Efficacy of Ranolazine in Lowering HbA1c in Patients with Type 2 Diabetes Mellitus: A Meta-analysis

Everly Faith Ramos, M.D.*; Angelique Bea Uy, M.D.*; Aldrin B. Loyola, M.D.**

Abstract

Introduction: Cardiovascular diseases and diabetes mellitus (DM) are two disease entities that commonly coexist in a single patient. Ranolazine is an active piperazine derivative approved by FDA in 2006 as an anti-anginal medication. It was noted to have HbA1c lowering effects in the trials on angina. The proposed mechanism of action is the inhibition of glucagon secretion by blocking the Na v1.3 isoform of sodium channels in pancreatic alpha cells leading to glucagon- and glucose-lowering effects. HbA1c lowering to a target of 6.5% in type 2 diabetes patients has been shown to reduce risk of microvascular complications. The objective of this study is to determine the efficacy and safety of Ranolazine in HbA1c lowering as an add-on therapy to existing anti-diabetic regimen.

Methods: A comprehensive literature search in PubMed, The Cochrane Central Register of Controlled Trials, the ClinicalTrials.gov website, Google Scholar databases and EMBASE databases were made using the search terms "Randomized controlled trial", "Ranolazine," "HbA1c," and "glycosylated hemoglobin", as well as various combinations of these, was done to identify randomized control trials. No restriction on language and time were done. The authors extracted data for characteristics, quality assessment and mean change in HbA1c after at least eight weeks of treatment with ranolazine. The program RevMan 5.3 was used to generate the statistical analysis of the data.

Results: Six RCTs were included to make up a total of 1,650 diabetic patients. Five studies had moderate risk of bias assessment while one had low risk of bias assessment and hence was not included in the analysis. The overall analysis showed an HbA1c reduction of 0.35% 0.68 to -0.03, *p*-value=0.03) however, the population was heterogenous (I^2=100%). The heterogeneity was not eliminated by sensitivity analysis.

Discussion: The results showed a statistically significant lowering of HbA1c with ranolazine. However, the population was heterogenous. The sources of heterogeneity could be the (1) differences in the level of glycemic control among subjects as indicated by baseline HbA1c levels, (2) the current anti-diabetic regimen of the study patients, i.e. whether or not they are on insulin therapy, (3) the presence or absence of ischemic heart disease and (5) duration of ranolazine therapy, and (4) the presence or absence of chronic kidney disease. When the analysis excluded the population with combination insulin therapy and ranolazine, the effect becomes non-significant. Thus, the HbA1c lowering effect may have been from the insulin therapy rather than the ranolazine.

Conclusion: Ranolazine as anti-diabetic therapy shows statistically significant HbA1c lowering effect. It can be a potential treatment option for patients with both DM and angina pectoris. However, well-designed, prospective trials are still recommended to determine the effect on a less heterogenous population. Likewise, more studies are needed to determine its safety.

Keywords: ranolazine, HbA1c

Introduction

Diabetes mellitus (DM) is one of the most common non-communicable diseases worldwide. It is a chronic disease that shows rising global disease burden, morbidity and mortality rates. By the year 2030, it is predicted that diabetes will be the seventh leading cause of death in the world and the primary cause of blindness, amputation and kidney failure. In patients afflicted with the disease, about 50-80% die of cardiovascular diseases.[1]

Glycosylated hemoglobin (HbA1c) test has been used as a measure of the average level of blood glucose in the past 60–120 days. HbA1c target of 6.5% is recommended for diabetic patients on the basis that it lowers the risk of developing diabetic complications. The UK Prospective Diabetes Study (UKPDS) established that intensive control of blood glucose in type 2 diabetes reduced the risk of microvascular complications, especially diabetic retinopathy, in patients with type 2 diabetes, while it did not find any effect on cardiovascular events.[2]

*Resident in Training, Department of Medicine, University of the Philippines-Philippine General Hospital
**Consultant, Section of Adult Medicine, Department of Medicine, University of the Philippines-Philippine General Hospital

