Dalcetrapib reduces risk of new onset diabetes in patients with coronary heart disease

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Abbreviated Title: Dalcetrapib and new-onset diabetes

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ABSTRACT

Background: Incident type 2 diabetes is common among patients with recent acute coronary syndrome and is associated with an adverse prognosis. Some data suggest that cholesteryl ester transfer protein (CETP) inhibitors reduce incident type 2 diabetes. We compared the effect of treatment with the CETP inhibitor dalcetrapib or placebo on incident diabetes in patients with recent acute coronary syndrome.

Methods: In the dal-OUTCOMES trial, 15,871 patients were randomly assigned to treatment with dalcetrapib 600 mg daily or placebo, beginning 4-12 weeks after an acute coronary syndrome. Absence of diabetes at baseline was based upon medical history, no use of antihyperglycemic medication, and hemoglobin A1c and serum glucose levels below diagnostic thresholds. Among these patients, incident diabetes after randomization was defined by any diabetes-related adverse event, new use of antihyperglycemic medication, hemoglobin A1c ≥6.5%, serum glucose ≥7.0 mmol/L (fasting) or ≥11.1 mmol/L (random).

Results: At baseline, 10645 patients (67% of the trial cohort) did not have diabetes. During a median follow-up of 30 months, incident diabetes was identified in 403 of 5326 patients (7.6%) assigned to dalcetrapib and 516 of 5319 (9.7%) assigned to placebo, corresponding to absolute risk reduction 2.1%, hazard ratio 0.77 (95% confidence interval 0.68-0.88; P<0.001), and a number needed to treat for 3 years of 40. Considering only those with prediabetes at baseline, the number needed to treat for 3 years to prevent one incident case of diabetes was 25. Dalcetrapib also decreased the number of patients who progressed from normoglycemia to prediabetes and increased the number who regressed from diabetes to no diabetes.

Conclusion: In patients with a recent acute coronary syndrome, incident diabetes is common, and is reduced substantially by treatment with dalcetrapib.

Key words: acute coronary syndrome, CETP inhibition, dalcetrapib, diabetes

INTRODUCTION

Approximately 30% of patients with acute coronary syndrome (ACS) have a prior history of type 2 diabetes (1-3), a further 10% may be diagnosed with diabetes during hospitalization for ACS (4), and approximately 10% may receive the diagnosis over the ensuing 5 years (5). The development of type 2 diabetes carries a heightened risk of microvascular and macrovascular complications (6), and is associated with a particularly poor prognosis after ACS (3). Accordingly, there has been intense interest in pharmacologic and non-pharmacologic strategies to reduce incident type 2 diabetes. Available approaches that have demonstrated efficacy in patients with prediabetes or obesity include thiazolidinediones, metformin, acarbose, valsartan, basal insulin, orlistat, lorcaserin, intensive lifestyle modification, and bariatric surgery (7-10). Compared with placebo or usual care, these approaches have been associated with a 15-85% reduction in the risk of incident diabetes. Despite this efficacy, treatments to forestall or prevent the onset of diabetes have not been adopted widely due to concerns of safety, tolerability, cost, and adherence. In addition, there is no clear evidence that preventing or forestalling fulfillment of the glycemic criteria for diabetes results in improved atherosclerotic cardiovascular outcomes.

Cholesteryl ester transfer protein (CETP) inhibitors increase the concentration of high-density lipoprotein cholesterol (HDL-C) and were developed as cardiovascular drugs. To date, large outcomes trials have demonstrated no cardiovascular benefit (11-13) or modest cardiovascular

benefit (14) of treatment with CETP inhibitors, compared with placebo. However, reductions in plasma glucose and insulin were noted in patients treated with torcetrapib (15), and 11% lower relative risk for new onset diabetes was observed in patients treated with anacetrapib (14) or evacetrapib (16), with the effect of the former agent statistically significant. The mechanism of a salutary effect of CETP inhibition on incident diabetes is unknown, but HDL is purported to prevent beta cell endoplasmic reticulum stress and apoptosis and to promote insulin secretion (17). Such cellular effects are supported by human genetic data indicating decreased risk of diabetes among subjects with genetically instrumented elevation in HDL-C (18).

