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REVIEW ARTICLE

The Effect of Ranolazine on Glycemic Control: a Narrative Review to Define the Target Population

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Abstract

Ranolazine is an anti-anginal medication that reduces the sodium-dependent calcium overload via the inhibition of the late sodium current. After its approval for the treatment of chronic angina in 2006 in the USA, ranolazine has been reported to have several pleiotropic effects on various cardiac conditions, such as atrial fibrillation, ventricular arrhythmias, diastolic and microvascular dysfunction, and pulmonary arterial hypertension. Recently, several studies reported some promising results on the potential benefits of ranolazine on glycemic control. Though the mechanism of the antihyperglycemic effect is still unknown, ranolazine may exert the effect through β cell preservation, inhibition of glucose secretion, and enhancement of insulin secretion in a glucose-dependent manner. Given the increased risk of cardiovascular disease in patients with diabetes, it will be useful if one medication can simultaneously improve chronic angina and diabetes. Therefore, ranolazine could be a favored choice among other anti-anginal agents for patients with comorbidity of chronic angina and diabetes mellitus. In this review, we summarize the available data from clinical studies and provide valuable insight into defining the target population for the antihyperglycemic effect of ranolazine.

Keywords Ranolazine · Glycemic control · Narrative review

Introduction

Diabetes is an established risk factor for cardiovascular disease, and the risk of cardiovascular disease increases with poor glycemic control. Among patients with cardiovascular disease and diabetes, angina is one of the most common symptoms noted upon patient presentation. Given the increased risk of cardiovascular disease in patients with diabetes, it will be useful if one medication can simultaneously improve chronic angina and diabetes. Ranolazine was approved in 2006 for the treatment of chronic angina by improving myocardial relaxation, diastolic function, and myocardial blood flow [1]. Recently, ranolazine has been reported to have some potential benefits in various cardiac conditions, such as atrial fibrillation, ventricular arrhythmias, diastolic and microvascular dysfunction, and pulmonary arterial hypertension [2]. Among these effects beyond angina, the effect of ranolazine on glycemic control has been reported in several studies and showed promising results. Several review articles have been published on the antihyperglycemic effect of ranolazine, but those were mainly focused on summarizing the clinical data on the general effect of ranolazine in the glycemic control [2–5]. This review article attempts to identify the target group of patients for the potential benefit of ranolazine in controlling hyperglycemia by providing an in-depth review of the antihyperglycemic effect of ranolazine through categorizing currently available data based on the dosage strength of ranolazine (high-dose ranolazine (1000 mg twice daily) vs low-dose ranolazine (< 1000 mg twice daily)) as well as the clinical history of diabetes mellitus.

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Mechanism of Action of the Antihyperglycemic Effect of Ranolazine

At therapeutic levels, ranolazine is believed to exert anti-anginal and anti-ischemic effects via the inhibition of the late phase of the inward sodium channels in ischemic cardiac

