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Meta-analysis

The efficacy of ranolazine in improving glycemic parameters in patients with type 2 diabetes mellitus: a meta-analysis

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ABSTRACT

Ranolazine is an anti-anginal drug that mediates its effects by inhibition of cardiac late sodium current. Although it is not indicated for the treatment of type 2 diabetes mellitus (T2DM), several clinical trials have shown that ranolazine was associated with a reduction in HbA1c. The objective of this meta-analysis is to determine the efficacy and safety of ranolazine in improving glycemic control in patients with T2DM. A total of five randomized controlled trials involving 2,680 patients were included in the analysis. The pooled analysis showed that ranolazine may improve glycemic control with a modest decrease in HbA1c and FBS. The difference in HbA1c was -0.38% (95% CI -0.59 to -0.17), favoring ranolazine. Sensitivity analysis showed a difference of HbA1c of -0.49% (CI -0.67, -0.31), still favoring the ranolazine group. There was also a statistically significant difference in fasting glucagon, favoring the ranolazine group (-2.70 pg/ml: 95% CI -5.24 to -0.16). The risk of hypoglycemia with ranolazine was comparable with placebo (RR 1.27 95% CI 0.84 to 1.91). Overall, ranolazine appears to be a safe and effective option for improving glycemic control in patients with T2DM, with a modest decrease in HbA1c and FBS, and a lower risk of hypoglycemia compared to placebo. However, further studies are needed to confirm these findings and to investigate the long-term safety and efficacy of ranolazine in this patient population.

Keywords: Ranolazine, Type 2 diabetes mellitus, Glycemic parameters, Meta-analysis, Diabetes treatment

INTRODUCTION

Diabetes mellitus (DM) has long been recognized as an independent risk factor for the development of cardiovascular disease (CVD) events.[1] The American diabetes association reported that from 2003 to 2006, CVD death rates were about 1.7 times higher among adults aged 18 years and above who are diagnosed with diabetes compared to adults who are not.[2] In fact, DM was classified as a coronary heart disease equivalent by the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult treatment panel III) of the national cholesterol education program.[3] Studies have shown that the presence of T2DM is linked with poorer prognosis in patients with coronary artery disease (CAD).[4,5] Hence, it may be advantageous to have a drug that targets both DM and CAD.

Ranolazine, a piperazine derivative, is a novel anti-anginal drug that exerts its effect by inhibiting the late sodium current through blockade of the cardiac isoform of the sodium channel, $Na_v1.5$.[6] It reduces intracellular calcium overload during ischemia and has no negative inotropic, chronotropic, or dromotropic effect, hence, has been considered as safe and effective for the management of patients with chronic stable angina.[7] In addition to its effects on angina, post hoc subgroup analysis from two

clinical trials (CARISA study and MERLIN-TIMI 36 trial) have shown that ranolazine is associated with significant reductions in HbA1c in subjects with chronic angina and DM.[6,8] In a study involving streptozotocin-treated mice, ranolazine 20 mg/kg per day was reported to lower fasting and non-fasting glucose levels and preserve pancreatic β cells.[9] A recent preclinical trial has shown that ranolazine inhibits glucagon secretion by blocking the $Na_v1.3$ isoform of sodium channels in pancreatic α-cells in animal models of diabetes. Considering that increases in glucagon secretion by pancreatic α-cells and failure of glucagon suppression following oral glucose are well reported in T2DM, these data indicate a possible mechanism as anti-diabetic of ranolazine. Thus, the aim of this meta-analysis is to identify and critically appraise clinical trials in terms of the efficacy of ranolazine on glycemic markers.

Research question

Among adult patients with T2DM, how effective is ranolazine in improving glycemic control?

Objectives

General objective

General objectives were to determine the efficacy of ranolazine in improving glycemic control in patients with T2DM.

Specific objectives

Specifically, the study aims to determine the efficacy of ranolazine in improving glycemic parameters (FPG, fasting glucagon, fasting insulin, and fasting C-peptide) in patients with T2DM. It also aims to determine the safety of ranolazine in terms of the incidence of hypoglycemic events.