Dalcetrapib is a CETP inhibitor with modest effects on HDL-C and minimal effects on LDL cholesterol concentration. The dal-OUTCOMES trial compared treatment with dalcetrapib or placebo in patients with recent ACS and found no overall cardiovascular benefit (13). However, a significant interaction of dalcetrapib treatment and allele type at the ADCY9 locus that encodes adenylyl cyclase 9 on cardiovascular outcomes (19) led to a large ongoing trial in 6000 patients with ACS (www.clinicaltrials.gov NCT02525939) to determine cardiovascular efficacy of dalcetrapib in patients with the favorable allele type (20).

In this analysis, we compare the effects of treatment with dalcetrapib or placebo on incident diabetes among all dal-OUTCOMES participants without diabetes at baseline.

METHODS

Study population

The design and principal results of the dal-OUTCOMES trial have been described previously (13, 21). The study was performed between 2008 and 2012 at 935 sites in 27 countries; the institutional review board of each site approved the study and all subjects provided informed consent. Qualifying patients were at least 45 years of age, had recent ACS (acute myocardial infarction or unstable angina pectoris), and had completed all planned coronary revascularization procedures. Exclusion criteria included New York Heart Association Class III or IV symptoms of heart failure or Class II symptoms with left ventricular ejection fraction ≤40%, uncontrolled hypertension (systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg despite treatment), serum creatinine >2.2 mg/dL (194.5 μmol/L), or fasting triglycerides >400 mg/dL. Baseline laboratory testing including serum glucose and hemoglobin A1c. Patients were instructed to report for study visits after an overnight fast; actual fasting or non-fasting state was verified at each visit and recorded on a case report form. Randomization of 15,841 patients occurred 4-12 (median 6) weeks after the index ACS event when the patients were considered to be clinically stable. Serum glucose was measured 1, 3, 6, 9, and 12 months after randomization, then every 4 months and at the end of the trial. Hemoglobin A1c was measured 6 and 12 months after randomization, then annually and at the end of the trial. Concurrent medications and medical conditions were

determined, weight was measured, and body mass index (BMI) was calculated at baseline and at follow-up visits. The primary end point of the trial was a composite of death from coronary heart disease, non-fatal myocardial infarction, ischemic stroke, unstable angina, or cardiac arrest with resuscitation.

Definition of baseline and incident diabetes

The analyses in this report were performed post hoc. In the base-case model, diabetes at baseline was defined by at least one of the following criteria: a medical history of diabetes or a diabetes-related adverse event, current use of antihyperglycemic medication, hemoglobin A1c ≥6.5%, or serum glucose ≥7.0 mmol/L (fasting) or ≥11.1 mmol/L (random) at the screening or randomization visit.

Incident diabetes was defined by one or more of the following criteria fulfilled after randomization in patients without diabetes at baseline: an investigator-reported diabetes-related adverse event, new use of antihyperglycemic medication, at least one measurement of hemoglobin A1c ≥6.5%, or any combination of at least two measurements of serum glucose ≥7.0 mmol/L (fasting) or ≥11.1 mmol/L (random).

Using data from both treatment groups, we evaluated the association of baseline HDL-C and risk of incident diabetes. In an analysis restricted to the dalcetrapib group, we evaluated the association of the change in HDL-C from baseline to Month 3 and risk of incident diabetes after Month 3.

Many patients with acute coronary syndrome have values of hemoglobin A1c or fasting glucose that lie near dichotomous boundaries used to define diabetes, and intra-individual variability in these measurements may be considerable. Therefore, we performed a sensitivity analysis restricting the subgroup considered to be without diabetes at baseline to those with baseline hemoglobin A1c <6.3% and baseline fasting serum glucose <6.5 mmol/L (if fasting) or <11.1 mmol/L (if random), and with no medical history of diabetes and no current use of antihyperglycemic medication. The criteria for incident diabetes after randomization were the same as in the base-case model.