Corresponding author: Everly Faith Ramos, M.D., University of the Philippines – Philippine General Hospital, Manila, Philippines
Email:everlyfaith.ramos@gmail.com

Ranolazine(((+)N-(2,6-dimethylphenyl)-4(2-hydroxy-3-(2-methoxyphenoxy)-propyl)-1-piperazineacetamide-dihydrochloride)) is an active piperazine derivative approved by FDA in 2006 for chronic angina. In experimental studies in canine myocytes and guinea pig hearts, ranolazine showed a concentration, voltage, and frequency-dependent inhibition of late sodium current. The delayed or incomplete inactivation of late sodium current is implicated in the heart failure model of canine ventricular myocytes and is noted to be increased in conditions associated with the pathological milieu of ischemia.[3,4] This in turn prevents intracellular sodium overload that causes intracellular calcium influx through the Na^{+}-Ca^{++}exchanger that is responsible for contractile dysfunction and cellular injury.

In the conduct of clinical trials evaluating the efficacy of ranolazine as an anti-anginal agent, HbA1c lowering was also observed among diabetic patients included in the study population. This putative anti-diabetic property of ranolazine has been tested in animal studies which yielded the following plausible mechanisms of action: (1) ranolazine was found to lower fasting and non-fasting glucose levels and preserve pancreatic beta cells in streptozotocin-treated mice and Zucker diabetic fatty rats and (2) ranolazine inhibits glucagon secretion by blocking the Na v1.3 isoform of sodium channels in pancreatic alpha cells leading to glucagon- and glucose-lowering effects.[5]

The hypothesis generated in these observations triggered the conduct of randomized controlled trials evaluating ranolazine as add-on medication to existing anti-diabetic regimen. To date, there is no published meta-analysis on the effect of ranolazine on HbA1c lowering. Since cardiovascular diseases and DM are two disease entities that commonly coexist in a single patient. If proven to be an effective anti-diabetic agent, ranolazine can become a primary regimen for patients with chronic angina and DM. Moreover, the glucagon-producing alpha cells as the target of action of ranolazine offers a novel therapeutic target in treating DM.

This study aims to answer the clinical question: among patients with type 2 DM, how effective is ranolazine in lowering HbA1c? This is a systematic review and meta-analysis on the effect of ranolazine in the glycemic control of patients with DM. Specifically, the study aimed to determine the effect of ranolazine on the HbA1c levels of diabetic patients. It also aimed to identify potential adverse events with its use.

Methods

This study included randomized control trials which evaluated the effect of ranolazine on HbA1c levels of adult patients with DM, expressed as mean change after at least 12 weeks of intervention.

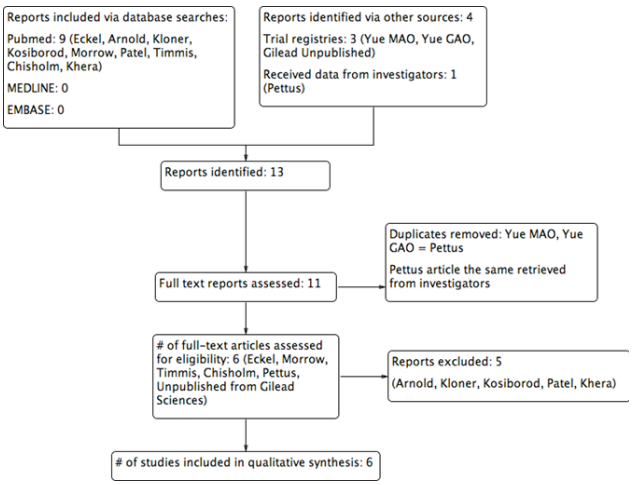

Figure 1. Study flow diagram. Study identification and selection process.

A systematic literature search on PubMed, The Cochrane Central Register of Controlled Trials, the ClinicalTrials.gov Website, Google Scholar databases and EMBASE databases using the search terms "Randomized controlled trial", "Ranolazine," "HbA1c," and "glycosylated hemoglobin", as well as various combinations of these, was done to identify potential studies. Cross-checking of references and citations in review articles were carried out. Gilead Sciences was contacted to obtain data on one unpublished randomized control trial done on diabetic patients. No language or time restriction was implemented. Only adult human trials were included. Figure 1 shows the literature search algorithm.

