Antihyperglycemic and Metabolic Effects of Ranolazine in Patients With Diabetes Mellitus

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The antianginal drug ranolazine, because of its unique mechanism of action, has been shown to have antihyperglycemic effects. Here, we review the reports on the antihyperglycemic and metabolic effects of ranolazine. MEDLINE was searched from 2000 to October 1, 2016 using the terms ranolazine, antihyperglycemic, diabetes, cardiology, and antianginal. Studies and reviews were included if they were in English and provided relevant data to inform practicing clinicians. Ranolazine has been shown to be effective as an antihyperglycemic while utilized as monotherapy or in combination with traditional diabetic regimens. A total of 6 studies were included in this review, with 5 being randomized controlled trials and 1 being a retrospective study. Of the 6 studies, 4 directly measured differences between baseline hemoglobin A1c (HbA1c), another measured endothelium function, and lastly the retrospective study evaluated outpatient clinic visit utilization, all-cause emergency department visits, inpatient admissions, and length of stay in a cohort of patients with angina and diabetes. In conclusion, ranolazine, because of its unique mechanism of action, may have a niche in therapy for patients with chronic stable angina pectoris and diabetes mellitus. Ranolazine has been shown to have positive antihyperglycemic and metabolic effects in patients with uncontrolled HbA1c. **(Am J Cardiol 2017;■■:■■–■■)**

The prevalence of diabetes has continually increased rapidly over the years.[1] Patients with concomitant diabetes and cardiovascular disease have shorter life spans, increased mortality from acute coronary syndromes, and a major financial impact on healthcare systems.[2,3] Lowering hemoglobin A1c (HbA1c) in type 2 diabetics has shown to prevent microangiopathies, neuropathies, and possibly macrovascular disease.[4–6] Ranolazine is an antianginal drug that reduces symptoms of ischemic heart disease by inhibiting late sodium current channels within cardiomyocytes, which improves left ventricular relaxation.[7,8] However, more recently, ranolazine has been shown to have anti-inflammatory, antioxidant, and antihyperglycemic effects.[9–11] The exact mechanism by which ranolazine effects glycemic control is not understood; however, it is proposed to inhibit glucagon secretion, increase insulin secretion, and preserve pancreatic β-cell function.[11–13] There is a paucity of data on the effects of ranolazine as it pertains to its antihyperglycemic and metabolic effects in the diabetic patient population. Here, we present a review of reports that measured antihyperglycemic or positive metabolic effects of ranolazine in patients with diabetes.

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A study performed by Page et al evaluated patients with concomitant chronic stable angina pectoris and diabetes who received ranolazine versus those who received traditional therapies, which was defined as β blockers, calcium channel blockers, and nitrates.[14] This retrospective quasi-experimental study evaluated healthcare resource utilization and cardiovascular-related outcomes such as clinic visits, emergency room visits, inpatient admissions, hospital length of stay, and need for revascularization. The study arm consisted of ranolazine plus a traditional agent versus a combination of 1 to 3 traditional agents alone plus sublingual nitroglycerin. Propensity matching was performed to match each patient on ranolazine to a traditional agent, including a cohort of patients with type 1 and type 2 diabetes. A total of 3,724 patients had type 1 or type 2 diabetes and included in the analysis. The calcium channel blocker cohort had 940 patients, the β blocker cohort had 933, the nitrate cohort had 937, and the ranolazine cohort had 914. Patients in the traditional therapy group required significantly more outpatient clinician visits (1.17, 95% confidence interval [CI] 1.12 to 1.22), more all-cause emergency department visits (1.16, 95% CI 1.02 to 1.32), inpatient admissions (1.20, 95% CI 1.07 to 1.34), and increased inpatient length of stay (1.32, 95% CI 1.14 to 1.53) compared with ranolazine. The author's concluded that the addition of ranolazine to patients with chronic stable angina and diabetes lowered healthcare resource utilization, had significantly lower rates of clinic and emergency room visits, and decreased inpatient admission with shorter lengths of stay.