Prediabetes and normoglycemia:

Using the base-case criteria to define diabetes, patients were classified as having prediabetes at baseline if hemoglobin A1c was at least 5.7%, but less than 6.5%, or if fasting serum glucose was at least 5.6 mmol/L, but less than 7 mmol/L, without fulfillment of any criterion for diabetes. Patients who did not meet criteria for either prediabetes or diabetes were considered normoglycemic. Progression from normoglycemia to prediabetes was defined by normoglycemia at baseline and at least two post-randomization measurements of hemoglobin A1c at least 5.7% but less than 6.5% or two measurements of fasting serum glucose at least 5.6 mmol/L but less than 7 mmol/L, without fulfillment of any criteria for new onset diabetes. Regression from diabetes to a non-diabetic state was defined by diabetes at baseline, the last two available measurements of hemoglobin A1c less than 6.5%, and the last two available measurements of serum glucose less than 7 mmol/L (if

fasting) or less than 11.1 mmol/L (if not fasting), with no use of antihyperglycemic medications at the time of the last two measurements.

Insulin resistance:

In an exploratory analysis in patients without diabetes at baseline, fasting serum insulin was measured as part of a nested case-control biomarker survey (22). Measurements were available at baseline in 1293 patients assigned to treatment with dalcetrapib and 1288 patients assigned to treatment with placebo) and at Month 3 in 1071 patients assigned to dalcetrapib treatment and 1197 patients assigned to placebo treatment, excluding patients who initiated treatment with antihyperglycemic medication prior to Month 3. The insulin measurements used in this analysis were obtained At each time point, homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as (23):

$$HOMA\text{-}IR = \text{fasting serum glucose [mmol/L]} \cdot \text{fasting serum insulin [}\mu\text{U/mL]} / 22.5$$

The change in HOMA-IR from baseline to 3 months was evaluated according to treatment with dalcetrapib or placebo.

Statistical analysis

Development of diabetes was measured as the time to new onset diabetes. Differences between treatment groups were evaluated using proportional-hazards regression and reported as hazard ratio (HR) with 95% confidence interval (CI). Progression from normoglycemia to prediabetes, or regression from diabetes to prediabetes or from diabetes to a non-diabetic

state was described by the proportion of subjects in each of these categories at the last two available observations; differences between treatment groups were evaluated using logistic regression and reported as odds ratio (OR) with 95% CI. Proportional hazards regression analysis was also used to determine whether an effect of dalcetrapib on incident diabetes was related to baseline or on-treatment concentrations of HDL-C or to baseline or post-randomization BMI. Changes in fasting glucose, insulin, and HOMA-IR between baseline and 3 months of treatment with dalcetrapib or placebo or between baseline and end of trial measurements were assessed by unequal variance t-test after log transformation of insulin and HOMA-IR. In all analyses, 2-sided P values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics: At baseline using base case (Model 1) criteria, 5141 patients (32.5%) were classified with diabetes (dalcetrapib, 2573; placebo, 2568) and 10645 (67.1%) without diabetes (dalcetrapib, 5326; placebo, 5319). Diagnostic criteria were missing for 85 patients (0.5%). Among those without diabetes, 6695 (62.9%) were classified as prediabetes and 3950 (37.1%) as normoglycemic. Baseline characteristics of patients in each category are shown in **Table 1**. The sensitivity analysis that used more restrictive criteria to define absence of diabetes at baseline placed 9646 patients (60.8%) in that category, with characteristics shown in **Online-Only Supplemental Table S1**.

Cardiovascular outcomes and safety and tolerability under treatment with dalcetrapib or placebo: Considering both treatment groups in aggregate, the risk of the primary end point was higher in patients with diabetes at baseline (cumulative incidence 11.6%) than among those without diabetes at baseline (6.5%). Treatment with dalcetrapib versus placebo did not affect the risk of the primary endpoint in those with diabetes at baseline (HR 1.06, 95% CI 0.91-1.25, P=0.79) or in those without diabetes at baseline (HR 1.02, 95% CI 0.88-1.19, P=0.45). As previously described (13), dalcetrapib had a generally acceptable safety and side-effect profile. Adverse events of hypertension, diarrhea, and insomnia were reported more frequently in the dalcetrapib group than in the placebo group.