METHODS

Types of studies

Randomized clinical trials (RCTs) that have a quality scale of A-B were included in this meta-analysis.

Types of participants

Subjects included in the studies were analyzed according to the following inclusion criteria: adult patients more than 18 years of age with T2DM, with or without history of CAD. Exclusion criteria included the following: type 1 DM, estimated glomerular filtration rate <30 ml/min/1.73 m^2 and previous ranolazine treatment.

Types of interventions

Administration of ranolazine at any determined dose and duration of treatment in a blinded fashion versus placebo.

Types of outcome measures

Primary efficacy outcome measures include the change in mean HbA1c, fasting plasma glucose (FPG), fasting glucagon, fasting insulin, and fasting C-peptide from baseline. The primary safety outcome parameter was hypoglycemic events.

Data sources and searches

Two authors independently searched for clinical trials in PubMed, Cochrane Library, Science Direct, and Google Scholar for the terms "ranolazine", "RS 43285-193", "T2DM", "glycohemoglobin", and "HbA1c", last June 30, 2017. The search strategy comprised both indexing terms and synonyms derived using Medical Subject Heading (MeSH). The search strategy was adapted for each of the other databases. Additionally, a bibliography search was conducted.

Study selection

Two authors independently reviewed titles and abstracts of all retrieved studies to identify relevant trials for inclusion. Included clinical trials that investigated the efficacy of ranolazine on improving glycemic markers versus placebo carried out in adults with T2DM (according to the American Diabetes Association classification), in either gender; age greater than 18 years, and with no limitation as to follow up the length, sample size, race or nationality. Case reports, editorials, letters to the editors, trials enrolling only non-diabetics, or subjects younger than 18 years were excluded.

Data extraction and quality assessment

The quality of randomized controlled trials was assessed following recommendations as described in the cochrane risk of bias tool (Modified) for quality assessment of randomized controlled trials. These recommendations include randomization, allocation concealment, blinding of participants, personnel, and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias.

Data synthesis and analysis

All outcomes were pooled using the RevMan 5.3 software developed by the Cochrane collaboration. For continuous outcome variables (e.g., mean change in HbA1c, fasting plasma glucose, fasting insulin, fasting glucagon, fasting C-peptide) and dichotomous data (e.g., hypoglycemic events), the differences were calculated by weighted mean differences (WMDs) and relative risk (RR), respectively.

Heterogeneity was measured using the I^2 statistic, wherein I^2 values of 25, 50, and 75% indicated low, medium, and high heterogeneity, respectively. When the I^2<50%, the fixed-effect model with the Mantel-Haenszel

method was used. On the other hand, I^2>50% represents statistical heterogeneity, and the random effects model was used to analyze the unknown reason for heterogeneity.

RESULTS

Study selection

As shown in Figure 1, a total of 50 studies were identified, 43 of which were determined to be irrelevant based on the review of titles and abstracts. Hence, a total of 7 studies were assessed for eligibility. A study by Pettus et al reported the results of two trials assessing the efficacy of ranolazine for glycemic control in patients with type 2 diabetes on metformin or glimepiride in one article.[10] One study by Selvarajan et al comparing the effect of ranolazine and trimetazidine on glycemic status in diabetic patients with CAD was excluded because there was no placebo arm.[11] Another study by Fanaroff et al was excluded due to a lack of data on the outcome of interest.[14] A total of 5 randomized controlled trials were enrolled for meta-analysis.[8,10,12,15] Of the 5 retrieved studies, 2,680 participants are represented with 1,320 and 1,360 patients in the ranolazine and placebo, respectively. The characteristics of the retrieved trials (including trial quality assessment) and the recorded outcomes are reported in Table 1.