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Lamendola et al evaluated the use of ranolazine in patients with diabetes and its effects on endothelial function of systemic arterial vessels.[15] This study was a blinded, randomized controlled trial comparing ranolazine for different study lengths versus placebo in terms of flow-mediated dilation (FMD). Patients were included in the study if there was no evidence of cardiovascular disease, or a history of chronic inflammatory disease, hepatic or renal failure, and an HbA1c <7.0%. The 3 study arms were as follows: ranolazine 375 mg twice daily (BID) for 3 weeks (group 1); ranolazine 375 mg BID for 2 weeks + 1 week of placebo (group 2); placebo BID for 3 weeks (group 3). Ten patients were randomized into each group for a total sample size of 30 patients. Baseline demographics were similar between each group and no patients endorsed any adverse effects from the use of ranolazine. Baseline FMDs were similar between the 3 groups; however, after 2 weeks of treatment, a statistically significant difference in FMD from baseline was seen in group 1 ($p < 0.001$) and group 2 ($p < 0.05$) but not in group 3 ($p = 0.75$). There was no difference in FMD 2 weeks after treatment between groups 1 and 2 ($p = 0.45$). The authors concluded that improvement in endothelial function could lead to improved outcomes among patients with endothelial dysfunction seen in cardiovascular disease and diabetes.

Ranolazine was evaluated as adjunct therapy to either metformin or glimepiride in 2 double-blind studies by Pettus et al in 2015.[16] Patients were randomized to either receive ranolazine 1,000 mg BID or placebo + metformin, or ranolazine 1,000 mg BID or placebo + glimepiride, with the primary end point being change in HbA1c from baseline. Patients included were 18 to 75 years old, with type 2 diabetes with an HbA1c between 7% and 10%. Patients received either glimepiride 2 to 4 mg/day or at least 1,500 mg/day of metformin for at least 90 days before screening of HbA1c. A total of 417 patients were included in the full analysis of the glimepiride study (208 placebo and 209 ranolazine), whereas 422 patients were included in the metformin trial (209 placebo and 213 ranolazine). Baseline characteristics were similar between each group. The mean age was 59 years old, body mass index of 32.5, and HbA1c of 8.09. The patients treated with glimepiride plus ranolazine in comparison with glimepiride plus placebo had a lower HbA1c at 90 days (–0.51%; 95% CI 0.32 to 0.71). Patients treated with ranolazine plus metformin in comparison with metformin plus placebo showed no difference in 90-day HbA1c (–0.11%; 95% CI –0.31 to 0.1). The authors concluded that the addition of ranolazine to patients receiving glimepiride showed HbA1c lowering effects but not when added to a sole metformin regimen.

An open-label extension study of the CARISA trial evaluated the use of ranolazine in diabetic patients.[10] Patients received ranolazine 750 mg (group 1), 1000 mg (group 2), or placebo BID (group 3). The patients were stratified based on whether they were diabetic or nondiabetic with further stratification of patients with diabetes based on whether or not they were receiving insulin. HbA1c was assessed post hoc to measure efficacy in patients with diabetes from baseline to the end of the trial. A total of 189 patients with diabetes were evaluated in the final analysis with 68 patients in group 1, 64 patients in group 2, and 57 patients in group 3. The majority of patients were on concomitant metformin, insulin, or sulfonylureas. Baseline HbA1c were obtained from 85% of patients at baseline and 74% after 12 weeks of treatment. Compared with placebo, ranolazine 750 mg and 1,000 mg reduced HbA1c by $0.48 \pm 0.18\%$ ($p = 0.008$) and $0.70 \pm 0.18\%$ ($p = 0.0002$), respectively. Patients in the ranolazine 1,000 mg BID group had a higher percentage of patients with HbA1c <7.0% with no associated weight changes ($p = 0.004$). The authors concluded that ranolazine is effective at treating chronic stable angina and has benefit specifically in diabetic patients.