myocytes during cardiac repolarization, which then reduces intracellular sodium concentrations, and thereby subsequently reduces calcium influx via Na^+-Ca^{2+} exchange [6]. The mechanism of ranolazine on glycemic control has not been fully understood yet, but several studies indicated that the effect of ranolazine on glycemic control may also be related to its blockade of sodium channels. Ranolazine also increased glucose-stimulated insulin secretion in rat and human islets in a glucose-dependent manner. A study by Dhalla et al. found that ranolazine may reduce glucagon release via blockade of voltage-gated Na^+ channels in pancreatic α cells [7]. In animal models of diabetes, ranolazine and a more selective Na^+ channels blocker (GS-458967) lowered postprandial and basal glucagon levels [8]. In an animal model reported by Ning et al., healthier islet morphology and significantly higher β cell mass were observed in streptozotocin-induced diabetic mice treated with ranolazine compared with the vehicle group, indicating a potential benefit of ranolazine on glycemic control via the preservation of functional β cell mass in the pancreas [9]. However, the results of Ning et al.'s study were inconsistent with fact that the benefits of ranolazine in reducing HbA1c have been observed in patients with T2DM who were already hyperinsulinaemic and in non-diabetic patients who had a normal β cell function. Fu et al. investigated the effect of ranolazine on muscle microvascular recruitment in overnight-fasted, anesthetized Sprague-Dawley rats, and they found at therapeutically effective dose, ranolazine increased muscle microvascular blood volume (~ 2-fold, $p < 0.05$) and increased insulin-mediated whole-body glucose disposal (~ 30%, $p = 0.02$) accompanied with an increased insulin delivery into the muscle ($p < 0.04$) [10]. Their results suggested that, via microvascular recruitment, ranolazine may improve glycemic control by expanding the microvascular endothelial surface area in muscle and subsequently increased muscle delivery and action of insulin [10]. Unfortunately, these studies with rats are of limited usefulness to human health, as they may not reflect the true mechanism of action of ranolazine in human beings. In addition, the rats used in the aforementioned animal studies were 4–5 weeks old, which roughly equates to two human years, whereas most human patients with type 2 diabetes mellitus are in general over 60 years old.

Effect of High-Dose Ranolazine (1000 mg Twice Daily) on Glycemic Control in Patients with Diagnosed Diabetes Mellitus

The effect of high-dose ranolazine in glycemic control in addition to antidiabetic therapy was first evaluated in a post hoc analysis of the Combination Assessment of Ranolazine In Stable Angina (CARISA) trial [11]. The CARISA trial was a randomized controlled three-arm parallel study, which compared the effects of ranolazine between diabetic and non-diabetic patients with chronic angina. The treatment arms of the trial included placebo, ranolazine 750 mg twice daily, and ranolazine 1000 mg twice daily, with a total of 823 patients enrolled. However, only 131 diabetic patients who completed both baseline and 12-week collection of HbA1c levels were included in this post hoc analysis with 37 patients in the placebo group, 47 patients in the ranolazine 750 mg twice daily group, and 47 patients in the ranolazine 1000 mg twice daily group. Among them, around 67% of the enrolled diabetic patients received antidiabetic medications during the trial, including secretagogues, biguanides, insulin, α-glucoside inhibitors, and thiazolidinediones. The baseline HbA1c levels of ranolazine and placebo groups were 7.92% ± 0.21 and 7.46% ± 0.21, respectively. After a 12-week treatment, high-dose ranolazine produced an additional reduction of HbA1c levels by 0.70% ± 0.018 ($p = 0.0002$) compared with placebo with background antidiabetic medications in both groups. Participants achieved HbA1c level < 7% in the high-dose ranolazine group before and after treatment were 25.5% and 55.3%, compared with 37.8% and 43.2% in the placebo group ($p = 0.004$ vs placebo). The effect of ranolazine on glycemic control remained unchanged in the 2-year long-term, open-label extension study. However, this study was limited by the small sample size; therefore, the data may not accurately reflect the long-term effects of ranolazine.

The largest trial to date investigating the antihyperglycemic effect of ranolazine was the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndromes (MERLIN)-TIMI 36 Trial [12]. It was a randomized, double-blinded, placebo-controlled, multinational clinical trial, which was designed to evaluate the effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes. Among the participants in the MERLIN-TIMI 36 trial, 4918 patients had HbA1c levels measured at baseline and during the study; therefore, a prospective evaluation of the effect of ranolazine on hyperglycemia was also conducted incidentally. Among patients included in this subgroup analysis, 1477 patients had a history of diabetes managed by antidiabetic therapy, and the mean baseline HbA1c levels of those patients in both the ranolazine and placebo groups were close to 7.5%. At 16 weeks, high-dose ranolazine significantly decreased HbA1c levels from 7.5 to 6.9% when compared with placebo (change in HbA1c levels − 0.64 vs − 0.22%, $p < 0.001$). Significantly more patients in the ranolazine group were observed to achieve HbA1c levels < 7% at 16 weeks (59 vs 49%, $p < 0.001$), as well as remain the reduced HbA1c levels until the end of the study (58 vs 50%, $p = 0.002$). Notably, the effect of ranolazine on glycemic control remained significant in patients taking ≥ 2 hypoglycemic agents.

