (93%)	69 (73%)	0.083
Hypertension	140 (89%)	46 (96%)	94 (85%)	0.059	13 (87%)	81 (85%)	0.89
Dyslipidemia	154 (97%)	47 (98%)	107 (97%)	0.81	15 (100%)	92 (97%)	0.49
Diabetes mellitus	76 (48%)	25 (52%)	51 (46%)	0.51	6 (40%)	45 (47%)	0.60
Smoker	95 (60%)	22 (46%)	73 (66%)	0.015	8 (53%)	65 (68%)	0.25
Family History of CAD	129 (82%)	40 (83%)	89 (81%)	0.72	13 (87%)	76 (80%)	0.54
Previous PCI	129 (82%)	40 (83%)	89 (81%)	0.72	11 (73%)	78 (82%)	0.42
Previous MI	91 (58%)	25 (52%)	66 (60%)	0.35	8 (53%)	58 (61%)	0.57
Previous coronary bypass	94 (59%)	26 (54%)	68 (62%)	0.37	11 (73%)	57 (60%)	0.32
3-Vessel CAD	100 (63%)	31 (65%)	69 (63%)	0.82	11 (73%)	58 (61%)	0.36
CCS Angina Class							
I	5 (3%)	0	5 (5%)	0.37	1 (7%)	4 (4%)	0.17
II	14 (9%)	3 (6%)	11 (10%)		3 (20%)	8 (8%)	
III	83 (53%)	27 (56%)	56 (51%)		4 (27%)	52 (55%)	
IV	53 (34%)	18 (38%)	35 (32%)		7 (47%)	28 (29%)	

CABG = coronary artery bypass graft; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Additionally, ranolazine status was obtained including effectiveness, side effects, and reasons for discontinuation.

Descriptive statistics are displayed as mean ± SD for continuous variables and number and percentage with characteristic for categorical variables. Continuous variables were compared using Student *t* test with standard Ch-sqaure and Fisher exact tests used for categorical variables. Time to discontinuation of ranolazine was analyzed using the Kaplan-Meier method. A p value of <0.05 was considered statistically significant and all p values are 2-sided. Statistical analyses were performed using Stata 15.1 (StataCorp, College Station, Texas). Institutional Review Board approval was obtained for data collection, follow-up, and data analysis.

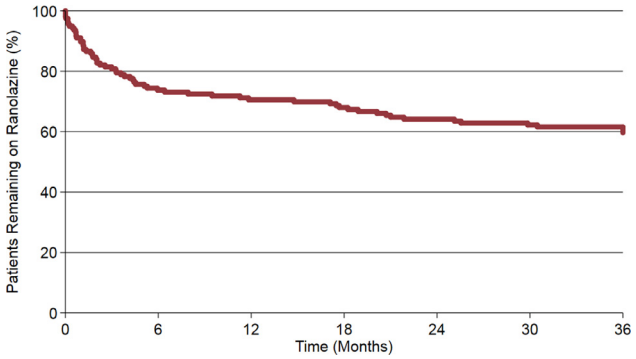

Figure 1. Cumulative ranolazine use at 3 years.

Results

The study population consists of 158 Ranolazine Refractory Angina Registry patients with at least 3 years of follow-up, who are predominantly male (73%; n = 116) with an average age of 64 ± 10 years (Table 1). These patients have a high prevalence of cardiac risk factors including 140 (90%) with hypertension, 154 (98%) with dyslipidemia, 76 (48%) with diabetes (Table 1).

At 3 years, 95 (60%) of patients remained on ranolazine and 63 (40%) of patients had discontinued ranolazine (Figure 1). The majority of patients who remained on ranolazine were taking 500 mg BID (70%), whereas only 30% were taking 1,000 mg BID. In the 63 patients that stopped ranolazine, the most common reason cited for discontinuation was side effects (35%), which included constipation, dizziness, lightheadedness, lower extremity edema, nausea, and tingling of hands and feet. Ineffectiveness and/or cost occurred in 31% of discontinuations and were the next most frequent reasons (Table 2). Of the 15 patients that discontinued ranolazine use after 1 year, the most common reason was cost for 5 patients (33%), followed by unknown in 4 (27%), side effects in 2 (13%), doctor discontinued in 2 (13%), no longer clinically indicated in 1 (7%), and ineffective in 1 (7%).

