

# openheart Effect of ranolazine on glycaemia in adults with and without diabetes: a meta-analysis of randomised controlled trials

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## ABSTRACT

**Background** Ranolazine is an antianginal drug reported to have hypoglycaemic effects.

**Objectives** To assess the effect of ranolazine versus placebo on glycaemic control for adults with and without diabetes.

**Methods** A systematic search of seven databases was conducted to identify all randomised controlled trials that compared the effect of ranolazine versus placebo on haemoglobin A1c (HbA1c) and/or fasting plasma glucose (FPG) and/or incidence of hypoglycaemia. We used mean differences in HbA1c and FPG to express intervention effect estimates and analysed the data with random-effects model for meta-analyses using Revman 5.3.

**Results** We identified seven trials including 6543 subjects to assess the effect of ranolazine on HbA1c and/or FPG. A separate trial that included 944 subjects was included to assess the effect of ranolazine on hypoglycaemia. The change in HbA1c for all patients was  $-0.36\%$  (95% CI  $-0.57\%$  to  $-0.15\%$ ;  $p=0.0004$ ,  $I^2=78\%$ ). In patients with diabetes, the change in HbA1c was  $-0.41\%$  (95% CI  $-0.58\%$  to  $-0.25\%$ ;  $p<0.00001$ ,  $I^2=65\%$ ). There was no significant difference in FPG between ranolazine and placebo groups ( $-2.58$  mmol/L, 95% CI  $-7.02$  to  $1.85$ ;  $p=0.25$ ;  $I^2=49\%$ ) or incidence of hypoglycaemia between ranolazine and placebo groups (OR 1.70, 95% CI 0.89 to 3.26;  $p=0.61$ ,  $I^2=0\%$ ).

**Conclusions** Our meta-analytic findings support the fact that ranolazine improves HbA1c without increasing the risk of hypoglycaemia. It therefore has a potential of having an additional benefit of improving glycaemic control in patients with chronic stable angina and diabetes.

## INTRODUCTION

Ranolazine, a piperazine derivative, is a first-in-class antianginal agent that works by reducing late inward sodium current ( $I_{pNa}$ ) in cardiomyocytes without any impact on heart rate or blood pressure.<sup>1</sup>  $I_{pNa}$  is responsible for sodium influx, which subsequently leads to increased sarcoplasmic calcium content. Its activity is enhanced in ischaemic myocardium and heart failure.<sup>12</sup> In ischaemic myocardium, increased sarcoplasmic calcium content leads to impaired diastolic relaxation, increased ventricular wall stress and end-diastolic pressure.<sup>3</sup> Reducing  $I_{pNa}$  therefore should

## Key questions

### What is already known about this subject?

► Ranolazine is a known antianginal agent that is reported to have glucose-lowering effect. A review article on ranolazine and its antiglycaemic effects has been published by Greiner *et al*. This study had individually reviewed four published trials and three unpublished trials and concluded that ranolazine therapy may decrease HbA1c among patients with type 2 diabetes only without an increase in hypoglycaemia. However, it did not undertake any statistical analysis to estimate the glucose-lowering effect of ranolazine or attempt to analyse all the available segments of blood glucose lowering (HbA1c, fasting plasma glucose and risk of hypoglycaemia).

### What does this study add?

► We have carried out a meta-analysis on seven published trials that studied the effect of ranolazine on HbA1c, fasting plasma glucose and risk of hypoglycaemia with ranolazine in patients with and without type 2 diabetes. This meta-analysis has provided a qualitative review on each randomised controlled trial and given a quantitative effect of ranolazine on HbA1c, fasting plasma glucose and risk of hypoglycaemia in both patient groups.

### How might this impact on clinical practice?

► Ranolazine has been proven to be an effective antianginal agent. It is useful to understand its glucose-lowering effect as more than half of the patients with ischaemic heart disease are found to have abnormal glucose metabolism. The information from this meta-analysis will improve clinicians' understanding about this drug and thereby facilitate decision making. As diabetes is a known risk factor for coronary artery disease, a dual antianginal and glucose-lowering effect, without increase in risk of hypoglycaemia, would be valuable for this patient population who already have diabetes or are at risk of developing it.

lead to a reduction in cardiac ischaemia. Randomised controlled trials (RCTs) with ranolazine has demonstrated its effectiveness in treating chronic angina both as monotherapy<sup>4</sup> and in combination with commonly prescribed cardiovascular drugs.<sup>5 6</sup> By its