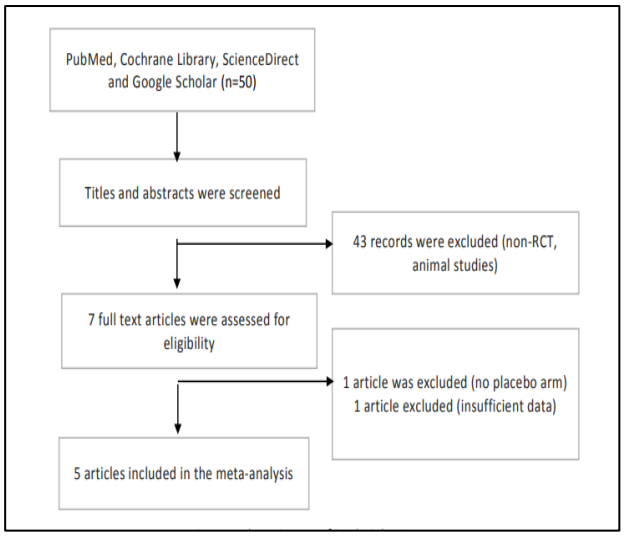

Figure 1: Flow diagram of study selection.

Effect on HbA1c

Five double-blinded RCTs were included in the meta-analysis, by Timmis et al (2006, CARISA trial), Morrow et al (MERLIN-TIMI 36 trial), Eckel et al, and two by Pettus et al.[10,13,15] Participants in the studies were individuals with T2DM. Existing prescriptions of patients were unchanged in all studies except that by Eckel and colleagues, where they gave ranolazine as anti-hyperglycemic monotherapy. Ranolazine treatment was uniformly administered as 1000 mg tablet BID; however, down titration was permitted in the investigation by the groups of Eckel and Pettus. All studies used a placebo as control. All of the researches were based in the USA, except for the MERLIN-TIMI 36 trial, which spanned 440 sites in 17 countries.

Timmis et al enrolled T2DM patients with a mean age of 65 years who had chronic angina >3 months, but not those who had an ACS or revascularization ≤2 months prior. The glycemic effect of ranolazine was done as a post-hoc analysis in the subgroup of diabetic participants.[12]

In the study by Morrow et al participants were in their mid-60s and diagnosed with non-ST elevation ACS. The effect of ranolazine on HbA1c was a planned subgroup analysis of the research.

Eckel et al conducted a multicenter trial that recruited patients with HbA1c of 7-10%, FSG of 130-240 mg/dl, BMI of 25-45 kg/m^2, and C-peptide ≥0.8 ng/ml. Criteria for exclusion were history of MI, ACS, revascularization, and stroke/TIA ≤3 months. Their participants had a mean age of 56 years. A washout period of 24 weeks for thiazolidinediones or 90 days for other anti-hyperglycemic was implemented. Those who demonstrated consistent hyperglycemia were given open-label rescue medication, but a continued non-resolution was cause for early termination of participation.[13]

The inclusion/exclusion criteria in the study by Pettus et al were essentially the same as in Eckel et al. In addition, they excluded patients who had been treated with ranolazine before. Furthermore, in this study, ranolazine was given as an add-on to either glimepiride or metformin.

The lowering of HbA1c in ranolazine groups was 0.38 percentage points compared to placebo (95% CI -0.59 to -0.17) however, there was high heterogeneity (I^2=73%; p=0.005) (Figure 2). The studies by Pettus were identified as outliers. This is likely due to co-interventions given in these studies.

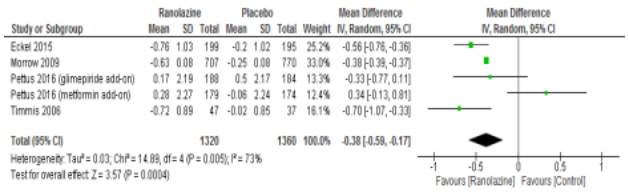

Figure 2: Comparison of changes in HbA1c (%): ranolazine vs. placebo groups.
Data from Pettus et al are least-squares mean change.

Sensitivity analysis showed a difference of HbA1c of -0.49% (CI -0.67, -0.31), favoring the ranolazine group. The heterogeneity improved but remains significant.

