Effect of Ranolazine on HbA1c and Glucose Levels in Hyperglycemic Patients with Non-ST Elevation Acute Coronary Syndrome

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Objectives: We determined the relationships between glycemia at randomization, concurrent anti-diabetic therapy and change in hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG) in patients with diabetes mellitus (DM) receiving standard treatment for DM and randomized to ranolazine or placebo within the MERLIN-TIMI 36 (MERLIN) study. Ranolazine is a novel first-in class drug approved for treating angina pectoris.

Research Design and Methods: Randomization and 4-month glycemic and anti-diabetes drug usage data from MERLIN were analyzed using Spotfire and SAS version 9.1 software.

Results: In patients with DM and HbA1c of ≥8-10% at randomization (n=171) there was an absolute HbA1c reduction in the ranolazine group of 1.2% (95%CI: -1.4 to -1.0) and the placebo (n=182) adjusted decrease in HbA1c by ranolazine was 0.59% (95%CI: -0.99 to -0.20, p<0.001). In patients with FPG 150-400 mg/dl at randomization, ranolazine (n=131) compared to placebo (n=147) reduced FPG by 25.7 mg/dl (95%CI: -43.3 to -8.1, p=0.001). When changes in either HbA1c or FPG were correlated to HbA1c or FPG at randomization the slopes were significantly steeper for ranolazine than placebo (HbA1c, p=0.046; FPG, p<0.001), indicating that lowering of HbA1c and FPG by ranolazine is related to hyperglycemia at randomization. Ranolazine, compared to placebo, was not associated with serious hypoglycemic events, significant changes in concurrent anti-diabetic therapy or dependent on a history of angina.

Conclusion: Ranolazine, when added to concurrent anti-diabetes treatment, lowers FPG and HbA1c in patients with cardiovascular disease and poorly controlled DM.
Diabetes Mellitus (DM) is an established risk factor for cardiovascular disease (CVD) and the risk of CVD increases with worsening hyperglycemia (1-3). Furthermore, Coronary Artery Disease (CAD) is the most common cause of death in patients with DM (4). Patients with CAD and a recent myocardial infarction (MI) or acute coronary syndrome (ACS) have an increased incidence of impaired fasting plasma glucose (FPG) and new onset-DM (5-7). Management of DM in patients with CVD is complicated by the fact that the cardiovascular safety of some oral glucose lowering agents has been questioned and outcome data are lacking (8).

Ranolazine is a first-in-class anti-anginal drug with cardioprotective properties without effects on heart rate or blood pressure (9). The drug inhibits the cardiac late sodium current (10,11). The late sodium current is enhanced during ischemia and in the failing heart, and contributes to the Na+ dependent cellular calcium overload associated with these pathological conditions (10,11). Ranolazine has been shown effective in treating chronic angina both as a monotherapy (MARISA trial) and in combination with commonly prescribed cardiovascular drugs (CARISA and ERICA trials) (12-14), with no increase in mortality in patients with established CAD, including those with DM (15,16).

Post-hoc analysis of data from the CARISA study demonstrated that ranolazine lowered hemoglobin A1c (HbA1c), a long-term biomarker of glucose control, in patients with chronic angina and DM, in a dose dependent manner (17). While the mechanism of glycemic improvement remains incompletely understood, preliminary studies using isolated rat and human pancreatic islets suggest ranolazine may promote glucose stimulated insulin secretion (18).

In the MERLIN-TIMI-36 (MERLIN) study, the effects of ranolazine to lower HbA1c and glucose were confirmed using pre-specified glycemic end-points (16). In this study patients with DM were receiving standard of care treatment for diabetes with mean HbA1c levels of 7.5% at randomization. Despite the relatively low mean HbA1c at randomization ranolazine was found to significantly reduce HbA1c in patients with DM and to reduce the incidence of newly elevated HbA1c in initially normoglycemic patients (16). The mean placebo-corrected reductions in HbA1c with ranolazine treatment at 4 months were 0.42% (p<0.001) and 0.18% (p<0.001) for patients with and without DM respectively. There were no differences in the reported incidence of hypoglycemia between placebo and ranolazine.