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novel mechanism, it improves symptoms of angina but does not affect cardiovascular or all cause mortality.<sup>7</sup>

Post hoc analysis of clinical trials in chronic angina demonstrated that ranolazine was associated with significant reductions in glycaemia. Combination Assessment of Ranolazine In Stable Angina (CARISA) trial showed that ranolazine lowered HbA1c among patients with chronic angina and diabetes, in a dose-dependent manner. In Metabolic Efficiency With Ranolazine for less Ischemia in Non-ST-Elevation Acute Coronary Syndromes (MERLIN-TIMI-36) trial, ranolazine lowered HbA1c in subjects with diabetes and reduced the incidence of newly elevated HbA1c in initially normoglycaemic subjects. There have been few studies that investigated the effect of ranolazine on glycaemia. Besides, the population size in the studies were small. Despite some evidence showing reduction in glycaemic indices (HbA1c or fasting plasma glucose (FPG)), the extent of this improvement or the impact on hypoglycaemia was not clear.

We, therefore, proposed to perform a meta-analysis of RCTs with ranolazine, which had reported glycaemic measures before and after the trial, to assess its impact on glycaemia and hypoglycaemia in patients with and without diabetes. Our hypothesis was that ranolazine reduces glycaemia, expressed as HbA1c and FPG, without any increase in hypoglycaemia incidence among patients with and without diabetes.

## METHOD

### Identification and selection of studies

We searched the MEDLINE (from 1985 to August 2016), Embase (1974 to 2016 Week 33), Cochrane Central Register of Controlled Trials (CENTRAL) (August 2016), Clinicaltrials.gov (August 2016), European (EU) Clinical Trials register (August 2016) and Google Scholar (September 2016).

Two separate searches were conducted. First search was conducted using terms including 'ranolazine', 'diabetes', 'HbA1c' and 'trial' to identify RCTs that studied the effect of ranolazine on HbA1c (online supplementary figure S1). Second search was conducted using terms 'ranolazine', 'diabetes', 'fasting plasma glucose' or 'fasting glucose' and 'trial' to locate RCTs that studied the effect of ranolazine on FPG (online supplementary figure S2). These searches were repeated to confirm their repeatability at the time of their inclusion into the meta-analysis.

We included patients of any adult age (18+ years), and either sex, with and without diabetes. To be eligible for inclusion, a study must satisfy the following criteria:

- It should be an RCT or post hoc analyses of an RCT.
- Studies should have reported baseline and post-treatment HbA1c and/or FPG.
- Duration of follow-up should be at least 8 weeks.
- The study must have compared data for ranolazine to placebo instead of another oral hypoglycaemic agent.

We identified seven trials that included 6543 subjects between them (online supplementary figure S1) to assess

the effect of ranolazine on HbA1c (in %, Diabetes Control and Complications Trial (DCCT) aligned method) and/or FPG (in mmol/L). The demographic details of the study participants are summarised in online supplementary table S1, and concomitant antidiabetic medications used in patients with diabetes in these trials are detailed in online supplementary table S2. Six of these seven trials except Budania *et al*<sup>8</sup>, which did not include data on HbA1c, were included in meta-analysis of effect of ranolazine on HbA1c. Six of these seven trials except Morrow *et al*, which did not include data on FPG, were included in meta-analysis of effect of ranolazine on FPG.

We had identified one other trial (Kosiborod *et al*) that had provided information on incidence of hypoglycaemia without studying post-treatment changes of patients' HbA1c or FPG.<sup>9</sup> This trial has been included in the meta-analysis for incidence of hypoglycaemia only.

Table 1 summarises the participants, intervention and duration of treatment of included trials. The details of their diabetes state is summarised in table 2.

### Outcome measures

Our outcome measures were:

- Post-treatment changes of HbA1c from baseline in all patients and among patients with diabetes.
- Post-treatment changes of FPG from baseline in patients with diabetes only, as none of the trials had provided data for change in FPG for patients without diabetes.
- Estimate the proportion of subjects developing adverse effects as hypoglycaemia, which could contribute towards reduction of HbA1c as reported in these trials.

We used mean differences in (in %, DCCT aligned method) and FPG (in mmol/L) to express intervention effect estimates. We used OR to assess intervention effect estimates for incidence of hypoglycaemia.