Included studies met the following specifications: (1) RCT design, (2) patients with Type 2 DM diagnosed by a fasting plasma glucose ≥126 mg/dl, HbA1c ≥ 6.5%, random blood glucose of ≥200 mg/dl with symptoms of hyperglycemia, two-hour oral glucose tolerance test of ≥200 mg/dl; (3) inclusion of subjects randomized to either placebo or ranolazine on top of current anti-diabetic regimen. The exclusion criteria are as follow: critically-ill patients, post-operative patients and patients with type 1 DM. Studies which reported mean HbA1c change after the pre-specified duration of treatment is included in the analysis. Mean HbA1c change was derived for studies which did not directly report this outcome

The primary endpoint is (1) mean change, expressed as least squares mean, in HbA1c after at least 12 weeks of ranolazine treatment (2) incidence of hypoglycemia and other adverse events with ranolazine therapy. No secondary outcomes were sought.

Results were expressed as weighted mean differences with their 95% CI computed. We evaluated heterogeneity across included studies using Chi^2 and I^2 statistics. Studies with an I^2 statistic of 25 to 50% were considered to have low

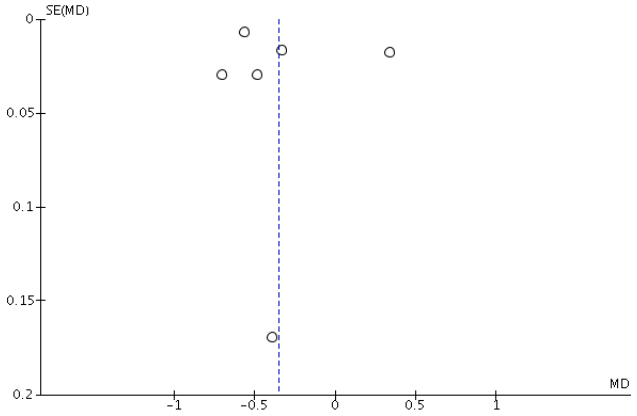

Figure 2. Funnel plot analysis.

heterogeneity, those with an I^2 statistic of 50-75% to have moderate heterogeneity, and those with an I^2 statistic of greater than 75% to have high degree of heterogeneity. In cases of heterogeneity, the random effects model was used. Subgroup analysis for the following groups were done: ranolazine dose of at least 1,000 mg BID, ranolazine on top of oral anti-diabetic agents, ranolazine in prospective trials in diabetic patients i.e., post hoc analyses of angina trials excluded.

All statistical analyses were performed using Review Manager Version 5.3. A *p*-value of less than 0.05 was considered statistically significant. Sensitivity analyses were performed using the one-study-out method in order to address the influence of each study by testing whether deleting each individually would significantly change the pooled results of the meta-analysis. Additionally, the random effect model was applied to all outcomes to assess if there were changes in the final effect.

Two reviewers (EFP and ABU) independently extracted data from the identified RCTs. Assessment of eligibility of studies were be done by applying the selection criteria. The Cochrane's Collaboration's tool for assessing risk of bias were used to assess the quality of the included RCTs. Disagreements were resolved by consensus or, if necessary, by a third party.

Results

Study selection and characteristics

The search strategy identified a total of 13 potential articles (Figure 1). After removing duplicates and articles that did not meet inclusion criteria, we screened 11 titles and abstracts. Of these, 11 were selected for further review. Ultimately, six RCTs satisfied all inclusion criteria. All selected studies were published in journals as full english manuscripts. One unpublished study from Gilead Sciences was included in this review. Data were obtained from clinicaltrials.gov. Two studies, namely, Timmis and the unpublished from Gilead Sciences were eventually not included in the analysis because the results were not expressed as mean change in HbA1c i.e., in least squares mean. The remaining four RCTs make up for a total of 1,650 diabetic patients. The excluded studies include that of Arnold and Kosiborod since HbA1c was not included in the study outcome, Kloner and Patel being review articles, and Khera an editorial. Funnel plot analysis (Figure 2) showed high quality, precise studies but with potential risk of bias.