The MERLIN-TIMI 36 trial evaluated the effect of ranolazine on ischemic events in non-ST elevated myocardial infarctions, but part of the trial design allowed the prospective evaluation of ranolazine on HbA1c.[17] This randomized double-blind, placebo-controlled trial included 4918 patients in which a baseline HbA1c was evaluated with a follow-up at any time point during the study. Patients in the ranolazine arm received 1,000 mg BID until the end of the study unless a prespecified protocol reduction in dose was warranted. The overall population saw a reduction in HbA1c when treated with ranolazine compared with placebo ($–0.30 \pm 0.03\%$, $p < 0.001$). Among patients with a previous diagnosis of diabetes mellitus, HbA1c declined by a faster rate at HbA1c checkpoint compared with placebo from baseline (0.64%, $p = 0.001$). Patients with diabetes and who were in the ranolazine arm were more likely to achieve an HbA1c <7% at the end of the study period as compared to placebo (59% vs 49%; $p = 0.001$). The authors concluded that ranolazine is an attractive antianginal agent for patients with chronic angina and impaired glucose metabolism.

The most direct study as it relates to the glycemic effects of ranolazine in patients with diabetes was by Eckel et al.[18] This randomized double-blind, placebo-controlled, multicenter phase 3 clinical trial evaluated ranolazine monotherapy to placebo in patients with diabetes who were inadequately controlled with diet and exercise alone. Patients who were treatment naïve or had ample amount of washout time with their previous antihyperglycemic medications were included. Patients were also included if they had an established diagnosis of diabetes, HbA1c 7% to 10%, and elevated fasting serum glucose values (130 to 240 mg/dl). Patients with a history of type 2 diabetes, myocardial infarction, acute coronary syndrome, stroke, or transient ischemic attack within the past 3 months were excluded. Ranolazine was started at a dose of 500 mg BID and titrated to 1,000 mg BID throughout the full 24-week treatment period. The primary end point of the study was the change from baseline HbA1c at 24 weeks. A total of 199 ranolazine patients and 198 placebo patients completed the study with baseline characteristics similar between both groups, with half the patients being female (50.9%), the mean age was 56 years of age with a baseline HbA1c of 8.04%. In comparison with placebo, ranolazine showed decline in HbA1c from baseline at 24 weeks (–0.56%, $p < 0.0001$). Similar to previous studies, the number of patients achieving HbA1c <7% after the study period was greater in the ranolazine group compared with placebo (41.2% vs 25.6%, $p = 0.0004$). The authors noted that ranolazine lowered not only fasting but also postprandial glucose values with minimal adverse events reported. The authors concluded that ranolazine as monotherapy for diabetes could potentially be an option in patients not achieving adequate glycemic control with diet and exercise alone.

Table 1
Overview of studies evaluated

Author/n	Treatment	Outcome	Results
Lamendola[15]; n=30	Ranolazine 375 mg BID × 3 weeks (Group 1) vs. Placebo Ranolazine 375 mg BID × 2 weeks (Group 2) vs. Placebo	Endothelium dependent vasodilation	Significant difference in FMD* from baseline in Group 1 and Group 2 but not in placebo
Pettus[16]; n=417 (Trial 1) n=422 (Trial 2)	Trial 1†: Glimepiride 2-4 mg daily + ranolazine 1 g BID Trial 2†: Metformin 500 mg BID + ranolazine 1 g BID	Change from baseline HbA1c at week 24	Trial 1: Had lower HbA1c with ranolazine Trial 2: No difference in HbA1c
Timmus[10]; n=189	Ranolazine 750 mg BID vs. Ranolazine 1 g BID vs. Placebo	Observed change from baseline HbA1c at week 12	Compared to placebo ranolazine (both doses) reduced HbA1c from baseline
Morrow[17]; n=4918	Ranolazine 1 g BID vs. placebo	Change from baseline HbA1c at week 12	Compared to placebo ranolazine reduced HbA1c from baseline
Eckel[18]; n=397	Ranolazine 500 mg BID x 7 days then 1 g BID vs. placebo	Change from baseline HbA1c at week 24	Compared to placebo ranolazine reduced HbA1c from baseline

* Flow-mediated dilation.
† Both trials compared against placebo.