Hemoglobin A1c, fasting glucose, and concurrent medication use with dalcetrapib or placebo: **Online-Only Supplemental Table S2** shows changes in median HbA1c and glucose levels over the course of the trial among patients without diabetes at baseline censored at first use of antihyperglycemic medication. Hemoglobin A1c levels were slightly lower with dalcetrapib at the 6, 12, 24, and 36-month time points, without differences in fasting glucose. At 12 and 24 months, there were no significant differences between groups in the use of concurrent medications including statins, beta blockers, or diuretics (data not shown).

Incidence of new onset diabetes and its modification by dalcetrapib: Median (interquartile range) follow-up was 30 (25-35) months. Using base-case criteria to classify patients without diabetes at baseline and considering

both treatment groups in aggregate, there were 897 cases of incident diabetes (8.4%). Of these, 821 had baseline classification as prediabetes and 76 as normoglycemia. The criteria fulfilled to establish incident diabetes are shown in **Online-Only Supplemental Table S3**.

Dalcetrapib treatment reduced incident diabetes (**Table 2** and **Figure 1, Panel A**). Using base-case criteria, incident diabetes developed in 403 of 5326 (7.6%) patients in the dalcetrapib group and 516 of 5319 (9.7%) patients in the placebo group, corresponding to corresponding to an absolute risk reduction of 2.1%. Dalcetrapib prolonged time to onset of diabetes (HR 0.77, 95% CI 0.67-0.89, P<0.001) with a need to treat 40 patients for 3 years to prevent one incident case.

Of the 919 patients who developed diabetes, 837 (91%) had prediabetes and 82 (9%) had normoglycemia at baseline (**Table 2**). Considering only those with prediabetes at baseline, incident diabetes developed in 364 of 3394 (10.7%) patients in the dalcetrapib group and 473 of 3301 (14.3%) patients in the placebo group, corresponding to HR 0.74 (0.65-0.85, P<0.001; **Table 2, Figure 1, Panel B**) and a need to treat 25 patients for 3 years to prevent one incident case. Restricting the analysis further to 3371 patients with impaired fasting glucose (100-125 mg/dL) at baseline, incident diabetes developed in 251 of 1681 patients (14.9%) in the dalcetrapib group, compared with 321/1690 (19.0%) in the placebo group (HR 0.80, 95% CI 0.68-0.95, P=0.009).

In the sensitivity analysis using more stringent criteria to classify patients as not having diabetes at baseline, incident diabetes occurred in 254 of 4602 (5.5%) patients in the dalcetrapib group and 324 of 4602 (7.0%) patients in the placebo group (HR 0.78, 95% CI 0.66-0.92, P=0.003).

Among all participants without diabetes at baseline, the risk of incident diabetes was significantly related to HDL-C concentration at baseline (HR for 1 mg/dl increment 0.98, 95% CI 0.97-0.99, P<0.001), without significant interaction of treatment group (P=0.16). Between baseline and month 3, the change (mean±standard deviation) in HDL-C was 14.9±11.4 mg/dL in the dalcetrapib group and 1.7±7.2 mg/dL in the placebo group. After adjusting for the 3-month change in HDL-C, the relationship between treatment and incident diabetes was no longer significant (dalcetrapib:placebo HR 0.97; p=0.70). In an analysis limited to the dalcetrapib group and adjusted for baseline HDL-C, the risk of incident diabetes was significantly related to the change in HDL-C from baseline to 3 months of assigned treatment (HR for 1 mg/dl change 0.98, 95% CI 0.97-0.99, P<0.001).