Table 1 shows the characteristics of the studies included in this systematic review and meta-analysis. Two studies were post hoc analyses of HbA1c data obtained from the diabetic population in ranolazine angina trials (MERLIN-TIMI 36 and CARISA).[10] Three studies had HbA1c lowering in diabetic patients as primary outcome.

The dose of ranolazine in the studies was either 500 mg, 750 mg or 1,000 mg taken twice daily per orem except that of Chisholm et al. which gave an initial dose of 1,000 mg intravenously before shifting to oral administration. The duration of treatment varied, with the shortest being at eight weeks and the longest at 24 weeks. Common outcome measures were change from baseline in HbA1c, fasting blood sugar and two-hour post prandial glucose. Six studies were judged to have low risk of bias while one had high risk of bias (Table II).

Quantitative data synthesis

The overall analysis included a total of 1,650 patients. It showed high heterogeneity with an I^2 of 100%. The results showed that ranolazine lowers HbA1c by 0.35% (-0.68 to -0.03, *p*-value=0.03)(Figure 3). Figure 4 shows analysis excluding Timmis 2005. This study had insulin as baseline anti-diabetic treatment and contributed the smallest population but the largest effect on HbA1c lowering. The result showed a trend favoring ranolazine however, this was not signficant (*p*=0.31).

Figure 5 shows analysis excluding Yue MAO which is the outlier in the overall analysis. The result showed a greater effect favoring ranolazine with an HbA1c lowering of 0.5% (-0.64 to -0.37, *p*-value=<0.00001). It also minimally lowered the heterogeneity with an I^2 of 98%.

Figure 6 shows the analysis including only the Yue GAO and Yue MAO studies. These studies were prospective trials on ranolazine as add-on therapy to either Glimeperide (GAO) or Metformin (MAO). They were done by the same authors and had similar inclusion and exclusion criteria. The result showed that ranolazine had no effect on HbA1c lowering, however this was not statistically significant (*p*=0.99) and had high heterogeneity I^2=100%.