The glucose lowering response to multiple anti-diabetic therapies is greater in patients with higher baseline HbA1c and glucose values (19). Therefore, the current analysis of the MERLIN data was undertaken to evaluate the effects of ranolazine on FPG and HbA1c in DM patients with moderate or severe hyperglycemia, defined as an HbA1c of 6-<8% or ≥8-10%, or FPG<150 or ≥150-400 mg/dl respectively, at randomization. Additionally, MERLIN data were assessed as to whether effects of ranolazine on glycemia were influenced by concurrent anti-diabetic therapy.

METHODS
Study overview. In the MERLIN trial, 6560 patients with non-ST elevation ACS
with at least one marker of moderate to high risk of recurrent ischemic events (including DM) were randomized at 440 sites in 17 countries. The study design, investigators, primary results of the trial and pre-specified end-points of glycemic control have been reported (15,16,20,21). As previously described (20), eligible patients were randomly assigned by a central interactive voice response system in a 1:1 ratio to receive either ranolazine or placebo which was initiated as an intravenous infusion and followed by oral administration at a dose of 1000 mg twice daily until the end of the study. Randomization was stratified by “intention to manage the patient with early invasive strategy (angiography within 48 hours and revascularization if necessary)”. There was no stratification based on the presence of new or established DM. Patients returned for study visits at 14 days, 4 months, and every 4 months thereafter until the end of the study at 16 months.

Following patient interviews and review of medical records investigators recorded a history of DM and its treatment on study case record forms. Patients with diabetes, regardless of treatment group, received standard of care treatment for diabetes and there was no pre-specified glycemic goal. The protocol stipulated that HbA1c and plasma glucose were to be measured locally at randomization (median 24 hours after symptom onset), 4 months, 8 months, 16 months, and the final study visit, with data recorded in the case report form as to whether the patient was fasting or not.

**Statistical Analyses.** Patients with HbA1c values at randomization and month-4 were included in this retrospective exploratory analysis performed using Spotfire Software (Tibco Software Inc., CA). In addition fasting plasma glucose was assessed in those with fasting measures. Spotfire filtering and visualization tools were used specifically to search the dataset for relationships between HbA1c and glucose at different levels of glycemic control. For each analysis, the studied population is described in the figure legend and the analysis was reproduced in SAS Version 9.1 (SAS Inc., Cary, NC) as described below.

Analyses of change from randomization in HbA1c, and separately FPG were estimated by two models. Firstly, using an analysis of covariance including factors for treatment, the randomization covariate of interest and the randomization stratification variable. The randomization covariate categories for HbA1c and FPG were defined to include all non-missing randomization values. Secondly, detailed analysis of treatment differences within covariate levels was prepared with a cell means version of the linear model. The cell means model included an intercept and one factor for each combination of treatment and randomization covariate category and a single factor for the randomization stratification variable. The estimates of the treatment effects from the analyses of covariance are Least Square Means. A Tukey-Kramer procedure was used to estimate the confidence limits and p-value. The analyses were performed using proc mixed, in SAS Version 9.1 (SAS Inc., Cary, NC).

All medications and dosages were recorded at each study visit by the investigator. Changes in anti-diabetic therapy were described as changes in the number or dosage of hypoglycemic agents. Patients were categorized as having either an increase, decrease or no
change in concurrent anti-diabetes therapy. In complex cases, the records were evaluated by expert review while blinded to treatment. A small number of patient records could not be categorized due to nonsensical data and were omitted from the frequency analysis. Differences in intensification and de-intensification (decrease in anti-diabetic therapy) frequencies between treatment groups were determined by Chi-Square analysis.

RESULTS

Study population. The current analysis includes patients with HbA1c data and/or fasting glucose data and a history of DM measured at both randomization and 4 months. Of the patients (placebo 2679, ranolazine 2565) reaching month-4 (Online Appendix Table A1), one third had a history of DM (placebo 892, ranolazine 842). Eighty-five percent of the patients with DM had HbA1c measurements at both randomization and month-4 (placebo 770, ranolazine 707), and 35% had FPG measurements at both times (placebo 328, ranolazine 310). All patients had access to standard of care anti-diabetes treatment and baseline characteristics were similar for the placebo and ranolazine treated groups (Table 1). The mean HBA1c and FPG values at randomization for patients included and excluded from this analysis due to missing data at randomization or month-4 were not different.