The result of the MERLIN-TIMI 36 trial was recently confirmed by another study conducted by Pettus et al. They evaluated the use of high-dose ranolazine for glycemic control in addition to glimepiride background therapy (4 mg/day) in type

2 diabetic patients with a mean baseline HbA1c levels of 8.1% [13]. No other antidiabetic medication was allowed during the trial. At week 24, high-dose ranolazine resulted in a 0.51% (95% CI −0.71 to −0.32) reduction in HbA1c levels compared with the placebo. A greater proportion of patients in a high-dose ranolazine group was observed to achieve HbA1c levels < 7% at 24 weeks (27.1 vs 14.1%, $p = 0.001$). However, non-significant changes were found in the glycemic measurements including fasting serum glucose, 2-h postprandial glucose, and mean glucose for 3 h after a mixed meal, indicating a relatively greater effect of ranolazine in lowering HbA1c compared with the reductions in fasting serum glucose or postprandial glucose.

Recently, 961 diabetic patients with a history of chronic angina that had incomplete revascularization following percutaneous coronary intervention were randomized to receive either high-dose ranolazine or placebo in the Ranolazine for Incomplete Vessel Revascularization (RIVER-PCI) Trial [14]. Participants were allowed to take their antidiabetic medications, but, if the participant used metformin, the metformin dose was adjusted to ≤ 1000 mg daily as ranolazine may increase metformin absorption [15]. There were 49.4% and 45.3% of patients taken metformin during the trial in the ranolazine and placebo groups, respectively. At week 52, there was a significant reduction in the HbA1c levels for ranolazine compared with placebo (−0.44% ± 2.48, $p < 0.001$) in diabetic patients. Moreover, ranolazine was found to be associated with less angina and better the Seattle Angina Questionnaire (SAQ) angina frequency scores at week 4 and week 24 among diabetic patients with worse HbA1c levels at baseline (HbA1c levels ≥ 7.5%) compared with patients with mild diabetes (HbA1c levels < 7.5% at baseline).

Effect of High-Dose Ranolazine (1000 mg Twice Daily) as Monotherapy with Lifestyle Modification on Glycemic Control

The direct evidence supporting the glycemic effect of ranolazine was reported by Eckel et al. [16]. In their study, the effect of ranolazine as monotherapy on glycemic control was evaluated in patients with type 2 diabetes managed by diet and exercise alone. This was a randomized, double-blinded, placebo-controlled multicenter phase 3 trial with 465 participants enrolled. Eligible participants were patients with an established diagnosis of type 2 diabetes who were treatment naïve or had been washed out from previous antidiabetic therapy for 90 days. Participants also should have HbA1c levels of 7–10% and a fasting serum glucose of 130–240 mg/dL. After randomization, participants were assigned to take ranolazine 1000 mg twice daily or placebo for a 24-week treatment period. The primary endpoint was the HbA1c levels change from baseline to week 24. The baseline characteristics of both groups were similar with a mean age of 56 years and mean HbA1c levels of 8.04% (the mean HbA1c were 8.01% and 8.06% in the placebo and ranolazine groups, respectively). About 80% of the participants were treatment naïve, and in participants on antidiabetic medications, metformin and sulfonylureas were most frequently used prior to study enrollment. Notably, statin use was similar in both groups. At week 24, a significant reduction of HbA1c levels was observed in the ranolazine group compared with the placebo group (−0.56%, $p < 0.0001$). There were 41.2% of participants achieved HbA1c levels < 7% in the ranolazine group, compared with 25.6% in the placebo group. The reduction of fasting and 2-hour postprandial glucose was also noted in the ranolazine group. The effect of ranolazine monotherapy on glycemic control was consistent with previous studies when ranolazine was combined with antidiabetic agents, indicating that the mechanism of action of ranolazine on glycemic control is independent of co-administered antidiabetic agents. In general, ranolazine was well tolerated with comparable incidents of adverse events to placebo.