Table I. Characteristics of included studies

Study	Population	Intervention	Outcome measure	Outcome	Methodology	Limitations
Eckel RH, et al.[5] Diabetes Care 2015	Patients with Type 2 Diabetes Mellitus with HbA1c 7-10% (N=465) • Treatment naïve • Washed off of all antihyperglycemic therapy for 90 days • Placebo (N=232) • Ranolazine (N=233)	Ranolazine 500 mg BID uptitrated to 1000 mg BID after 7 days vs Placebo	• 24-week change from baseline in HbA1c • Change from baseline in FSG • Proportion of subjects with HbA1c <7.0% • Change from baseline in 2-h post-prandial glucose	-0.56 ±0.014	Randomized, double-blind, placebo controlled	Mean difference derived
Timmis AD, et al.[6] European Heart Journal 2006	CARISA Trial Patients with CAD and a minimum 3-month history of exertional angina (N=823) • Diabetes Mellitus (N=189)	Diabetic population • Placebo + non-insulin medication (N=38) • Placebo + insulin (N=11) • Ranolazine 750 mg BID + non-insulin medication (N=54) • Ranolazine 750 mg BID + insulin medication (N=13) • Ranolazine 1000 mg BID + non-insulin medication (N=52) Ranolazine 1000 mg BID + insulin medication (N=11)	• 12-week change from baseline in HbA1c as least-squares mean in Diabetic patients as post hoc analysis	-0.19 ±0.16 0.42 ± 0.26 -0.54 ± 0.15 (p=0.087) -0.41 ± 0.23 (p=0.016) -0.74 ± 0.15 (p=0.007) -0.63 ± 0.3 (p=0.008)	Randomized, double-blind, 3-group parallel trial	Post hoc analysis of data from angina trial
Chisholm JW, et al.[7] Diabetes Care 2010	MERLIN-TIMI 36 Trial • Patients with NSTE-ACS (N=6560) • Diabetic patients (N=1734) • Diabetic patients with A1c measurements at randomization and month 4 (N=1477)	• Placebo + insulin medication (N=217) • Placebo + antihyperglycemicmonotherapy (N=385) • Placebo + antihyperglycemic dual therapy (N=218) • Placebo + 3 or more antihyperglycemic drugs (N=38) • Placebo + no antidiabetic drug (N=128) • Ranolazine 1000 mg BID + insulin medication (N=193) • Ranolazine 1000 mg + antihyperglycemicmono-therapy (N=335) • Ranolazine 1000 mg + antihyperglycemic dual therapy (N=204) • Placebo + 3 or more antihyperglycemic drugs (N=34) • Ranolazine 1000 mg + no antidiabetic drug (N=134)	4-month change in HbA1c from baseline as retrospective exploratory analysis	• A1c 6-<8% group 0.28% (p=0.045) • A1c ≥8-10% 0.59% (p=0.001) • HbA1c ≥6.5-10% -0.39% (p=0.007)	Randomized, double-blind, placebo controlled	Post hoc analysis of data from angina trial
Gilead Sciences Yue (GAO) NCT01494987 Pettus J, et al.[8] Diabetes, Obesity and Metabolism 2016	Patients 18-75 years with Type 2 Diabetes Mellitus on Glimeperide/ Glipizide/ Glyburide/ Glibenclamide (N=431)	• Placebo + Glimeperide 2-4 mg/ day OR Glipizide/Glyburide/ Glibenclamide≥7.5 mg/ day OR Gliclazide> 160 mg/day (N= 216) • Ranolazine 1000 mg BID + Glimeperide 2-4 mg/day ORGlipizide/ Glyburide/ Glibenclamide≥7.5 mg/day OR Gliclazide> 160 mg/day (N= 215)	Mean and LSM change at 24 weeks in: • HbA1c • FSG • 2-h PP • FSG-corrected 2-h PP glucose rise • Mean glucose for 3h after mixed meals	0.03% (0.949) -0.47% (0.971)	Randomized, double-blind, placebo-controlled	

Table I. Characteristics of included studies (continuation)

Gilead Sciences Yue (MAO)[8] NCT01555164 Pettus J, et al. Diabetes, Obesity and Metabolism 2016	Patients 18-75 years with Type 2 Diabetes Mellitus on Metformin ≥1500 mg/day for ≥90 days (N=442)	• Placebo + Metformin ≥1500 mg/day (N=222) • Ranolazine 1000 mg BID + Metformin ≥1500 mg/day (N=220)	Mean and LSM change at 24 weeks in: • HbA1c • FSG • 2-h PP • FSG-corrected 2-h PP glucose rise • Mean glucose for 3h after mixed meals	-0.2% (0.949) -0.37% (0.916)	Randomized, double-blind, placebo-controlled	
Gilead Sciences[9] NCT01163721 Unpublished	Patients with Type 2 Diabetes Mellitus on non-insulin antidiabetic therapy (N=80)	• Placebo on top of non-insulin antidiabetic therapy (N=41) • Ranolazine 1000 mg BID on top of non-insulin anti-diabetic therapy (N=39)	Mean change at 12 weeks in(least squares mean): • HbA1c • FSG • 2-h PP	-0.08% (0.142) -0.61% (0.142)	Randomized, double-blind, placebo-controlled	Significant drop-out rate Data on baseline antidiabetic therapy not available