Table 2
Expected glycemic lowering with noninsulin agents

Medication/Class	Decrease in HbA1c%
Metformin	1.5%
Sulfonylureas	1-2%
Thiazolidinediones	0.5-1.5%
Glinides	0.5-1.5%
DPP-4 inhibitors	0.5-1%
GLP-1 agonist	0.5-1%
α-glucosidase inhibitors	0.5-0.8%
Ranolazine	0.5-0.6%
Bile-acid sequestrants	0.5%

Although there are increasing positive data for the utilization of ranolazine in patients with stable angina pectoris and diabetes mellitus, it is important to note that a majority of the data did not come from large randomized controlled trials, which looked at metabolic parameters as their primary end point. Also, the long-term effects of ranolazine use in this patient population are not known. The increasing prevalence of diabetes justifies the drive to discover novel therapies for diabetes management. The studies reviewed provide promising results regarding the benefits of incorporating ranolazine into diabetic treatment regimens (Table 1). In comparison with some of the other non-insulin-based antihyperglycemic regimens ranolazine provides roughly the same HbA1c lowering capabilities other agents with a relatively mild adverse effect profile (Table 2). Ranolazine is proposed to work through the inhibition of the late sodium current in angina, thus exhibiting a selective blockade of sodium channels.[19] This finding gave rise to the hypothesis for the potential antihyperglycemic effects due to the sodium-dependent glucagon release in pancreatic cells. The decrease in electrical activity due to the blockade of the late sodium current peak suppresses glucagon release. Although traditionally utilized as an antianginal agent, this unique mechanism of action may provide insight to its use as an antihyperglycemic. However, the exact mechanism of ranolazine on glycemic improvement remains largely debated and is an opportunity for further research. The proposed suppression of glucagon release by ranolazine is characteristic of current diabetic treatment therapies.[11,12] Comparing the previously reviewed articles, there is a trend of lowering of HbA1c with ranolazine for patients with diabetes. The results reviewed varied between 0.48% and 0.70% absolute reductions in HbA1c, depending on adjunctive therapy, dose, duration, and baseline characteristics. This reduction in HbA1c is comparable with current second-line oral antidiabetic agents and could theoretically place ranolazine as an alternative second-line antidiabetic adjunctive treatment option pending future research.[20] The potential benefit of ranolazine to aid in the glycemic management of patients with diabetes may ultimately impact the negative secondary complications associated with diabetes. Diabetes has been associated with a marked increase in the risk of coronary heart disease.[21] It has been shown that the risk of having an initial myocardial infarction in patients with diabetes is similar to the risk of a recurrent myocardial infarction in patients without diabetes.[22] By utilizing a medication that has been proven to successfully manage the symptoms of ischemic heart disease and additional proposed antihyperglycemic properties, ranolazine could fill a void needed in the management of this high-risk patient population. The occurrence of patients presenting with coronary artery disease and diabetes is increasing with the growing prevalence of obesity. Because of the commonly overlapping presentation of these 2 high-risk disease states, it is most advantageous to further explore effective antianginal options with established metabolic and glycemic benefits such as ranolazine.[23] The prevalence of diabetes is expected to rise steadily worldwide congruent to its 2 main predictive demographic factors, age, and obesity. One study estimates that the worldwide prevalence will increase from 2.8% in 2000 to 4.4% in 2030.[24] As mentioned previously, with the lowering of HbA1c, ranolazine could potentially offer significant benefits in the diabetic population with angina through positive disease state management and decreasing healthcare-related costs.

Disclosures

The authors have no conflicts of interest to disclose.

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