Effect of High-Dose Ranolazine (1000 mg Twice Daily) on Glycemic Control in Non-diabetic Patients

In the MERLIN-TIMI 36 trial, 3626 patients without previously diagnosed diabetes were included in a subgroup analysis [12]. Notably, 13% ($n = 466$) of these patients had HbA1c levels of ≥ 6.5%, and 6% ($n = 271$) had a fasting blood glucose > 126 mg/dL or a random blood glucose ≥ 200 mg/dL. Ranolazine 1000 mg twice daily resulted a small but significant reduction at week 16 in HbA1c levels in non-diabetic patients randomized to ranolazine as compared with a rise in HbA1c levels in non-diabetic patients received placebo (% change from baseline, −0.12 ± 0.03 vs 0.06 ± 0.02, $p < 0.001$). The presence ($n = 630$) or absence ($n = 771$) of metabolic syndrome did not appear to influence changes in HbA1c levels in the ranolazine group. Moreover, the probability of developing newly increased fasting glucose > 110 mg/dL or HbA1c levels ≥ 6% was significantly reduced by ranolazine as compared with placebo (31.8 vs 41.2%, $p = 0.003$) at the 1-year mark in patients who had normal glucose readings at the time of enrollment ($n = 664$). However, no difference between ranolazine and placebo was noted in new-onset diabetes at the 1-year mark (10.8 vs 11.5%, $p = 0.28$).

Similar results were also reported in the aforementioned RIVER-PCI trial. A total of 1643 non-diabetic patients were included in this trial with 835 patients in the ranolazine group and 808 patients in the placebo group [14]. Compared with placebo, ranolazine 1000 mg twice daily significantly decreased HbA1c levels by 0.19% ± 0.02 and 0.20% ± 0.02 at 6 and 12 months, respectively. There was a significantly lower incidence of new diabetes diagnoses at 6-month follow-up in patients treated with ranolazine, as compared to placebo (1.8

vs 3.5%, $p = 0.031$). However, this finding was no longer significant at 12-month follow-up (2.3 vs 3.9%, $p = 0.079$). Non-diabetic patients allocated to ranolazine were also significantly less likely to have an increase in HbA1c levels ≥ 1% at both 6-month (30.2 vs 52.9%, $p < 0.01$) and 12-month (29.1 vs 51.8%) follow-up.

The Relationship Between Baseline HbA1c Levels and Antihyperglycemic Effect of High-Dose Ranolazine (1000 mg Twice Daily)

The relationship between baseline HbA1c levels and antihyperglycemic effect of high-dose ranolazine was evaluated in a post hoc analysis of the MERLIN-TIMI-36 trial by Chisholm et al. with 1477 patients with diabetes and non-ST segment elevation myocardial infarction (NSTEMI) [17]. Glycemic control was evaluated at randomization and 4 months by measuring HbA1c levels (placebo group $n = 770$, ranolazine group $n = 707$) and/or fasting plasma glucose (placebo group $n = 328$, ranolazine group $n = 310$). HbA1c values were used to stratify the patients into good/moderate (HbA1c levels 6–< 8%) and poor glycemic control (HbA1c levels 8–10%). The placebo-corrected HbA1c reduction was significant for both groups with a greater reduction observed in the patients with poor glycemic control (0.28% (95% CI − 0.55 to 0.00, $p = 0.045$) vs 0.59% (95% CI − 0.99 to − 0.20, $p < 0.001$)). A weak positive correlation relation between baseline HbA1c levels and a decrease in HbA1c levels was noted with a correlation coefficient of 0.41. Similar results were also reported in patients had fasting serum glucose measured. In patients with baseline fasting plasma glucose > 150 mg/dl, there was a direct relationship between baseline fasting plasma glucose and fasting plasma glucose reduction. A greater chance of achieving goal HbA1c levels (≤ 7%) was observed in patients receiving ranolazine plus oral hypoglycemic agents with or without insulin compared to patients only receiving ranolazine; however, these results cannot be used to extrapolate the effect of ranolazine on glycemic control due to the antihyperglycemic effects of the concurrent antidiabetic therapy. The placebo-corrected effect of ranolazine was similar among subgroups received different types of concurrent diabetes medications in patients with HbA1c levels 6–10%.