Table II. Assessment of risk of bias of individual studies

Study	Randomization	Allocation concealment	Performance bias	Detection bias	Attrition bias	Reporting bias	Overall grading of bias
Eckel RH, et al. Diabetes Care 2015	Low	Unclear	Low	Low	Unclear	Low	Moderate
Timmis AD, et al. European Heart Journal 2006	Low	Unclear	Low	Low	Unclear	Low	Moderate
Chisholm JW, et al. Diabetes Care 2010	Low	Unclear	Low	Low	Unclear	Low	Moderate
Gilead Sciences Yue (GAO) NCT01494987 Pettus J, et al. Diabetes, Obesity and Metabolism 2016	Low	Unclear	Low	Low	Drop-out rate 13%	Low	Moderate
Gilead Sciences Yue (MAO) NCT01555164 Pettus J, et al. Diabetes, Obesity and Metabolism 2016	Low	Unclear	Moderate	Low	Drop-out rate 17%	Low	Moderate
Gilead Sciences NCT01163721 Unpublished	Low	Unclear	Low	Low	Drop-out rate 25%	Low	High

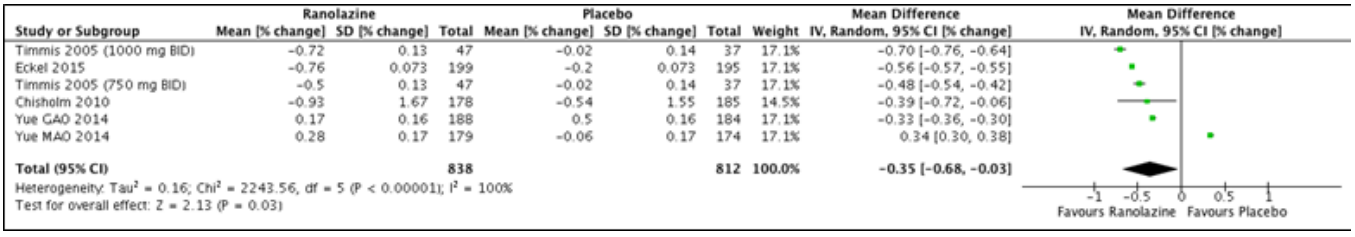

Figure 3. Overall analysis of the effect of ranolazine on HbA1c

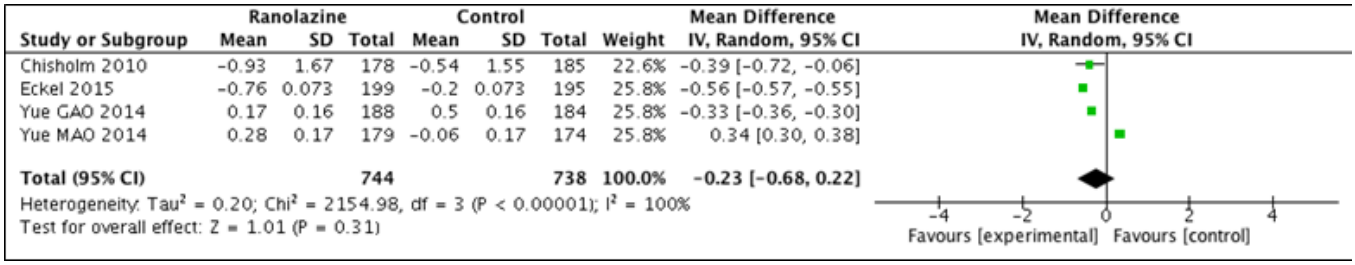

Figure 4. Sensitivity analysis excluding Timmis 2005

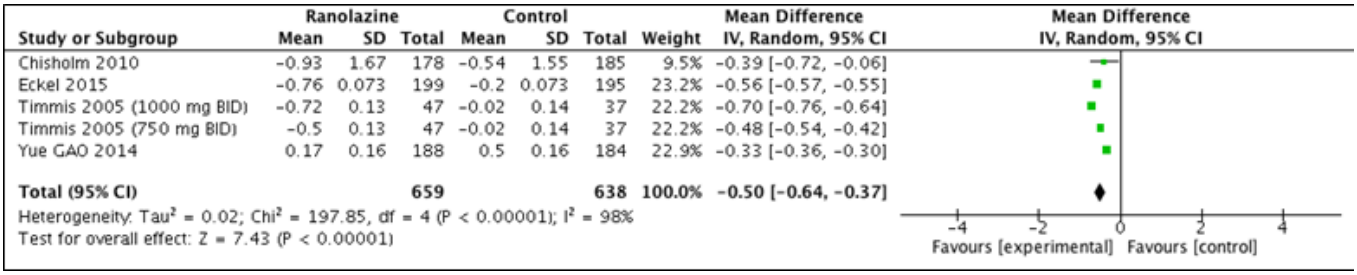

Figure 5. Sensitivity analysis excluding Yue MAO 2014

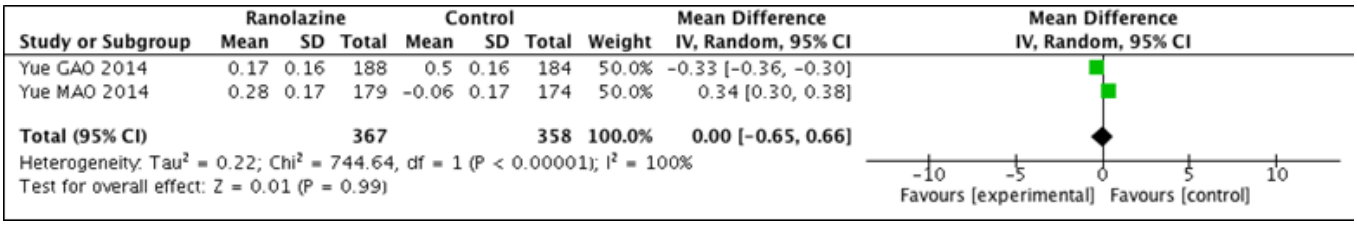

Figure 6. Sensitivity analysis comparing the studies Yue GAO and Yue MAO.