### Data extraction

One author extracted data from studies and another author independently checked the data.

### Statistical analysis

Study data were analysed using Revman 5.3.<sup>10</sup> The primary analysis for RCTs was considered separately, while a meta-analysis of all studies was also performed. A preliminary assessment of the degree of heterogeneity between study results was obtained by calculating the  $I^2$  statistic. Random effects model was used for all analyses.

The mean differences in HbA1c before and after intervention were analysed using weighted mean differences. We derived SE of the mean difference, when this statistic was not reported in the trial.<sup>11</sup> As the trial described in Timmis *et al*<sup>12</sup> was a three-armed trial comparing placebo to ranolazine 750 mg BD and ranolazine 1000 mg BD, we have combined the ranolazine 750 mg BD and ranolazine 1000 mg BD patient groups as one group for our statistical analysis.

**Table 1** Participants, intervention and duration of treatment

Study, year	Participants	Intervention	Duration of treatment
Budania <i>et al</i> , <sup>8</sup> 2013	Patients with documented history of both type 2 diabetes and coronary artery disease.	Patients randomised to placebo or ranolazine 500 mg twice daily.	8 weeks
Eckel <i>et al</i> , <sup>18</sup> 2015	Patients with established type 2 diabetes, HbA1c 7%–10% and FPG 130–240 mg/dL, and treatment naïve or washed off all antidiabetic therapy.	Patients randomised to placebo or ranolazine 500 mg twice daily for 7 days followed by 1000 mg twice daily.	24 weeks
Kipnes <i>et al</i> , <sup>19</sup> 2011	Patients with type 2 diabetes, HbA1c 7%–11%, on non-insulin medical therapy.	Patient randomised to placebo or ranolazine 1000 mg twice daily.	12 weeks
Kosiborod <i>et al</i> , <sup>9</sup> 2013	Patients with type 2 diabetes, coronary artery disease and stable angina treated with 1–2 antianginals.	Patients were randomised to placebo or ranolazine 500 mg or 1000 mg twice daily.	8 weeks
Morrow <i>et al</i> , <sup>14</sup> 2009	Post hoc analysis of MERTIN-TIMI-36 trial, which recruited patients with non-ST elevation acute coronary syndrome.	Patients randomised to placebo or ranolazine as in intravenous infusion and followed by oral dose of 1000 mg twice daily.	17 weeks
Pettus <i>et al</i> , 2015 – glimepiride add-on study	Patients with type 2 diabetes who have been on sulphonylureas. Glycaemic inclusion criteria included HbA1c 7%–9.5% and FPG 7.2–13.3 mmol/L (130–240 mg/dL).	Patients went through a stabilisation period of 2 weeks or 8 weeks on glimepiride (4 mg/day) and then randomised to placebo or ranolazine in addition to this background glimepiride therapy. Ranolazine started at 500 mg twice daily, and then up titrated to 1000 mg twice daily after 7 days. Patients were permitted to down titrate to 500 mg (or matched placebo) for intolerability.	24 weeks
Pettus <i>et al</i> , 2015 – metformin add-on study	Patients with type 2 diabetes who have been on metformin. Glycaemic inclusion criteria included HbA1c 7%–9.5% and FPG 7.2–13.3 mmol/L (130–240 mg/dL).	Patients went through 8-week stabilisation period, during which metformin was titrated to 2000 mg/day. Patients randomised to ranolazine had their metformin dose reduced to 500 mg twice daily to avoid increased metformin exposure in ranolazine group as ranolazine 100 mg twice daily increases serum levels of metformin by 1.7-fold.	24 weeks
Timmis <i>et al</i> , 2005	Post hoc analysis of CARISA trial, which recruited patients with chronic angina and documented coronary artery disease. Study has explored post-treatment HbA1c change in patients with diabetes only. Study provided data for post-treatment FPG change in both diabetic and non-patients with diabetes.	Patients randomised to placebo, ranolazine 750 mg twice daily or ranolazine 1000 mg twice daily.	12 weeks

FPG, fasting plasma glucose.

We compared the incidence of hypoglycaemia in subjects treated with ranolazine to placebo. We used a random-effects model for meta-analysis, considering the heterogeneity of various studies.

Other statistical analyses were performed using SPSS V.23.0.