Kipnes et al. conducted a prospective, double-blind, randomized, placebo-controlled trial in 80 patients with type 2 diabetes mellitus to further assess the glycemic effects of ranolazine. Patients were randomized to receive placebo or ranolazine at 1000 mg twice daily in addition to non-insulin medical therapy [18]. Mean baseline HbA1c values were similar in the placebo and ranolazine groups at 8.5% and 8.4%. After the 12-week treatment, placebo-corrected HbA1c values were significantly reduced in the ranolazine group (− 0.53%, $p = 0.010$). However, in the subgroup analysis, the significant reduction in HbA1c levels was only observed in patients with baseline HbA1c levels > 7.5% (− 0.62%, $p = 0.023$), and surprisingly no significant difference was detected in the groups with baseline HbA1c levels ≤ 7.5% and > 10%. There was no statistically significant improvement in fasting serum glucose in all subjects and subgroups with baseline fasting serum glucose > 140 mg/dL either. It should be noted that this study was limited by the small number of patients. In the groups with baseline HbA1c levels ≤ 7.5% and > 10%, the number of enrolled patients was 21 and 10, respectively. Therefore, the risk of type 2 error in these groups was high due to insufficient statistical power.

In summary, currently, there is no clinical evidence to support the antihyperglycemic effect of high-dose ranolazine in diabetic patients with HbA1c levels < 6% nor > 10%. The benefit of high-dose ranolazine in reducing HbA1c levels was significant in those diabetic patients with HbA1c levels around 6–10%.

Effect of Low-Dose Ranolazine (< 1000 mg Twice Daily) on Glycemic Control

Unlike the positive results observed with administration of high-dose ranolazine in glycemic control, adding low-dose ranolazine (< 1000 mg twice daily) to background antidiabetic medications showed some conflicting evidence regarding the additional reduction in HbA1c levels in the diabetic patient [19]. A 3-month randomized controlled trial including 47 participants was conducted in India to compare ranolazine 500 mg twice daily with trimetazidine 35 mg twice daily for glycemic effect in patients with coronary artery disease and diabetes mellitus. Trimetazidine is a drug for angina pectoris, which has not been approved by the U.S. Food and Drug Administration for use and sale in the USA. When the oxygen supply is low, β-oxidation of free fatty acid (FFA) can inhibit glucose oxidation, leading to the uncoupling of glycolysis and an increase in proton production, which potentially accelerate sodium and calcium overload in the heart causing an exacerbation of ischemic injury and decreased cardiac efficiency during reperfusion. Trimetazidine inhibits the enzyme long-chain 3-ketoacyl coenzyme A thiolase (LC 3-KAT), which is the final enzyme in the FFA β-oxidation pathway [20]. Thus, trimetazidine can inhibit FFA oxidation and subsequently enhance glucose oxidation without a reduction in intracellular ATP levels and proton production [20].