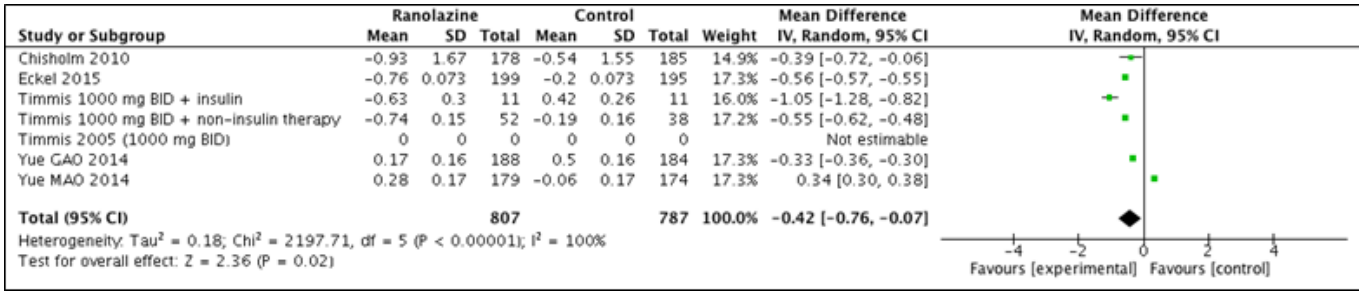

Figure 7. Sensitivity analysis of ranolazine 1000 mg BID dose.

A sensitivity analysis on the effect of ranolazine 1000 mg dose was done to determine if there is any dose-response relationship (Figure 7). It showed that ranolazine lowered HbA1c by 0.42% (-0.76 to -0.07, *p*-value=0.02). This difference, however was not statistically significant from the effect in the overall analysis.

Qualitative data synthesis

Only two studies reported adverse events, summarized in Table III. The studies did not report significant differences in the occurence of adverse events between the study groups.

Discussion

This is a systematic review and meta-analysis on the effect of ranolazine on HbA1c levels among patients with type 2 DM. To our knowledge this is the first meta-analysis of RCTs to examine such efficacy and safety. This study included a total of 1,650 diabetic patients from five RCTs. The analysis generated the following results: (1) there is a trend favoring the effect of ranolazine on HbA1c lowering, (2) the magnitude of the lowering did not increase when analysis was limited to higher doses of the drug, i.e. 1000 mg BID, (3) the exploration of the safety profile of ranolazine is still limited.