Effect of ranolazine on HbA1c and FPG. The DM study population was divided into good/moderate and poor glycemic control groups defined as HbA1c 6-<8% or ≥8-10%. There was a significant reduction in HbA1c with ranolazine in addition to standard of care anti-diabetes treatment for both the HbA1c 6-<8% and HbA1c ≥8-10% groups (Figure 1A). The absolute reduction in HbA1c in the ranolazine treated patients with better glycemic control (HbA1c 6-<8%) was 0.28% (95% confidence limits (95%CI): -0.38 to -0.19) and for those with poorer glycemic control (HbA1c ≥8-10%) HbA1c was reduced 1.2% (95%CI: -1.4 to -1.0). The placebo-corrected decrease in HbA1c with ranolazine was 0.28% (95%CI: -0.55 to 0.00, p=0.045) for the HbA1c 6-<8% group and 0.59% (95%CI: -0.99 to -0.20, p<0.001) for patients with HbA1c 8-10%.

In this study, the FPG level at randomization corresponding to an HbA1c of 8% was ~150 mg/dl (data not shown). As a result, patients (placebo n=327, ranolazine n=306) were similarly divided into two groups, good/moderate glycemic control (<150 mg/dl) and poor glycemic control (≥150-400 mg/dl, Figure 1B). The FPG ≥150 mg/dl group was limited to 400 mg/dl to exclude five patients with very high initial FPG values and potential confounding concomitant illnesses. There was a significant placebo-corrected reduction in FPG of 25.7 mg/dl (95%CI: -43.3 to -8.1, p=0.001) by ranolazine for patients with marked hyperglycemia (FPG ≥150-400 mg/dl), whereas there was no change in FPG (6.8 mg/dl, 95%CI: -8.8 to 22.3, p=0.68) in those patients with normal to moderate fasting hyperglycemia (FPG <150).

The finding that both HbA1c and FPG lowering by ranolazine were greater in hyperglycemic patients suggested a relationship between glycemia at randomization and HbA1c or FPG lowering by ranolazine. As shown in Figure 1C, there was a linear relationship between HbA1c at randomization and decrease in HbA1c with both placebo and ranolazine. However, the inverse relationship was stronger for ranolazine (R=0.41 vs. R=0.26 for placebo) and the
slope was significantly steeper for ranolazine (slope=-0.44 (95%CI: -0.53 to -0.36) compared to placebo (slope=-0.31 (95%CI: -0.41 to -0.21, p=0.046). Similarly, when FPG at randomization was correlated with the change in FPG at 4 months there was a linear relationship between FPG at randomization and decrease in FPG with treatment (Figure 1D). The inverse relationship was stronger for ranolazine (R=0.72 vs. R=0.48 for placebo) and the slope was significantly steeper for ranolazine slope=-0.79, (95%CI: -0.88 to -0.70) compared to placebo, slope=-0.51 (95%CI: -0.6 to -0.42, p<0.001). The linear regression lines intersected at an FPG value of 141 mg/dl (Figure 1D) indicating a greater effect for ranolazine than placebo in lowering FPG in patients with FPG >141 mg/dl. This finding is consistent with the previous analysis (Figure 1B) showing that ranolazine did not lower mean FPG in patients with more moderate dysglycemia (FPG <150 mg/dl) whereas it did lower FPG in those with more marked hyperglycemia (FPG>150 mg/dl). In patients without a history of DM, but with new or undiagnosed DM, as defined by an HbA1c of ≥6.5-10% or FPG of ≥126-400 mg/dl, the effect of ranolazine to reduce FPG and HbA1c was similar to that observed patients with a history of DM at comparable HbA1c and FPG levels (Online Appendix Table A2).