In this study, the levels of HbA1c, fasting blood glucose, and postprandial blood glucose were collected before and after 12 weeks, and no significant change was identified in both treatment groups without p value reported. For the ranolazine group, HbA1c levels before and after 12 weeks were found to be 9.0% ± 1.6 and 8.7% ± 1.5 respectively, and fasting blood glucose before and after 12 weeks were 163.9 ± 45.2 mg/dL and 158.2 ± 41.6 mg/dL respectively. Postprandial blood glucose in the ranolazine group increased from 271.1 ± 78.4 mg/

dL at baseline to 295.3 ± 91.6 mg/dL after 12 weeks. For the trimetazidine group, HbA1c levels before and after 12 weeks were found to be 8.6% ± 1.5 and 8.6% ± 2.4 respectively, and fasting blood glucose before and after 12 weeks were 153.6 ± 60.8 mg/dL and 168.1 ± 68.1 mg/dL respectively. Postprandial blood glucose in the ranolazine group increased from 248.3 ± 78.7 mg/dL at baseline to 259.7 ± 75.5 mg/dL after 12 weeks. The authors explained that their negative results could be explained by the low dose of ranolazine and short treatment duration compared with other trials demonstrating positive glycemic effects.

The efficacy of ranolazine 750 mg twice daily in reducing HbA1c levels compared with placebo was reported in the aforementioned post hoc analysis of the CARISA trial [11]. Ranolazine 750 mg twice daily reduced HbA1c levels by 0.48% ± 0.18 (SEM) ($p = 0.008$) compared with placebo, although this was lower than the efficacy of ranolazine 1000 mg twice daily (0.70% ± 0.18 (SEM), $p = 0.0002$). The number of patients with HbA1c levels < 7% in ranolazine 750 mg twice daily group was 17 (36.2%) at baseline and 24 (51.1%) at week 12. It needs to be emphasized that the metformin dose was not adjusted in the CARISA trial and it is unclear if metformin dose adjustment is necessary when combined with ranolazine 750 mg twice daily. Currently, ranolazine 750 mg tablet is not supplied in the USA.

In an observational study with 52 veterans conducted by Greiner et al., the low dose of ranolazine (500 mg twice daily) was found to be associated with a significant decrease in HbA1c levels by 0.3% ($p = .001$), and significantly more veterans achieved HbA1c levels < 7% after ranolazine therapy (42.3% before ranolazine therapy vs 73.1% after ranolazine therapy, $p = .001$) [21]. As expected, this study was limited by the nature of observational design and small sample size.

Overall, the utilization of low-dose ranolazine (< 1000 mg twice daily) in the setting of glycemic control was found to remain a controversial issue due to lack of evidence. The small number of participants included in both trials and the short duration prevent any firm conclusions being made on the efficacy of low-dose ranolazine in glycemic control.

Safety Profiles and Risk of Hypoglycemia

Ranolazine was well tolerated and safe with a similar number of adverse events compared to the control group. The most common adverse effects reported for ranolazine were constipation, headache, nausea, and dizziness. Reported by Eckel et al., four subjects in the ranolazine group experienced hypoglycemia during the treatment period; nevertheless, the authors concluded that no patient experienced severe hypoglycemia or had documented hypoglycemia in this trial [16]. Overall, ranolazine was not found to increase the incidence of hypoglycemia among included trials.

The other common adverse reactions associated with ranolazine are dizziness, nausea, asthenia, constipation, and headache [22]. Ranolazine blocks potassium current and prolongs the QTc interval in a dose-related manner; therefore, there is little experience with very high doses of ranolazine (> 1000 mg twice daily) [22].

Discussion

Our narrative review including nine clinical studies found that, compared with the placebo group, adding high-dose ranolazine to background antidiabetic medications resulted in an additional approximately 0.5% reduction in HbA1c levels in diabetic patients with angina. The characteristics of the included trials were summarized in the Table 1. This result was consistent with the effect of high-dose ranolazine in diabetic patients managed by lifestyle modification only. Furthermore, a weak positive correlation between baseline HbA1c levels and reduction in HbA1c levels was observed in diabetic patients taking a high dose of ranolazine. However, the utilization of low-dose ranolazine in the setting of glycemic control remains a controversial issue due to the lack of evidence .