## RESULTS

### Study selection

A literature search conducted in September 2016 identified 73 records that potentially explored the effects of ranolazine on HbA1c. Twenty-eight duplicates, 22 records that are not RCTs and 15 records that are not relevant have been excluded. One study<sup>13</sup> has been

excluded as it performed post hoc analysis on the same population as another study,<sup>14</sup> which was included in our meta-analysis. The latter was selected as it provided more comprehensive data and included patients without diabetes. One study<sup>15</sup> has been excluded as it compared ranolazine with trimetazidine, as the latter is known to have significant impact on glucose metabolism,<sup>16</sup> instead of placebo. Budania *et al*<sup>8</sup> has also been excluded from this meta-analysis as it had not explored HbA1c changes in subjects. Therefore, five studies, including six trials, have been selected to enter meta-analysis to study effect of ranolazine on HbA1c. Excluded studies are shown in online supplementary table S3.

**Table 2** Baseline mean HbA1c, baseline mean fasting plasma glucose (FPG), percentage of known diabetes and diabetes duration

Study, year	Study group	Baseline mean HbA1 (%)	Baseline mean FPG (mmol/L)	Percentage of known diabetes	Diabetes duration (year)
Budania <i>et al</i> , <sup>8</sup> 2013	Ranolazine	n/a	7.8	100	n/a
	Placebo	n/a	7.2	100	n/a
Eckel <i>et al</i> , <sup>18</sup> 2015	Ranolazine	8.1	9.6	100	3
	Placebo	8.0	9.6	100	3
Kipnes <i>et al</i> , <sup>19</sup> 2011	Ranolazine	8.4	8.6	100	8.7
	Placebo	8.5	9.6	100	9.7
Kosiborod <i>et al</i> , <sup>9</sup> 2013	Ranolazine	7.3		100	7.2
	Placebo	7.3		100	7.7
Morrow <i>et al</i> , 2009	Ranolazine	6.2 (all) 7.5 (diabetic)	n/a	33.1	n/a
	Placebo	6.2 (all) 7.5 (diabetic)	n/a	35.3	n/a
Pettus <i>et al</i> , 2015 – glimepiride add-on study	Ranolazine	9.8	9.8	100	7.1
	Placebo	9.8	9.8	100	7
Pettus <i>et al</i> , 2015 – metformin add-on study	Ranolazine	9.4	9.4	100	6.4
	Placebo	9.4	9.4	100	6.7
Timmis <i>et al</i> , 2005	Ranolazine 1000 mg twice daily	7.92	9.2 (n=57, diabetic)	100	n/a
	Ranolazine 750 mg twice daily	7.65	9.4 (n=63, diabetic)	100	n/a
	Placebo	7.46	9.9 (n=49, diabetic)	100	n/a

Another literature search conducted in September 2016 identified 48 records that potentially investigated the effects of ranolazine on FPG. Twenty-two duplicates, 16 non-RCTs and 15 non-relevant records were removed. Chisholm *et al*<sup>13</sup> and Sandhiya *et al*<sup>17</sup> have been excluded due to reasons explained above. Timmis *et al*<sup>12</sup> and Morrow *et al*<sup>14</sup> have also been excluded, as they did not include enough data on post-treatment FPG to be included into our meta-analysis. Six trials therefore have been selected to enter meta-analysis to explore effect of ranolazine on FPG.

Only five RCTs provided data on incidence of hypoglycaemia when treated with ranolazine or placebo (Eckel *et al*,<sup>18</sup> Kipnes *et al*,<sup>19</sup> Pettus *et al* – glimepiride add-on (GAO) study,<sup>20</sup> Pettus *et al* – metformin add-on (MAO) study<sup>20</sup> and Kosiborod *et al*<sup>9</sup>). All these trials included patients with diabetes. Among trials that included patients without diabetes, there were no reporting of hypoglycaemia in their publications. The outcome measures from different trials are summarised in online supplementary table S4.

#### Post-treatment change from baseline HbA1c

Six trials provided data on the effect of ranolazine on HbA1c for patients with and without diabetes. All but one trial (Pettus *et al* – MAO study) showed outcome that favours ranolazine over placebo in reducing subjects' HbA1c level. Meta-analysis shows that there

was a statistically significant reduction of 0.36% (95% CI -0.57% to -0.15%;  $p=0.0004$ ,  $I^2=78\%$ ) in HbA1c for ranolazine-treated group compared with placebo (figure 1A).