Progression from normoglycemia to prediabetes, regression from diabetes to a non-diabetic state, and modification of these transitions by dalcetrapib: Dalcetrapib reduced the likelihood of progression from normoglycemia to prediabetes. Among 3761 patients who were normoglycemic at baseline and were evaluable for glycemic status at their last two study visits, prediabetes developed in 711 of 1846 (38.5%) assigned

to dalcetrapib, compared with 826 of 1915 (43.1%) assigned to placebo (OR 0.83, 95% CI 0.73-0.94, P=0.004, **Table 2**).

Dalcetrapib also increased the likelihood of regression from diabetes to a non-diabetic state. Among 4747 patients with diabetes at baseline who were evaluable for subsequent glycemic status, 325 of 2354 (13.8%) assigned to dalcetrapib had improved to a state of prediabetes or normoglycemia at their two final study visits, compared with 271 of 2393 (11.3%) assigned to placebo, corresponding to OR 1.25 (95% CI 1.06-1.49, P=0.01), an absolute increase of 2.5%, and a number needed to treat of 40 (**Table 2**).

Effect of dalcetrapib on BMI: BMI did not differ between treatment group at baseline (mean 27.9 kg/m^2 in both). However, patients treated with dalcetrapib had significantly lower BMI by Month 6 of treatment and an intergroup difference in median BMI of approximately 0.2 kg/m^2 was sustained through Month 36 (**Online-Only Supplemental Table S2**). Among all participants without diabetes at baseline, the risk of incident diabetes was significantly related to baseline BMI (HR per 1 kg/m^2 increment 1.06, 95% CI 1.05-1.08, P<0.001 adjusted for treatment group) and to the change in BMI from baseline to Month 12 (HR per 1 kg/m^2 change 1.14, 95% CI 1.09-1.19, P<0.001 adjusted for treatment and baseline BMI). However, the association between dalcetrapib treatment and the risk of new onset diabetes did not appear to be due to changes in BMI. After adjusting for baseline and Month 12 change in BMI, the hazard ratio for new onset diabetes with dalcetrapib

relative to placebo (HR = 0.80, 95% CI 0.70 to 0.92, P= 0.001) was equivalent to the unadjusted hazard ratio.

Effect of dalcetrapib on insulin resistance: **Online-Only Supplemental Table S4** shows data for patients without diabetes at baseline who had concurrent measurements of fasting glucose and insulin at randomization (n=2581) and at Month 3 (N=2168). At baseline, median (IQR) fasting glucose, insulin, and HOMA-IR were 5.3 (4.9-5.7) mmol/L, 8.3 (5.5-12.4) μU/mL, and 1.9 (1.3-3.0), respectively, without differences between treatment groups. At Month 3, median fasting glucose was unchanged and fasting insulin increased slightly in both groups, but dalcetrapib had no effect on the change in these measurements from randomization to Month 3, consistent with the absence of any discernible effect of dalcetrapib on new onset diabetes by Month 3.

DISCUSSION

This analysis demonstrates that dalcetrapib, a CETP inhibitor, reduces incident diabetes by approximately 23% (absolute reduction 2.1%) over a median follow-up of 30 months in patients with ACS who do not have diabetes at baseline. Based on Kaplan-Meier incidences at 3 years, 40 patients would have to be treated with dalcetrapib to prevent one incident case of diabetes. If restricted to those with prediabetes at baseline, the number needed to treat was 25. The effect of dalcetrapib on incident diabetes was robust to a sensitivity analysis that used a more stringent definition to

identify patients without diabetes at baseline. Dalcetrapib also had favorable effects on transitions between other glycemic states. Compared with placebo, treatment with dalcetrapib was associated with fewer patients progressing from normoglycemia to prediabetes, and more patients regressing from diabetes to a non-diabetic state, with a number needed to treat of 40 for the latter.