There was no statistically significant difference in fasting

blood glucose reduction in ranolazine groups as compared to those who took placebo (2.5 mg/dl, 95% CI -9.7 to 4.7) (Figure 3). Furthermore, there was moderate heterogeneity across studies (I^2=56%; p=0.08).

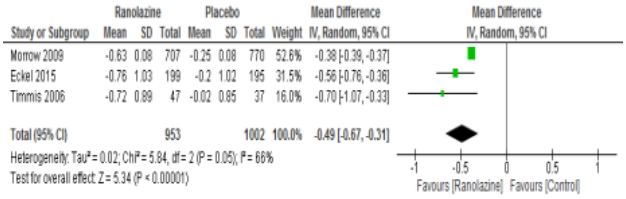

Figure 3: Sensitivity analysis excluding the trials by Pettus: Comparison of changes in HbA1c (%).

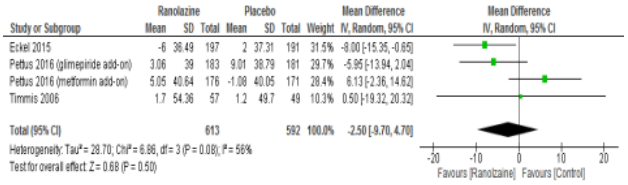

Figure 4: Comparison of changes in FBG (mg/dl) for ranolazine and placebo groups.
Data from Pettus et al are least-squares mean change.

Sensitivity analysis excluding the trials by Pettus showed a difference in FBS of -6.97 mg/dl (CI -13.86 to -0.09) favoring ranolazine. Furthermore, the heterogeneity across the studies was minimized (Figure 4).

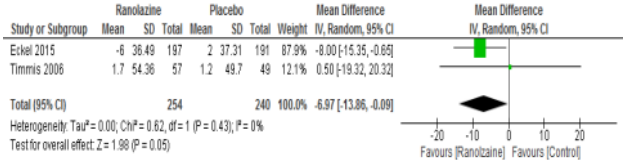

Figure 5: Sensitivity analysis excluding the trials by Pettus: comparison of fasting blood glucose.

There was a statistically significant difference in fasting glucagon, favoring the ranolazine group (-2.70 pg/ml: 95% CI -5.24 to -0.16) (Figure 6). However, there was high heterogeneity across the studies (I^2 = 83%; p=0.003).

There was no statistically significant difference in fasting insulin between ranolazine and placebo (-0.47 µIU/ml; 95% CI -1.56 to 0.62) (Figure 7). There was moderate heterogeneity across studies (I^2=38%; p=0.20).

There was no statistically significant difference in fasting C-peptide in ranolazine groups (95% CI -0.25 to 0.19) -0.03 ng/ml compared to placebo (Figure 8). There was moderate heterogeneity detected across studies (I^2=70%, p=0.04).

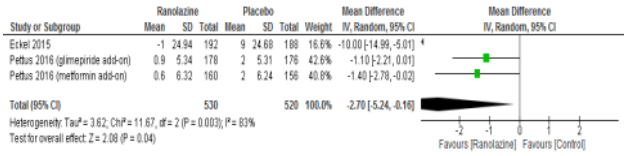

Figure 6: Comparison of changes in fasting glucagon (pg/ml) for ranolazine and placebo groups.
Data from Pettus et al are least-squares mean change.

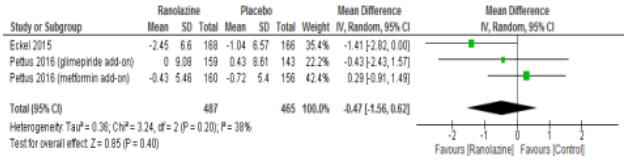

Figure 7: Comparison of changes in fasting insulin (µIU/ml) for ranolazine and placebo groups.
Data from Pettus et al are least-squares mean change.