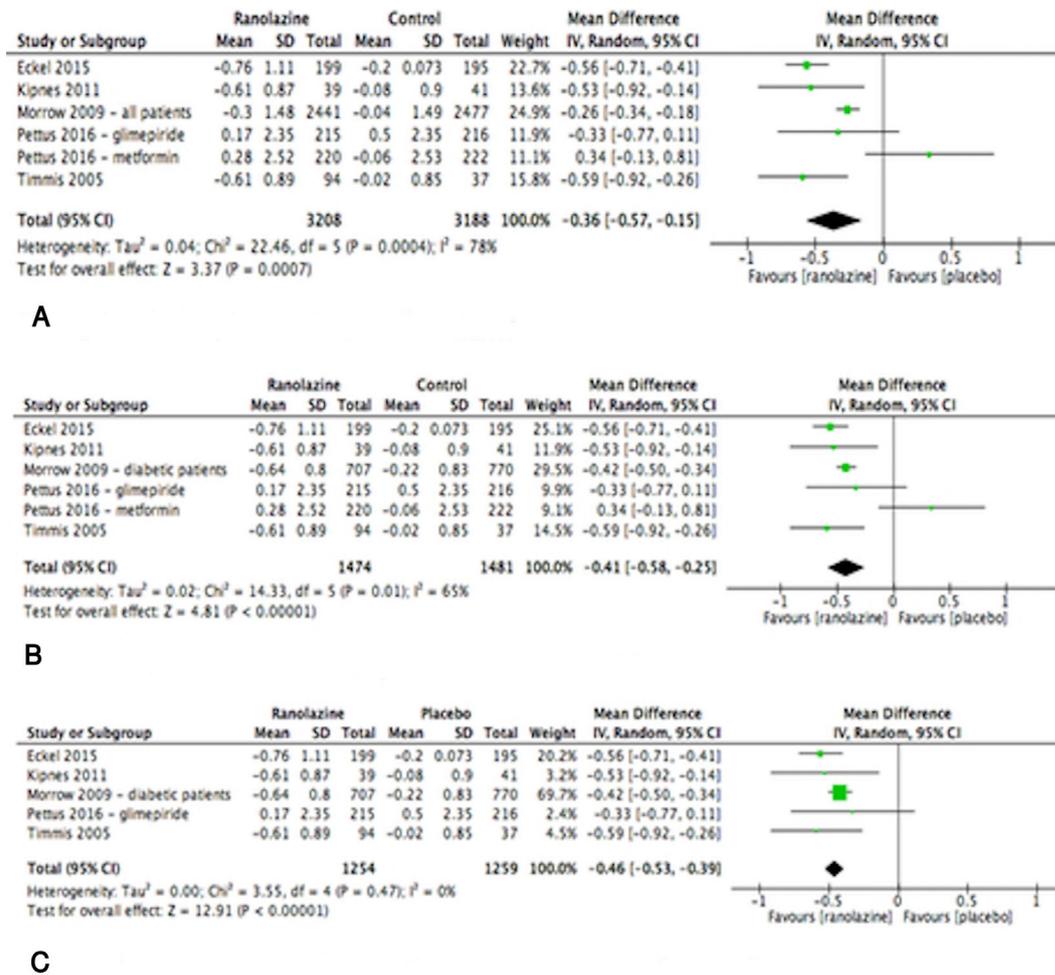
Meta-analysis in patients with diabetes revealed that mean difference of HbA1c post-ranolazine treatment was 0.41% (95% CI -0.58% to -0.25%,  $p<0.00001$ ,  $I^2=65\%$ ) compared with placebo. The effect size was bigger in patients with diabetes compared with groups that included both patients with and without diabetes (figure 1B).

Heterogeneity in these two meta-analyses ( $I^2=78\%$  in meta-analysis including both patients with and without diabetes, and  $I^2=65\%$  in meta-analysis including patients with diabetes only) was mainly attributed to one trial (Pettus *et al* – MAO study). After exclusion of Pettus *et al* – MAO study, meta-analysis of remaining five trials demonstrated that mean HbA1c change was -0.46% (95% CI -0.53% to -0.39%,  $p<0.00001$ ,  $I^2=0\%$ ) in favour of ranolazine (figure 1C).