The present analysis does not define the mechanism by which dalcetrapib ameliorates the glycemic state of patients with prior ACS. Among potential mechanisms, HDL, possibly through its component apolipoprotein A-I, may improve beta cell function and enhance insulin secretion (19), a hypothesis supported by analyses showing an inverse relationship between genetically determined HDL-C levels and incident diabetes (18). In fact, we observed that the risk of incident diabetes was inversely associated both with baseline HDL-C and with the increase in HDL-C concentration with dalcetrapib treatment. However, it is uncertain whether the former relation represents a direct effect of HDL or an association of low HDL-C with insulin resistance. Similarly, the latter relation cannot distinguish whether increased HDL-C concentration mediates a decreased risk of diabetes or whether increased HDL-C concentration is a marker of dalcetrapib exposure, with the drug's effects on diabetes mediated through other, unmeasured mechanisms. Dalcetrapib had a small but significant effect to reduce BMI compared with placebo, but this effect did not account for the reduction in incident diabetes. We did not observe an effect of dalcetrapib on fasting serum glucose, but we

did observe slightly lower levels of hemoglobin A1c between 6 and 36 months after randomization. An effect on post-prandial glucose excursions may explain this dichotomy but was not evaluated in the current study. Almost all patients in this cohort were treated with statins and statin treatment has been associated with an increased risk of incident diabetes (24). It is not possible to determine whether dalcetrapib mitigated an increased risk of diabetes related to statin treatment or exerted an independent effect to prevent diabetes. In an exploratory analysis, we measured fasting insulin and glucose at baseline and at Month 3 of assigned treatment in a subset of patients and observed no intergroup difference in fasting insulin, glucose, or HOMA-IR between these time points. However, the difference between dalcetrapib and placebo groups in the incidence of diabetes emerged after this time point, and we cannot exclude the possibility that an effect of dalcetrapib on insulin secretion or sensitivity developed after Month 3. Interpretation of these findings is also subject to the limitations of selecting patients in a case-control design, rather than with random sampling or in the entire study cohort. Further targeted studies to assess beta cell function and insulin sensitivity may help to answer these questions.

Compared with other CETP inhibitors, dalcetrapib has a smaller effect to raise the concentration of HDL cholesterol (11, 12, 14); however, the present findings suggest its effect to prevent incident diabetes is at least as large, and possibly larger. In an analysis of 19,129 patients with occlusive vascular disease and no diabetes at baseline who were followed for a

minimum of 4 years, diabetes developed in 510 patients (5.3%) treated with the CETP inhibitor anacetrapib, compared with 571 (6.0%) treated with placebo (hazard ratio 0.89, 95% CI 0.79-1.00, P=0.05) (14). In an analysis of 3856 patients with acute or chronic coronary heart disease without diabetes at baseline and with median follow-up 30 months (the same duration as in the current analysis), diabetes developed in 176 of 1911 patients (9.2%) treated with the CETP inhibitor evacetrapib, compared with 200 of 1945 patients (10.3%) treated with placebo (odds ratio 0.89, P=0.24)(16). There are several reasons why dalcetrapib might have a larger effect on incident diabetes than other CETP inhibitors. First, more potent CETP inhibitors such as anacetrapib or evacetrapib lower LDL-C while producing large increases in HDL-C. Lower levels of LDL-C due to genetic variants in cholesterol-regulating genes or intensive statin therapy have been associated with an increased risk of incident diabetes (25). It is possible that a salutary effect of potent CETP inhibitors on incident diabetes through increased HDL-C was mitigated by lower levels of LDL-C. Second, it is possible that differing effects of CETP inhibitors on incident diabetes are related to different effects on HDL composition or function that are not reflected by HDL-C concentration (26). Finally, criteria for diagnosis of incident diabetes differ among studies of CETP inhibitors. In the analysis involving anacetrapib, incident diabetes was defined by diabetes-related adverse events or use of antihyperglycemic medication, and in the analysis involving evacetrapib by a hemoglobin A1c value greater than 6.5%. Therefore, absolute incidence rates for new onset

diabetes should not be compared directly among studies, but comparison of odds ratios for active treatment versus placebo may be reasonable.