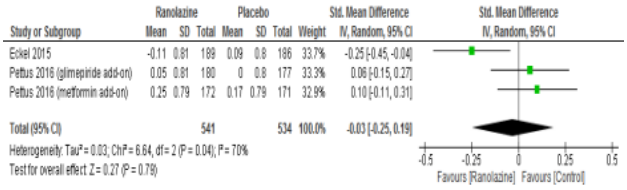

Figure 8: Comparison of changes in fasting C-peptide (ng/ml) for ranolazine and placebo groups.

Data from Pettus et al are least-squares mean change.

Table 1: Baseline characteristics and quality assessment of trials included in the meta-analysis.

Study (year)	Participants	Study design	Interventions	Study duration (weeks)	Key findings	Risk of bias	Quality assessment
Carisa, 2006	N: 121 T2DM with CAD, mean age: 64.5 years	RCT (post-hoc subgroup analysis)	Ranolazine 000 mg tab BID vs placebo	12 weeks	HbA1c; lipid profile; adverse events*	None	A
Merlin Timi, 2009	N: 1,577 T2DM with NSTEMI Mean age: 64 years old	RCT (post-hoc subgroup analysis)	Ranolazine 1000mg tab BID vs placebo	64 weeks	HbA1c; plasma glucose; lipid profile; adverse events*	Dropout rate was not mentioned	B

Continued.

Study (year)	Participants	Study design	Interventions	Study duration (weeks)	Key findings	Risk of bias	Quality assessment
Eckel (2015)	N: 394 T2DM without a history of CVD Mean age: 56 years old	RCT	Ranolazine 1000 mg tab BID vs placebo	24 weeks	HbA1c; fasting plasma glucose; fasting serum C-peptide; fasting plasma glucagon; adverse events	None	A
Pettus glimepiride add-on (GAO), 2016	N: 372 overweight and obese T2DM without a history of CVD mean age: 59 years old	RCT	Ranolazine 1000 mg tab BID as add on to glimepiride 2-4 mg/day vs placebo	24 weeks	HbA1c; fasting plasma glucose; fasting serum C-peptide; fasting plasma glucagon; adverse events	Dropout rate was not mentioned	B
Pettus, metformin add on (MAO), 2016	N: 353 overweight and obese T2DM without history of CVD. Mean age: 56 years old	RCT	Ranolazine 500 mg tab BID as add-on to metformin at least 1500 mg/day vs placebo	24 weeks	HbA1c; fasting plasma glucose; fasting serum C-peptide; fasting plasma glucagon; adverse events	Dropout rate was not mentioned	B

NSTEMI-non ST-elevation myocardial infarction; PCI-percutaneous coronary intervention; A-low bias risk; B-unclear bias risk, *hypoglycemia as an adverse event was not specified in these studies.

Table 2: Tabulation of HbA1c (%).

Study (Years)	Experimental		Control	
Eckel, 2015				
Time	Baseline	24 weeks	Baseline	24 weeks
Mean±SD	8.06±0.735	7.26±1.101	8.02±0.728	7.70±1.183
N	199	199	195	195
Morrow, 2009				
Time	Baseline	4 months	Baseline	4 months
Mean±SD	7.53±1.60	6.9±1.33	7.45±1.66	7.2±1.66
N	707	707	770	770
Pettus, 2016 (GAO)				
Time	Baseline	24 weeks	Baseline	24 weeks
Mean±SD	9.8±2.1	9.9±2.4	9.8±1.8	10.2±2.3
N	188	188	184	184
Pettus, 2016 (MAO)				
Time	Baseline	24 weeks	Baseline	24 weeks
Mean±SD	9.4±1.8	9.4±2.5	9.4±2.1	9.1±2.1
N	179	179	174	174
Timmis, 2006				
Time	Baseline	12 weeks	Baseline	12 weeks
Mean±SD	7.92±1.44	6.93±0.89	7.46±1.28	7.62±0.85
N	47	47	37	37

Table 3: Tabulation of FSG (mg/dl).