Table 2
Patient-reported reasons for discontinued use of ranolazine

Reasons for discontinuation	Frequency (n = 63)
Side effects	23 (35%)
Ineffective	11 (17%)
Cost	9 (14%)
Post-PCI	6 (9%)
MD discontinued	4 (6%)
Ineffective/Cost	4 (6%)
Unknown	3 (5%)
Pill too large	1 (2%)
Lightheadedness	1 (2%)
Dry mouth	1 (2%)
No longer needed	1 (2%)
Med change	1 (2%)
No longer clinically indicated	1 (2%)

MD = medical doctor; PCI = percutaneous coronary intervention.

Baseline characteristics comparing patients who continued therapy for 3 years are compared to those who discontinued in

Table 3
CCS angina class improvement

Change in CCS class	All patients (n = 158; 132 known CCS)	Continued past 1 year (n = 110; 92 known CCS)	Continued to 3 years (n = 95; 80 known CCS)
Improved by 2+	62 (47%)	45 (49%)	38 (48%)
Improved by 1	34 (26%)	23 (25%)	19 (24%)
None	25 (19%)	16 (17%)	15 (19%)
Worsened by 1	10 (8%)	7 (8%)	7 (9%)
Worsened by 2+	1	1 (1%)	1 (1%)

CCS = Canadian Cardiovascular Society.

Table 4
Incidence of adverse cardiac events

Variable	All patients (n = 158)	Discontinued within 1 year (n = 48)	Continued past 1 year (n = 110)	Discontinued between 1 and 3 years (n = 15)	Continued to 3 years (n = 95)
Cardiac hospitalization	104 (66%)	38 (79%)	66 (60%)	12 (80%)	54 (57%)
Percutaneous coronary intervention	56 (35%)	21 (44%)	35 (32%)	7 (47%)	28 (29%)
Myocardial infarction	20 (13%)	5 (10%)	15 (14%)	3 (20%)	12 (13%)
Coronary artery bypass graft	3 (2%)	2 (4%)	1 (1%)	1 (7%)	0
Death	4 (3%)	2 (4%)	2 (2%)	0	2 (2%)
Total MACE*	62 (39%)	21 (44%)	41 (37%)	9 (60%)	32 (34%)

MACE = major adverse cardiac event.
* MACE defined as death, MI, and PCI/CABG.

Table 1. The baseline characteristics of two groups were well matched with predominantly male patients with high risk of cardiac risk factors. Patients who continued use to 3 years were more likely to have a history of smoking ($p < 0.01$). The majority of patients had CCS class III angina, 3-vessel coronary disease (66%) with a high percentage of previous percutaneous intervention (PCI) (82%), coronary bypass grafting (60%) and MI (58%).

At 3 years, most (n = 38; 48%) patients had a ≥2 CCS angina class improvement, followed by 24% with a 1 class improvement, 19% with no class change, 9% worsened by 1 class, and 1% worsened by 2 or more classes (Table 3). Table 4 summarizes the incidence of cardiac events during 3-year follow up. The difference between cardiac hospitalization in patients who continued ranolazine versus those who did not was statistically significant ($p = 0.003$). Cardiac hospitalization was the most common reported event, followed by PCI and MI. PCI was surprisingly common (35%) in a patient population that is considered suboptimal for revascularization and occurred more frequently in patients who discontinued ranolazine (44%) than those who continued (29%).[8] Mortality was also low, at only 3% overall at 3-year follow-up.

Discussion

Our results demonstrate that ranolazine is an effective antianginal therapy in a large subset of patients with RAP. The overall number of adverse cardiovascular events for those who continued Ranolazine was significantly lower. In particular at 3 years, there was a statistically significant difference in cardiac hospitalization between those patients who continued ranolazine versus those who did not ($p = 0.003$), suggesting ranolazine was effective in preventing cardiac readmission. At 3 years, patients on ranolazine also had a lower rate of revascularization and total MACE compared with those who discontinued use. At 3 years, 60% of patients on Ranolazine had evidence for clinical benefit. The majority of patients that discontinued therapy did so within the first year. The principle reasons for discontinuation included side effects, ineffectiveness, cost, and progression of disease. As we have previously shown, a significant proportion of people labeled "No Option" undergo subsequent revascularization, the majority of which are related to new lesions or restenosis.[8] The overall low mortality despite a high-risk patient population with advanced coronary artery disease is even lower (1% per year) than our recent experience.[1] In summary, although not formally studied in patients with RAP, Ranolazine appears to be an important therapeutic agent for this challenging population.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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