Angina history and glycemic lowering by ranolazine. All patients (n=1477) in the present analysis had ACS and 65% also had a history of angina. Thus, the affect of angina status on glucose lowering by ranolazine was determined. The placebo-corrected change in HbA1c by ranolazine was independent of angina history (p=0.213; angina: -0.5%, 95%CI: -0.9 to -0.1, p=0.014; no angina: -0.8%, 95%CI: -1.2 to -0.3, p<0.001; Online Appendix Figure 1A available at http://care.diabetesjournals.org). The absolute HbA1c reduction in ranolazine treated patients with and without angina was 1.1% (95%CI: -1.4 to -0.9) and 1.2% (95%CI: -1.5 to -0.9) respectively. In patients having an FPG of ≥150-400 mg/dl the placebo-corrected effect of ranolazine (angina: -26.2 mg/dl, 95%CI, -48.2 to -4.3, p=0.02; no angina; -25.1 mg/dl, 95%CI, -49.5 to -0.7, p=0.04) on FPG was independent of a history of angina (p=0.408; Online Appendix Figure 1B). Therefore, ranolazine improves glycemia equally in patients with or without history of angina pectoris.

Concurrent anti-diabetic therapy. The usage rate and type of anti-diabetic therapy for placebo and ranolazine treated patients with a history of DM was similar between both ranolazine and placebo treated groups at month-4 (Table 1). The majority of patients were taking either a biguanide (metformin) (placebo 37.4%; ranolazine 36.4%) and/or a sulphonylureas (placebo 39.4%; ranolazine 42.9%). There were no major differences in insulin, TZD, alpha-glucosidase inhibitor or meglitinide usage. Additionally the frequency of patients receiving monotherapy (placebo 50.0%; ranolazine 47.4%) and/or a sulphonylureas (placebo 39.4%; ranolazine 42.9%) for diabetes was similar between placebo and ranolazine groups. When changes to anti-diabetic therapy (new or intensified hypoglycemic therapy) were evaluated between 0 and 4 months there were no significant differences between the placebo and ranolazine groups within any of the study populations. As a result, the effect of ranolazine to lower FPG and HbA1c does not appear to be attributable to intensification of concurrent anti-diabetic therapy in ranolazine treated
patients. Similarly, a reduction in anti-diabetic therapy could underestimate the effect of ranolazine to lower HbA1c and FPG, however there were no significant differences in the frequency of reductions in hypoglycemic agents between placebo and ranolazine in any of the study populations.

Furthermore, there were no significant differences in the reported number of severe hypoglycemic adverse events between placebo and ranolazine treated patients between randomization and month-4 (placebo 16; ranolazine 19, p=0.69).

**Probability of ranolazine treated patients achieving an HbA1c goal of ≤7% by anti-diabetic treatment.** Patients with a history of DM were divided into three groups based on the type of anti-diabetic treatment (Online Appendix Table A3): no anti-diabetes drugs (placebo 16.6%, ranolazine 19.0%), oral hypoglycemic agents (OHA) but no insulin (placebo 55.2%, ranolazine 53.7%) and insulin with or without any combination of other diabetes drugs (insulin +/- OHA, placebo 28.2%, ranolazine 27.3%). To determine whether the effect of HbA1c lowering by ranolazine was influenced by concurrent anti-diabetic therapy, the Odds Ratio (OR) for a patient with an HbA1c >7% at randomization to achieve a HbA1c of ≤7% after 4 months on ranolazine, compared to placebo, was calculated (Figure 2). The OR for all patients with a history of DM and a HbA1c >7% (placebo 399, ranolazine 378) was 1.6 (95%CI: 1.2 to 2.2, p<0.001). The OR for the respective subgroups was as follows; no anti-diabetic drugs (placebo 34, ranolazine 37) OR 1.7 (95%CI: 0.7 to 4.3, p=0.24); OHA (placebo 219, ranolazine 203) OR 1.9 (95%CI: 1.4 to 2.5, p<0.001); insulin ± OHA (placebo 146, ranolazine 138) OR 1.6 (95%CI: 1.1 to 2.3, p<0.007). While there were few patients not receiving anti-diabetes pharmacologic therapy, the OR favored ranolazine and indicated that patients taking ranolazine had a 60-90% greater probability of achieving an HbA1c ≤7% than did patients not taking ranolazine. Furthermore, the effect of ranolazine to lower HbA1c does not appear to be modulated by the type of concurrent anti-diabetic therapy. Consistent with this observation the placebo-corrected effect of ranolazine on HbA1c in patients with an HbA1c of ≥6-10% categorized by concomitant DM medication was similar among groups (no DM drugs, metformin only, sulphonyleureas only, metformin plus sulphonyleurea and insulin only; Online Appendix Figure 2).