Ranolazine is indicated for chronic angina, and currently not approved for the treatment of type 2 diabetes. Given the evidence in reducing HbA1c levels summarized in our review, it appears that ranolazine could be a potential therapeutic option in the management of diabetes in certain patients with chronic angina.

In non-diabetic patients, there was a small but statistically significant reduction in HbA1c levels by taking high-dose ranolazine; however, no significant difference was identified in new-onset diabetes at the 1-year mark in two clinical trials. Hence, it is uncertain if the reduction of HbA1c levels in non-diabetic patients could be clinically beneficial.

While there was no solid evidence to support the utilization of low-dose ranolazine in the setting of glycemic control, adding high-dose ranolazine to background antidiabetic medications may provide some benefits in some selected diabetic patients. The significant benefit was observed in patients with moderate-to-severe diabetes (HbA1c levels 6–10%). That said, it is still unclear if high-dose ranolazine could be used for the treatment of diabetes mellitus in patients without angina, given the lack of evidence of large clinical trials in this population. In our opinion, the mild efficacy of high-dose ranolazine on glycemic control is more like an extra "bonus" for diabetic patients who are treated with this medication for chronic angina. Thus, the utilization of ranolazine should be determined by weighing the benefits of ranolazine in managing chronic angina and its risk of adverse reaction. If ranolazine is needed for treating chronic angina and patients have a history of diabetes, an additional benefit of ranolazine