Study (Years)	Experimental		Control	
Eckel, 2015				
Time	Baseline	24 weeks	Baseline	24 weeks
Mean±SD	172±34.5	165±40.4	171±34.6	169±40.3
N	197	197	191	191
Pettus, 2016 (GAO)				
Time	Baseline	24 weeks	Baseline	24 weeks
Mean±SD	176.58±37.84	178.38±43.24	176.58±32.43	183.78±41.44
N	183	183	181	181
Pettus, 2016 (MAO)				
Time	Baseline	24 weeks	Baseline	24 weeks

Continued.

Study (Years)	Experimental		Control	
Mean±SD	169.37±32.43	169.37±45.05	169.37±37.84	163.96±37.84
N	176	176	171	171
Timmis, 2006				
Time	Baseline	12 weeks	Baseline	12 weeks
Mean±SD	165.2±7.8	-	177.8±10.8	-
N	57	57	49	49

Table 4: Tabulation of fasting glucagon (pg/ml).

Study (Years)	Experimental		Control	
Eckel, 2015				
Time	Baseline	24 weeks	Baseline	24 weeks
Mean±SD	85±28.9	84±28.5	86±26.1	93±32.3
N	192	192	188	188
Pettus, 2016 (GAO)				
Time	Baseline	24 weeks	Baseline	24 weeks
Mean±SD	25±8	26±8	24±8	26±8
N	178	178	176	176
Pettus, 2016 (MAO)				
Time	Baseline	24 weeks	Baseline	24 weeks
Mean±SD	26±7	26±8	26±8	28±9
N	160	160	156	156

Table 5: Tabulation of fasting insulin (µIU/ml).

Study (Years)	Experimental		Control	
Eckel, 2015				
Time	Baseline	24 weeks	Baseline	24 weeks
Mean ± SD	13.85±9.081	11.66±7.484	14.84±10.79	13.18±10.46
N	168	168	166	166
Pettus, 2016 (GAO)				
Time	Baseline	24 weeks	Baseline	24 weeks
Mean ± SD	14.54±11.23	14.54±14.25	12.96±7.78	13.68±9.36
N	159	159	143	143
Pettus, 2016 (MAO)				
Time	Baseline	24 weeks	Baseline	24 weeks
Mean ± SD	12.53±8.35	12.24±7.63	12.67±10.08	11.66±7.78
N	160	160	156	156

Table 6: Tabulation of fasting C-peptide (ng/ml).

Variables	Experimental		Control	
Eckel, 2015				
Time	Baseline	24 weeks	Baseline	24 weeks
Mean ± SD	2.55±1.002	2.46±0.943	2.65±1.106	2.68±1.175
N	189	189	186	186
Pettus, 2016 (GAO)				
Time	Baseline	24 weeks	Baseline	24 weeks
Mean ± SD	2.67±1.05	2.70±0.99	2.58±1.02	2.58±0.96
N	180	180	177	177
Pettus, 2016 (MAO)				
Time	Baseline	24 weeks	Baseline	24 weeks
Mean ± SD	2.40±1.08	2.64±1.08	2.31±1.08	2.49±0.93
N	172	172	171	171

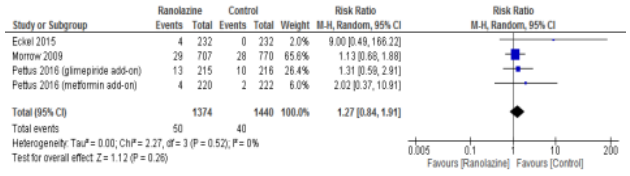

Figure 9: Comparison of events of hypoglycemia for ranolazine and placebo groups.

There was no statistically significant difference in the incidence of hypoglycemia between ranolazine and placebo (RR 1.27 95% CI 0.84 to 1.91) (Figure 9). Heterogeneity across studies was not statistically detected (I^2=0%, p=0.52).

DISCUSSION

The role of glucagon in T2DM has been studied extensively, with several studies implicating its contribution to rise in fasting and postprandial glycemia. Ranolazine, a novel antianginal drug, has shown promising results in reducing HBA1C, which is the standard marker in determining blood sugar control for the past 3 months. Ranolazine acts on $Na_v1.3$ isoform of sodium channels in pancreatic α-cells in animal models of diabetes, blocking glucagon release. By this mechanism, it is theorized that fluctuations in serum glucose level are avoided, translating to controlled glycemic status.