**DISCUSSION** Findings from the MERLIN-TIMI 36 trial demonstrate that ranolazine reduces HbA1c in patients with a history of DM (13,16,17). The current analysis of the MERLIN data extends these observations by examining the relationships between HbA1c and FPG concentrations at randomization and the magnitude of the glycemic lowering effect of ranolazine when added to standard of care. Consistent with the efficacy of other anti-diabetic drugs, HbA1c lowering by ranolazine was greater in patients with more marked hyperglycemia (HbA1c ≥8-10% or FPG ≥150-400 mg/dl at randomization). While the magnitude of HbA1c lowering with ranolazine compared to placebo may appear small, it is important to recognize that effects were assessed as add-on to established therapies with dose adjustments of concomitant medications permitted. This is not typical for studies examining glycemia as the primary endpoint.
Ranolazine was not associated with increased rates of severe hypoglycemic adverse events. These findings are particularly noteworthy as ranolazine has established cardiovascular safety in patients with ACS, a particularly vulnerable population that has been infrequently investigated during early development of diabetes specific therapies.

Furthermore, ranolazine appears more effective than placebo for glycemic improvement regardless of background anti-diabetes therapy. For patients with HbA1c >7, above the current treatment goal recommended by the American Diabetes Association and the European Association for the Study of Diabetes (22), the effect of ranolazine to lower HbA1c to ≤7 appears independent of the concurrent anti-diabetic therapy. The lack of significant effect in patients with DM not receiving anti-diabetes drugs may be explained by the very low number of patients in this group with an initial HbA1c >7% (placebo 34, ranolazine 37). Additionally, both treatment groups had very large improvements in HbA1c at 4 months (placebo -0.9%, ranolazine -1.3%), perhaps representing more newly diagnosed disease or increased physician or patient attentiveness.

Ranolazine significantly reduced placebo-adjusted FPG by -25.7 mg/dl in patients with elevated FPG (≥150-400 mg/dl), but not in patients with milder dysglycemia (FPG <150 mg/dl) at randomization. This finding is in agreement with data from adverse event reporting indicating that ranolazine is not associated with excess hypoglycemia compared to placebo. In the subgroup of DM patients with better glycemic control (FPG <150 mg/dl) treated with a sulphonylurea, changes in FPG were similar between placebo and ranolazine suggesting that the risk of hypoglycemia with a sulphonylurea is not increased by ranolazine. It is noteworthy that ranolazine previously has been shown to reduce incident diabetes by 32% (16).

Patients in the study with a history of DM generally had good/moderate glycemic control (placebo HbA1c 7.4%; ranolazine HbA1c 7.5%) at study entry and all patients received regular medical and anti-diabetic care. As a result, both the placebo and ranolazine treatment groups had improvements in glycemic control. There was no stabilization period possible in the MERLIN-TIMI 36 trial, as the enrollment eligibility was based on having an acute coronary syndrome event followed by immediate stratified randomization and initiation of treatment. Furthermore, the study design limits the direct comparison of the anti-diabetic effects of ranolazine with other drugs evaluated in conventional anti-diabetic drug trials.

These results indicate that the previously reported lowering of HbA1c by ranolazine is positively correlated with HbA1c levels at randomization and is associated with a reduction in FPG in patients with hyperglycemia (13,16). These findings address the previous concern of a potential lack of correlation between HbA1c and glucose changes with ranolazine (13,16).

We have focused exclusively on the patients that had glycemic data available at both randomization and 4-months post-randomization for the following reasons. The average duration of treatment in the trial was 8 months (16), however 4 months is sufficient time to evaluate changes in HbA1c and the number of patients with a history of DM and glycemic data was greater at 4 (n=1477) than at 8 (n=1133) and 16 (n=234) months. Moreover, because this
was an intent to treat trial the 4-month time minimizes the impact of the patients in the ranolazine group that were no longer taking ranolazine. The discontinuation rate for the placebo and ranolazine groups during the entire study period was 22% and 28% respectively (15). While nearly all patients had glucose measurements at 0 and 4 months, fasting was not strictly enforced, and only ≈50% of those with HbA1c data had true FPG measurements based on case report forms. We have not attempted to divide the treatment populations by gender, ethnicity, individual anti-diabetic drug treatment, cardiovascular drug treatment or study site as the number of patients with glycemic data would have been limiting.