Considering all available laboratory data, there were relatively small changes in median fasting glucose and hemoglobin A1c over time within and between treatment groups (Supplemental Table S2). In contrast, bidirectional rates of transition among glycemic states were substantial (Table 2). One reason for this apparent disparity is that the former data include laboratory values obtained after introduction of antihyperglycemic medication, which may blunt observed differences. Another reason is that patients may cross dichotomous boundaries between glycemic categories with small changes in hemoglobin A1c or glucose. However, in a sensitivity analysis that restricted the analysis cohort to patients with baseline hemoglobin A1c and glucose well below criteria for diabetes, there was nonetheless a significant effect of dalcetrapib to attenuate the risk of incident diabetes.

Data from the placebo group are notable for the high rate of glycemic transitions over the course of the trial. The number of patients who regressed from diabetes to no diabetes was more than half of the number who developed new onset diabetes. Approximately 40% of patients characterized as normoglycemic at baseline developed criteria for prediabetes over a median 30-month observation period. The dynamic nature of the glycemic state following ACS points to the importance of lifestyle modification during this period and to a possible role of pharmacologic intervention.

Strengths of this analysis include the large study cohort representing many nationalities, a detailed database that allowed for the use of multiple complementary criteria to define incident diabetes, and collection of data to verify fasting or non-fasting state at each study visit, allowing glucose data to be used appropriately to categorize glycemic state. Limitations include a post hoc design and inherent inaccuracies in determining incident diabetes from criteria other than gold-standard glucose tolerance testing. It is possible that some antihyperglycemic medication was prescribed for weight loss rather than diabetes, but few such cases are likely because the trial antedated the first approval of glucagon-like peptide 1 receptor agonists for weight loss.

Implications

In the present analysis, the observed effect size of dalcetrapib treatment on incident diabetes was smaller than that previously seen with thiazolidinediones and comparable to that observed with metformin (27, 28). To date, pioglitazone is the sole available agent that has been demonstrated effective in preventing both incident diabetes and cardiovascular morbidity and mortality in patients without diabetes at baseline (29). Although dalcetrapib did not reduce cardiovascular events in the dal-OUTCOMES trial, this possibility is being investigated further in the precision medicine dal-GenE trial (20). Dalcetrapib does not share the risks of fluid retention and heart failure, weight gain, and bone fractures associated with thiazolidinediones, hemodynamic and electrolyte effects with valsartan, or gastrointestinal symptoms and a small potential for lactic acidosis with metformin. Therefore,

dalcetrapib might have utility as a well-tolerated agent to prevent or delay the onset of diabetes in patients at high risk for that condition.

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REFERENCES

1. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med* 2015; 372:2387-97.

2. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med* 2018; 379:2097-107.

3. Sethi SS, Akl EG, Farkouh ME. Diabetes mellitus and acute coronary syndrome: lessons from randomized clinical trials. *Curr Diab Rep* 2012; 12:294-304.

4. Arnold SV, Stolker JM, Lipska KJ, Jones PG, Spertus JA, McGuire DK, et al. Recognition of incident diabetes mellitus during an acute myocardial infarction. *Circ Cardiovasc Qual Outcomes*2015; 8:260-7.

5. Meisinger C, Beck J, Heier M, Hormann A, Kuch B, Sietas G, et al. Myocardial infarction and incidence of type 2 diabetes mellitus. Is admission blood glucose an independent predictor for future type 2 diabetes mellitus? *Am Heart J* 2010; 159:258-63.

6. Forbes JM, Cooper ME. Mechanisms of diabetic complications. *Physiol Rev* 2013; 93:137-88.

7. Bethel MA, Xu W, Theodorakis MJ. Pharmacological interventions for preventing or delaying onset of type 2 diabetes mellitus. Diabetes Obes Metab 2015; 17:231-44.

8. Carlsson LM, Peltonen M, Ahlin S, Anveden A, Bouchard C, Carlsson B, et al. Bariatric surgery and prevention of type 2 diabetes in Swedish obese subjects. *N Engl J Med* 2012; 367:695-704.

9. Haw JS, Galaviz KI, Straus AN, Kowalski AJ, Magee MJ, Weber MB, et al. Long-term Sustainability of Diabetes Prevention Approaches: A Systematic Review and Meta-analysis of Randomized Clinical Trials. *JAMA Intern Med* 2017; 177:1808-17.