Result of this meta-analysis showed statistically significant difference in HbA1c favoring ranolazine. In sensitivity analysis, there was -0.49% (CI -0.67, -0.31) HbA1c difference between ranolazine compared to placebo. Likewise, there was a significant difference in FBS of -6.97 mg/dl (CI -13.86 to -0.09), favoring ranolazine. These glycemic effects are comparable to the HbA1c and FBS reduction of less potent oral anti-diabetic agents such as alpha-glucosidase inhibitors or even DPP4 enzyme inhibitors.

Our findings are similar to previous studies that have investigated the efficacy of ranolazine in reducing HBA1C levels. For instance, a study conducted by Chaitman et al found that ranolazine reduced HBA1C levels by 0.5% compared to placebo.[14] Similarly, a study by Morrow et al found that ranolazine reduced FBS levels by 8.4 mg/dl compared to placebo.[15] In another study by Kosiborod et al ranolazine was also found to significantly reduce HBA1C levels compared to placebo after 12 weeks of treatment.[16]

However, the moderate to high heterogeneity across the studies, even after sensitivity analysis, hinders a more solid conclusion. In addition, while our findings support the efficacy and safety profile of ranolazine in improving glucose control in patients with T2DM, further research is needed to confirm these results and determine the optimal dosing regimen.

Lastly, our analysis revealed a significant difference in fasting glucagon of -2.7 pg/ml (95% CI -5.24, -0.16), favoring ranolazine. As previously discussed, the action of ranolazine is to decrease glucagon secretion. This explains the reduction in HbA1c and FBS seen in the ranolazine group. This is an expected finding and is consistent with previous studies that have investigated the effect of ranolazine on glucagon secretion. For instance, a study by Suzuki et al found that ranolazine significantly reduced fasting glucagon levels compared to placebo.[17]

Despite the difference in FBS and HbA1c, the risk of hypoglycemia with ranolazine is comparable with placebo (RR 1.27 95% CI 0.84 to 1.91).

These findings support the efficacy and safety profile of this drug in improving glucose control in patients with T2DM.

Limitations

Among the 5 eligible articles, one study has not been included. The study only investigated the effect of ranolazine on hbA1c as a secondary outcome, only after exposing patients to ranolazine post-PCI. Data supplemented by the study was not adequate for sufficient extraction. Efforts to contact the authors were made; however, insufficient data were provided at the time of manuscript writing.

CONCLUSION

Among patients with T2DM, ranolazine may improve glycemic control with a modest decrease in HBA1c and FBS. It appears to be safe with a risk for hypoglycemia comparable to placebo. However, data on its use as an add-on to metformin or glimepiride are less robust. The glycemic effect is likely due to its ability to reduce glucagon, as seen in the pooled analysis. This mechanism of action is supported by available pre-clinical data. It may be a useful medication for patients with T2DM suffering from chronic stable angina, as it may help alleviate the cardiac symptom with the added benefit of improvement in glycemic control. Future studies may want to investigate the effect of ranolazine among T2DM patients with high cardiovascular risk. It may be worthwhile to look at clinical outcomes such as the risk of microvascular or macrovascular complications and major adverse cardiovascular events in this population. Furthermore, a longer duration of follow-up may also elucidate ranolazine's long-term safety and efficacy. Lastly, its efficacy and safety as an add-on therapy to other anti-diabetic agents need further investigation.