We also analysed the relationship of change in HbA1c with the duration of the studies. There was no significant correlation between these two parameters (Spearman's ' $r$ '=0.463;  $p=0.355$ ).

#### Post-treatment change from baseline FPG

Meta-analysis of mean difference in FPG post-treatment was carried out for patients with diabetes only as no trial



**Figure 1** (A) Change in HbA1c for all patients. (B) Change in HbA1c in patients with diabetes. (C) Change in HbA1c in patients with diabetes (Pettus *et al* metformin add-on trial excluded).

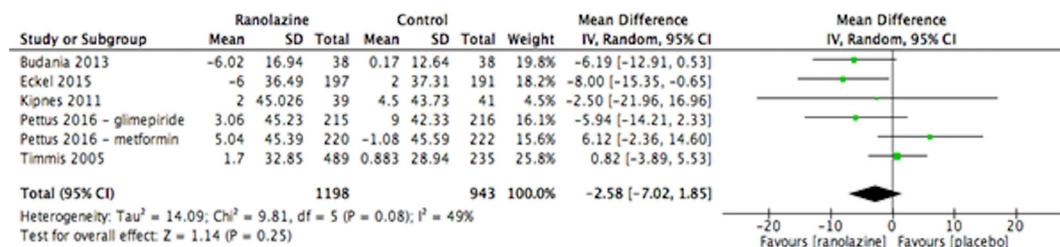
had provided data on change of FPG for patients without diabetes. There was no statistically significant difference in FPG between ranolazine and placebo groups (mean difference  $-2.58$  mmol/L in favour of ranolazine, 95% CI 7.02 to 1.85,  $p=0.25$ ;  $I^2=49\%$ ; six trials) (figure 2).

### Incidence of hypoglycaemia

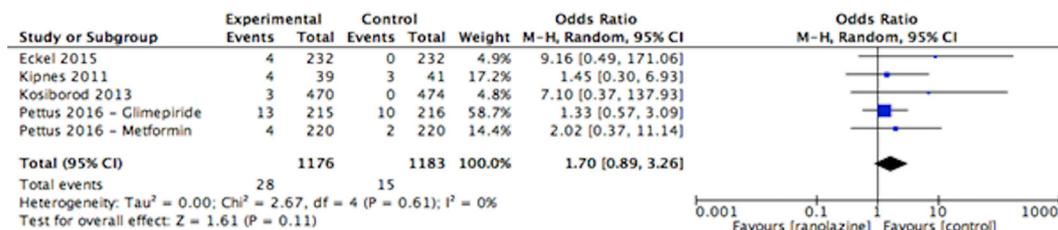
We also performed meta-analysis on hypoglycaemia incidence for all subjects from five trials (Eckel *et al*,<sup>18</sup> Kipnes *et al*,<sup>19</sup> Pettus *et al*<sup>20</sup> – GAO study, Pettus *et al*<sup>20</sup> – MAO study and Kosiborod *et al*<sup>6</sup>) that provided these data. There was no significant difference in hypoglycaemia incidence between ranolazine and placebo group (OR 1.70, 95% CI 0.89 to 3.26,  $p=0.61$ ; five trials) (figure 3).

### Publication bias

Overall, there is low or unclear risk of publication bias. There is low risk for random sequence generation as all studies described their subjects being assigned to groups in a random fashion. There is, however, unclear risk for allocation concealment for all studies as there was insufficient description on methods of concealment. There is high risk of performance and detection bias in Budania *et al*<sup>8</sup> as it was an open-labelled trial. Eckel *et al*<sup>18</sup> and Timmis *et al* were deemed to be at high risk of reporting bias as they did not use intention-to-treat analysis. Summary data on the risk of bias can be found in online supplementary table S5.



**Figure 2** Change in fasting plasma glucose in patients with diabetes.



**Figure 3** ORs of incidence of hypoglycaemia in patients treated with ranolazine.

Funnel plot was not generated from this meta-analysis due to the small number of studies included here.<sup>11</sup>