Table III. Adverse events reported on ranolazine treatment.

Adverse effect	Number of events	Study
Discontinuation due to adverse events	21/364 (5.8%)	Eckel, et al. Timmis, et al.
Any AE	97/232 (41.8%)	Eckel, et al.
Hyperglycemia	19/232 (8.2%)	Eckel et al.
Constipation	27/364 (7.4%)	Eckel, et al. Timmis, et al.
Dizziness	12/364 (3.3%)	Eckel, et al. Timmis, et al.
Nausea	14/364 (3.8%)	Eckel, et al. Timmis, et al.
Angina	4/132 (3.0%)	Timmis, et al.
Asthenia	6/132 4.5%	Timmis, et al.

The results, although statistically significant, should be taken with caution as the population is very heterogenous. The studies included in this review were both post hoc analysis of data obtained from diabetic patients included in angina trials of ranolazine as well as two prospective studies which evaluated the effect of ranolazine on HbA1c when used as add-on therapy to baseline anti-diabetes medications. While the baseline characteristics of the population studied in the angina trials showed no significant differences, isolating the diabetic subgroup from this population may have removed the effect of randomization. Specifically, the sources of heterogeneity could be the (1) differences in the level of glycemic control among subjects as indicated by baseline HbA1c levels, (2) the current anti-diabetic regimen of the study patients, i.e. whether or not they are on insulin therapy, (3) the presence or absence of ischemic heart disease and (5) duration of ranolazine therapy, and (4) the presence or absence of chronic kidney disease. Ranolazine, being a relatively new drug do not have established pharmacokinetic and drug interaction profile yet. Its interaction with the different baseline anti-diabetic medications of the patients could have also contributed to heterogeneity. Heterogeneity was not eliminated even when sensitivity analysis was performed.

The sensitivity analysis excluding Timmis 2005 differed because it showed non-significant HbA1c lowering with ranolazine treatment Figure 4. Although it was a relatively small study contributing only 112 patients, the ranolazine added to insulin arm of this study contributed the highest reduction in HbA1c at 1.05% (-1.28 to -0.82). The greater lowering in HbA1c observed in this arm, therefore, could have been from the insulin therapy and not from ranolazine. In the pooled analysis, it was noted that the study Yue MAO favors placebo (Figure 3). It was also expected that heterogeneity will decrease when the Yue GAO and Yue MAO studies were compared. Upon review, the authors concluded that the difference in the result stemmed from the study design. The investigators in Yue MAO adjusted the metformin doses in the intervention group to account for the theoretical pharmacokinetic interaction between metformin and ranolazine. This was based on Phase I clinical studies in patients with type 2 DM showing a 1.53-fold increase in plasma Metformin concentration among patients taking ranolazine 1000 mg and Metformin 1000 mg.[11] This dose adjustment in the study design resulted in the possible underdosing of the medications and this translated into an increased HbA1c. Thus, when the Yue MAO and Yue GAO were compared (Figure 6), heterogeneity was not eliminated despite having similar baseline patient characteristics. In conclusion, the attempt to cluster the two studies because they were the only ones done prospectively on diabetic patients not in angina trial, was an unfair comparison.

Only two studies (Eckel et al. and Timmis et al.) reported adverse events and the observation period spanned only 12-24 weeks. Pettus et al. cited that the study of Eckel et al. have established cardiovascular safety of ranolazine among patients with type 2 DM. However, the authors believe that further studies are needed because of the limited follow-up duration and population size. ranolazine's drug interaction with Metformin, as well as the other anti-diabetic medications, if indeed clinically significant should be investigated.

Conclusion

Ranolazine as an anti-diabetic therapy shows statistically significant HbA1c lowering effect. It can be a potential treatment option forpatients with both DM and angina pectoris. However, well-designed, prospective trials are still recommended to determine the effect on a less heterogenous population. Likewise, more studies are needed to determine safety.

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