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REFERENCES

1. NA. Diabetes Mellitus: A Major Risk Factor for Cardiovascular Disease. Circulation. 1999;100(10):1132-3.
2. Statistics about Diabetes. 2017. Available at: http://www.diabetes.org/diabetesbasics/statistics. Accessed on 25 July 2023.
3. Adult Treatment Panel III. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. Circulation. 2002;106:3143-421.
4. Herlitz J, Wognsen GB, Karlson BW, Sjöland H, Karlsson T, Caidahl K, et al. Mortality, mode of death and risk indicators for death during 5 years after coronary artery bypass grafting among patients with and without a history of diabetes mellitus. Coron Artery Dis. 2000;11(4):339-46.
5. Duarte R, Castela S, Reis RP, Correia MJ, Ramos A, Pereira AP, et al. Acute coronary syndrome in a diabetic population-risk factors and clinical and angiographic characteristics. Rev Port Cardiol. 2003;22(9):1077-88.
6. Chaitman BR, Pepine CJ, Parker JO, Skopal J, Chumakova G, Kuch J, et al. Combination Assessment of Ranolazine in Stable Angina (CARISA) Investigators. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. JAMA 2004;291(3):309-16.
7. Belardinelli L, Shryock JC, Fraser H. The mechanism of ranolazine action to reduce ischemia-induced diastolic dysfunction. Eur Heart J. 2006;8:A10-13.
8. Morrow DA, Scirica BM, Chaitman BR, McGuire DK, Murphy SA, Karwatowska-Prokopczuk E, et al. Evaluation of the glycometabolic effects of ranolazine in patients with and without diabetes mellitus in the MERLIN-TIMI 36 randomized controlled trial. Circulation. 2009;119(15):2032-9.
9. Ning Y, Zhen W, Fu Z, Jiang J, Liu D, Belardinelli L, et al. Ranolazine increases b-cell survival and improves glucose homeostasis in low-dose streptozotocin-induced diabetes in mice. J Pharmacol Exp Ther. 2011;337(1):50-58.
10. Pettus J, McNabb B, Eckel RH, Skyler JS, Dhalla A, Guan S, et al. Effect of ranolazine on glycaemic control in patients with type 2 diabetes treated with either glimepiride or metformin. Diabetes Obesity Metabol. 2016;18(5):463-74.
11. Selvarajan S, Dkhar SA, Pillai AA, George M, Jayaraman B, Chandrasekaran A. Comparison of Ranolazine and Trimetazidine on Glycemic Status in Diabetic Patients with Coronary Artery Disease-A Randomized Controlled Trial. J Clin Diagnostic Res. 2015;9(1):OC01-5.
12. Timmis AD, Chaitman BR, Crager M. Effects of ranolazine on exercise tolerance and HbA1c in patients with chronic angina and diabetes (subgroup analysis of patients in Combination Assessment of Ranolazine in Stable Angina (CARISA) trial). European Heart J. 2006;27(1):42-8.
13. Eckel RH, Henry RR, Yue P, Dhalla A, Wong P, Jochelson P, et al. Effect of Ranolazine Monotherapy on Glycemic Control in Subjects with Type 2 Diabetes. Diabetes Care. 2015;38(7):1189-96.
14. Chaitman BR, Skopal J, Pepine CJ, Parker JO, Chumakova G, Kuch J, et al. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. J Am College Cardiol. 2010;56(14):934-42.
15. Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, Murphy SA, Budaj A, Varshavsky S, et al. Effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes: the MERLIN-TIMI 36 randomized trial. JAMA. 2017;297(16):1775-83.
16. Kosiborod M, Lam CS, Kohsaka S, Kim DJ, Karasik A, Shaw J, et al. Cardiovascular events associated with SGLT-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL 2 study. Journal of the American College of Cardiol. 2018;71(23):2628-39.
17. Suzuki T, Hirata Y, Yoshida M, Ishii J, Suzuki S, Hinokio Y. Ranolazine suppresses glucagon secretion via inhibition of voltage gated sodium channel Nav1.3 in pancreatic alpha cells. Diabetologia, 2015;58(3):464-72.
18. Fanaroff A, James SK, Weisz G, Prather K, Anstrom KJ, Mark DB, et al. Ranolazine After Incomplete Percutaneous Coronary Revascularization in Patients with Versus Without Diabetes Mellitus (RIVER-PCI Trial). J Am Coll Cardiol. 2017;69(18):2304-13.

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