## DISCUSSION

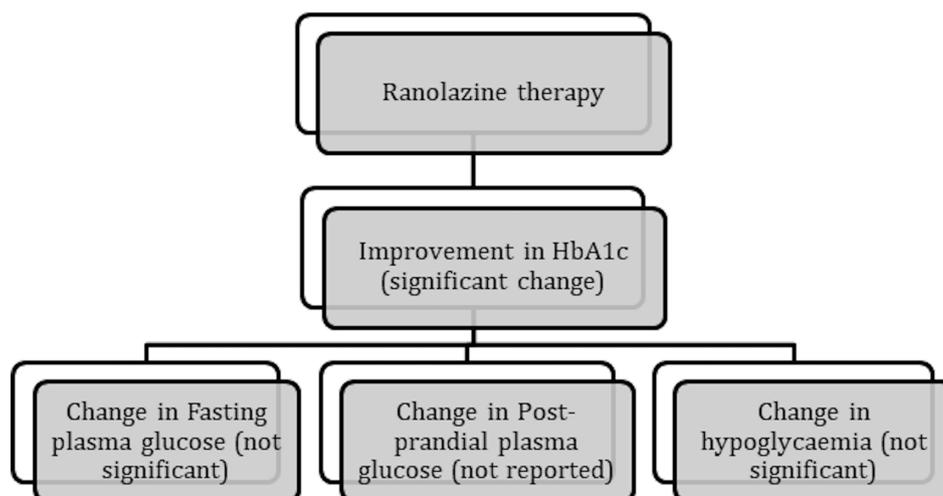
Ranolazine is one of the novel antianginal drugs, which is reported to improve glycaemic state. We included seven RCTs with 6543 subjects in this meta-analysis to investigate the magnitude of glycaemic change by this drug with a follow-up duration of a minimum of 8 weeks. HbA1c is a measure of average glycaemia over a long period of time. It has been traditionally thought to reflect the average over previous 12 weeks following the theoretical modelling by Beach.<sup>21</sup> A recent article found that following intervention, HbA1c values plateaued by 4 weeks.<sup>22</sup> We therefore included studies with a minimum of 8 weeks follow-up period to reflect any stabilised change in glycaemia and to maximise the number of trials in this meta-analysis, as the total number of clinical trials to be included were very small. We ran three different meta-analysis: one to estimate the impact on HbA1c, second to estimate the effect on FPG and the third was to estimate the risk of hypoglycaemia among patients treated with this drug.

In Pettus *et al* – MAO study, patients randomised to ranolazine had their metformin dose reduced to 1000 mg/day, whereas the placebo group continued to take metformin at 2000 mg/day. Their rationale was to avoid increased metformin exposure in the ranolazine group as previous studies had shown ranolazine 1000 mg twice daily to increase serum levels of metformin by 1.7-fold via

inhibition of organic cation transporter.<sup>23</sup> However, this precaution was not carried out in any other trials even when subjects received concomitant metformin. The reason that Pettus *et al* – MAO study produced a result that favours the placebo could potentially be attributed to this dose reduction.

The addition of ranolazine to the treatment of people with diabetes led to reduction in glycaemia. This effect was observed in both meta-analysis performed on trials including patients with and without diabetes and trials including patients with diabetes only. A greater reduction in HbA1c was observed in patients with diabetes. There was, however, no significant reduction in FPG for ranolazine-treated patients in relative to placebo. This would suggest that the improvement in overall glycaemia was due to an improved profile of postprandial glycaemia, rather than fasting glycaemia. In addition, there was no increased risk of hypoglycaemia in ranolazine-treated patients compared with placebo among patients with diabetes: which was the group where these data were reported among the clinical trials. **Figure 4** summarises how ranolazine induced change in glycaemia and its components.

FPG is managed by control of glycogenolysis, while postprandial glucose control is controlled by nutrient-induced insulin response. At a molecular level, ranolazine potentially targets either nutrient-induced insulin secretion pathway or influencing GLUT receptors that influence glucose transport into the cells. There have been



**Figure 4** Summary of ranolazine induced change in glycaemia and its common components.

various postulates proposed to explain the glycaemic improvement in patients treated with ranolazine.

Ranolazine treatment leads to improvement in beta-cell function of the islets. This has been demonstrated when ranolazine 20 mg/kg twice daily, administered for 8 weeks to mice with streptozotocin-induced diabetes, led to reduced fasting glucose and HbA1c in ranolazine-treated group than vehicle group. Ranolazine-treated mice had healthier islet morphology and significantly higher beta-cell mass compared with the vehicle group. Ranolazine also increased glucose-stimulated insulin secretion in rat and human islets in a glucose-dependent manner.<sup>24</sup> A pilot study of 40 patients without diabetes found the group randomised to use ranolazine had a reduction in HOMA-B over a 12-week period, when compared with the placebo arm.<sup>25</sup> These findings suggest that ranolazine may work as a glucose-lowering agent by causing beta-cell preservation and enhancing insulin secretion in a glucose-dependent manner. This would also explain the lack of increased risk of hypoglycaemia in patients treated with ranolazine.