CONCLUSION

In conclusion, ranolazine in addition to its anti-anginal and anti-ischemic action has clinically meaningful effects on glucose and HbA1c in CAD patients receiving standard of care diabetes treatment. The magnitude of the effect on glycemic control is increased in patients with elevated FPG or HbA1c. In patients with normal glucose, ranolazine does not lower FPG compared to placebo. Although there are insufficient data to conclusively state that ranolazine does not cause hypoglycemia, there is no evidence that patients treated with ranolazine were more likely than those in the placebo group to develop hypoglycemia. The mechanism of action of ranolazine to lower FPG and HbA1c is currently being investigated, however preliminary data from studies using rat and human pancreatic islets suggests that ranolazine may promote glucose-stimulated insulin secretion (18).

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REFERENCES


### Table 1- Patient characterization at randomization and anti-diabetic drug usage
data at 4 months for patients with a history of DM

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**Anti-diabetes drug usage**

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<tr>
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<th>% (n)</th>
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<td>37.4 (288)</td>
<td>36.4 (257)</td>
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<td>4.8 (34)</td>
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*Patient characterization data was reproduced from Morrow et al and is provided for reference (16). BMI- Body mass index; TZD- Thiazolidinedione
Figure Legends

Figure 1- Relationship between glycemia at randomization and lowering of HbA1c and FPG by ranolazine in patients with a history of DM.

(A.) In a cell means model, with parameters for combinations of treatment, HbA1c category and DM, the placebo-adjusted effect of ranolazine on HbA1c was -0.28% (95%CI: -0.55 to 0.003, p=0.045) for patients with HbA1c 6-<8% and -0.59% (95%CI: -0.99 to -0.20, p<0.001) for patients with HbA1c ≥8-10%. (B.) In a cell means model, with parameters for combinations of treatment, FPG category and DM, the placebo adjusted effect on FPG for these patients was 6.8 mg/dl (95%CI: -8.8 to 22.3, p=0.677) for patients with FPG <150 mg/dl and -25.7 mg/dl (95%CI: -43.3 to -8.1, p=0.001) for patients with FPG ≥150-400 mg/dl. Changes in HbA1c and FPG at month 4 are summarized by mean, associated 95% CI and number of patients (n). (C.) Relationship between HbA1c at randomization and the change in HbA1c at month 4. The slope for placebo was -0.31 (95%CI: -0.41 to -0.21), R= 0.26 and n=558. For ranolazine the slope was -0.44 (95%CI: -0.53 to -0.36), R= 0.41 and n=508. The slopes were significantly different (p=0.045). (D.) Relationship between FPG at randomization and the change in FPG at month 4. The slope for placebo was -0.55 (95%CI: -0.64 to -0.46) R= 0.54 and n=328. For ranolazine the slope was -0.81 (95%CI: -0.89 to -0.73), R= 0.76 and n=310. The slopes were significantly different (p<0.001). Least Squares Regression was performed by Graphpad Prism 5.0 and the best-fit line and 95% confidence interval for the fit are shown for each group. Similar results were obtained using an analysis of covariance model with a term for treatment, HbA1c or FPG at randomization and the interaction of treatment.

Figure 2- Effect of concurrent anti-diabetes drug treatment on patients treated with ranolazine reaching an HbA1c goal of ≤7%.
Patients with DM that were hyperglycemic at randomization (HbA1c >7%) were grouped by drug treatment. These patients were re-examined at 4 months and categorized as responders if HbA1c was ≤7%. The Odds Ratio (OR) for hyperglycemic patients in each group to reach an HbA1c ≤7% was calculated using a logistics analysis model (SAS software, Cary, NC). Data are plotted as OR (95%CI). OHA (oral hypoglycemic agents), Ins (Insulin) ± OHA and No OHA (no oral hypoglycemic agents).
Figure 1

A. HbA1c (%) change from randomization

B. FPG (mg/dl) change from randomization

C. HbA1c (%) change from randomization

D. FPG (mg/dl) change from randomization

Figure 2

Patients with DM

OHA

Ins ± OHA

No OHA

Odds Ratio for patients with HbA1c >7 at randomization achieving an HbA1c of ≤7 with ranolazine

p=0.001

p<0.001

p=0.007

p=0.237