Table 1 Overview of studies included

	Intervention	Background antidiabetic treatment	Follow-up duration	Patient characteristics	Mean HbA1c levels at baseline	Outcomes
Timmis 2006 [10]	Placebo $n = 37$ Ranolazine 750 mg BID $n = 47$ Ranolazine 1000 mg BID $n = 47$	Yes	12 weeks	Patients with chronic angina on anti-anginal agents with DM	Placebo 7.46% (SEM 0.21) Ranolazine 750 mg BID 7.65% (SEM 0.20) Ranolazine 1000 mg BID 7.92% (SEM 0.21)	Mean HbA1c after treatment: Placebo 7.62% (SEM 0.14) Ranolazine 750 mg BID 7.14% (SEM 0.13) Ranolazine 1000 mg BID 6.93% (SEM 0.13)
MERLIN-TIMI 36 (Morrow 2009 [11], Chisholm 2010 [16])	Ranolazine + DM $n = 707$ Placebo + DM $n = 770$ Ranolazine + non-DM n = 1401 Placebo + non-DM n = 1428	No	16 weeks	Patients with NSTEMI and at least one indicator of moderate to high risk of recurrent ischemic events without significant hepatic disease, end-stage renal disease, life expectancy < 12 months or taking medications that may prolong QT interval	Ranolazine + DM 7.53% (0.06) Placebo + DM 7.45% (0.06) Ranolazine + non-DM 5.58% (0.03) Placebo + non-DM 5.58% (0.02)	Change in HbA1c (Morrow 2009): In patients with DM: Ranolazine −0.64% ($p < 0.01$) vs placebo −0.22% ($p < 0.01$); In patients without DM: Ranolazine -0.12% vs placebo 0.06%; Placebo-corrected change in HbA1c (Chisholm 2010): In patients with HbA1c 6–< 8%: −0.28% (95% CI −0.55 to 0.00, $p = 0.045$) In patients with HbA1c 8–10% −0.59% (95% CI −0.99 to −0.20, $p < 0.001$)
Kipnes 2011 [17]	All patient $n = 78$ Ranolazine vs placebo	Yes, non-insulin medical therapy	12 weeks	HbA1c 7-11% on non-insulin medical therapy	Placebo 8.5% Ranolazine 8.4%	Placebo-corrected change in HbA1c: −0.53%, $p = 0.010$
Eckel 2015 [15]	Ranolazine $n = 199$ Placebo $n = 195$	No	24 weeks	Type 2 diabetes Treatment naïve or washed off of all antihyperglycemic therapy for 90 days	Ranolazine 8.06% (SD 0.732) Placebo 8.01% (SD 0.727)	Mean HbA1c after treatment: Ranolazine 7.26% (SD 1.101) Placebo 7.70% (SD 1.183)
Sandhiya 2015 [18]	Ranolazine $n = 23$ Trimetazidine $n = 24$	Yes	12 weeks	Diagnosed with CAD and DM	Ranolazine 9.2% (SD 1.7) Trimetazidine 8.6% (SD 1.5)	Mean HbA1c after treatment: Ranolazine 8.7% (SD 1.5) Trimetazidine 8.6% (SD 2.4)
Pettus 2016 [12]	Placebo+glimepiride $n = 216$ Ranolazine 1000 mg BID + glimepiride $n = 215$	Yes, glimepiride 4 mg/day	24 weeks	Diagnosed with type 2 diabetes receiving antidiabetic drug with baseline HbA1c 7-10%	Placebo+glimepiride 8.1% (SD 0.7) Ranolazine 1000 mg BID + glimepiride 8.1% (SD 0.8)	Mean HbA1c after treatment: Placebo+glimepiride 8.1% (SD 1.1) Ranolazine 1000 mg BID + glimepiride 7.6% (SD 1.1)
Fanaroff 2017 [13]	Ranolazine + DM $n = 482$ Placebo + DM $n = 479$ Ranolazine + non-DM $n = 835$ Placebo + non-DM $n = 808$	Yes, for patients with DM	52 weeks	Had a history of chronic angina who had undergone PCI with resultant incomplete revascularization	N/A	Placebo-corrected change in HbA1c: In patients with DM −0.64% (SEM 0.08); In patients without DM −0.20% (SEM 0.02);
Greiner 2018 [19]	Ranolazine 500 mg BID $n = 52$ Ranolazine 1000 mg BID $n = 14$	Yes	6 months	Veterans with a diagnosis of type 2 DM received ranolazine therapy	Ranolazine 500 mg BID 6.9% Ranolazine 1000 mg BID 6.9%	Mean HbA1c after treatment: Ranolazine 500 mg BID 6.6% (−0.3%, $p = .001$) Ranolazine 1000 mg BID 6.5% (−0.4%, $p = 0.09$)

BID, twice daily; *CAD*, coronary artery disease; *DM*, diabetes mellitus; *HbA1c*, hemoglobin A1c; *N/A*, not applicable; *NSTEMI*, non-ST-elevation myocardial infarction; *PCI*, percutaneous coronary intervention; *SEM*, standard error of measurement; *SD*, standard deviation

in reducing HbA1c in patients with HbA1c levels 6–10% could be expected.

This review is limited by the fact that, though all included trials reported the glucose-lowering effect of ranolazine in patients, only one trial conducted by Eckel et al. defined changes in HbA1c levels as a primary endpoint. All other trials were not designed to investigate the antihyperglycemic effect of ranolazine. Nonetheless, our review made a contemporary in-depth evaluation of the clinical evidence of ranolazine in the management of patients with or without diabetes and provided valuable insight into defining the target population for the antihyperglycemic effect of ranolazine.

Conclusion

In conclusion, ranolazine is shown to have a mild but safe promising effect on glycemic control in diabetic patients with a history of chronic angina. The most significant benefit of ranolazine in reducing HbA1c levels was observed in patients with moderate-to-severe diabetes. However, more data is needed to explore the role of ranolazine in the treatment of diabetes, especially in patients without chronic angina. Large randomized controlled trials would be necessary to provide more data about the benefits of ranolazine in reducing diabetes-related vascular complications and death, as well as safety profiles of hypoglycemia.

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