Ranolazine works as a sodium channel blocker to exert its antianginal effect. Recent studies have found that glucagon release in human pancreatic islets is mediated by the Nav1.3 isoform.<sup>26</sup> In animal models of diabetes, ranolazine and a more selective sodium channel blocker reduced postprandial and basal glucagon levels, leading to reduction in hyperglycaemia, confirming that glucose-lowering effects of ranolazine could be mediated by blockade of sodium channels in the pancreatic alpha-cells.<sup>27</sup> However, *Dhalla et al* have suggested that ranolazine and a more selective sodium channel blocker reduced postprandial and basal glucagon levels, leading to reduction in hyperglycaemia, suggesting that glucose-lowering effects of ranolazine may be due to the blockade of sodium channels leading to reduction in glucagon secretion.<sup>27</sup>

Skeletal muscle vasodilatation by ranolazine is mediated via non-endothelium-mediated mechanisms<sup>28</sup> and weak  $\alpha$ -agonist action.<sup>29</sup> These vasodilatory effects are postulated to increase delivery of glucose and insulin to skeletal myocytes and thereby increase glucose uptake and metabolism by skeletal muscles and thereby reduce overall glycaemic load.

The statistically insignificant relationship of change in HbA1c with the duration of the studies could be due the small number of studies currently available. A large study with a decent duration of median follow-up period will be able to address this question.

### Limitation of this meta-analysis

This meta-analysis has several limitations. There are only a small number of trials currently available as the glycaemic benefits of ranolazine had not been evaluated in all clinical trials and there is no clinical trial that has specifically investigated glucose lowering as its primary outcome. The validity of this meta-analysis is also hindered by the disparate nature of the studies.

Characteristics of study population are variable. Most patients are taking different regimen of antidiabetic medications, except Pettus *et al*<sup>20</sup> – GAO study and Pettus *et al*<sup>20</sup> – MAO study. In Pettus *et al*<sup>20</sup> – GAO study, all patients were on sulphonylurea, whereas in Pettus *et al*<sup>20</sup> – MAO study, all patients were on metformin but none used any sulphonylurea. One of the trials (*Morrow et al*) included patients with type 1 and 2 diabetes who have quite different pathophysiological mechanisms of insulin response. Mean duration of diabetes among the trial participants also varied, possibly due to inclusion of patients with type 1 diabetes in *Morrow et al* as its diabetes duration is significantly longer compared with other trials. Duration of treatment in these trials varied from 8 weeks to 24 weeks. The minimum trial duration of 8 weeks may not be long enough to assess the effect on HbA1c properly. Study with shorter duration tends to suggest a bigger HbA1c improvement with ranolazine. A bigger number of trials with longer study duration would be useful in investigating the long-term antidiabetic effect of ranolazine.

*Timmis et al* extracted data from the CARISA trial database as a post hoc analysis. They did not explain the dropout rate among the participants. Therefore, this is likely to provide us a biased result of the efficacy of ranolazine as subjects who dropped out have not been included in their statistical analysis. The data for this meta-analysis came only from published trials so there is a potential for publication bias.

### SUMMARY

There is significant evidence from this meta-analysis to suggest that ranolazine may improve glycaemia in patients with diabetes with a low concomitant risk of hypoglycaemia. It is likely that it can be used safely with other hypoglycaemic agents. Ranolazine, an agent approved for chronic angina management, has also been established to have a good cardiovascular profile. As patients are commonly concomitantly affected by diabetes and ischaemic heart disease, ranolazine can prove to be a valuable option for this patient population. However, well-designed studies are needed to explore the glycaemic effect of ranolazine in comparison with other hypoglycaemic agents. More studies will also be needed to explore effect of ranolazine with coadministration of ranolazine with other antidiabetic agents.

**Contributors** MB has provided the conception and design of this meta-analysis. IHT carried out the literature search, data extracting and statistical analysis under MB guidance. All IHT work has later been independently checked by MB. IHT drafted the manuscript, whereas MB revised the manuscript critically for important intellectual content.

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