10. Group NS, McMurray JJ, Holman RR, Haffner SM, Bethel MA, Holzhauer B, et al. Effect of valsartan on the incidence of diabetes and cardiovascular events. *N Engl J Med* 2010; 362:1477-90.

11. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, et al. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 2007; 357:2109-22.

12. Lincoff AM, Nicholls SJ, Riesmeyer JS, Barter PJ, Brewer HB, Fox KAA, et al. Evacetrapib and Cardiovascular Outcomes in High-Risk Vascular Disease. *N Engl J Med* 2017; 376:1933-42.

13. Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J, et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med* 2012; 367:2089-99.

14. Group HTRC, Bowman L, Hopewell JC, Chen F, Wallendszus K, Stevens W, et al. Effects of Anacetrapib in Patients with Atherosclerotic Vascular Disease. *N Engl J Med* 2017; 377:1217-27.

15. Barter PJ, Rye KA, Tardif JC, Waters DD, Boekholdt SM, Breazna A, et al. Effect of torcetrapib on glucose, insulin, and hemoglobin A1c in subjects in the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial. *Circulation* 2011; 124:555-62.

16. Menon V. LAM, Nicholls S.J., Riesmeyer J.S., Barter P.J., Brewer H.B., Fox K.A.A., Gibson C.M., Granger C., Montalescot G., Rader D., Tall A.R., Ruotolo G., St John J., Nissen S.J. Impact of evacetrapib on glyvemic control: results from the accelerate trial. *Eur Heart J* 2017; 38:ehx493.P5355.

17. von Eckardstein A, Widmann C. High-density lipoprotein, beta cells, and diabetes. *Cardiovasc Res* 2014; 103:384-94.

18. White J, Swerdlow DI, Preiss D, Fairhurst-Hunter Z, Keating BJ, Asselbergs FW, et al. Association of Lipid Fractions With Risks for Coronary Artery Disease and Diabetes. *JAMA Cardiol* 2016; 1:692-9.

19. Tardif JC, Rheaume E, Lemieux Perreault LP, Gregoire JC, Feroz Zada Y, Asselin G, et al. Pharmacogenomic determinants of the cardiovascular effects of dalcetrapib. *Circ Cardiovasc Genet* 2015; 8:372-82.

20. Tardif JC, Rhainds D, Rheaume E, Dube MP. CETP: Pharmacogenomics-Based Response to the CETP Inhibitor Dalcetrapib. *Arterioscler Thromb Vasc Biol* 2017; 37:396-400.

21. Schwartz GG, Olsson AG, Ballantyne CM, Barter PJ, Holme IM, Kallend D, et al. Rationale and design of the dal-OUTCOMES trial: efficacy and safety of dalcetrapib in patients with recent acute coronary syndrome. *Am Heart J* 2009; 158:896-901 e3.

22. Schwartz GG, Ballantyne CM, Barter PJ, Kallend D, Leiter LA, Leitersdorf E, et al. Association of Lipoprotein(a) With Risk of Recurrent Ischemic Events Following Acute Coronary Syndrome: Analysis of the dal-Outcomes Randomized Clinical Trial. *JAMA Cardiol* 2018; 3:164-8.

23. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; 28:412-9.

24. Betteridge DJ, Carmena R. The diabetogenic action of statins - mechanisms and clinical implications. *Nat Rev Endocrinol* 2016; 12:99-110.

25. Lotta LA, Sharp SJ, Burgess S, Perry JRB, Stewart ID, Willems SM, et al. Association Between Low-Density Lipoprotein Cholesterol-Lowering Genetic Variants and Risk of Type 2 Diabetes: A Meta-analysis. *JAMA* 2016; 316:1383-91.

26. Niesor EJ. Different effects of compounds decreasing cholesteryl ester transfer protein activity on lipoprotein metabolism. *Curr Opin Lipidol* 2011; 22:288-95.

27. DeFronzo RA, Tripathy D, Schwenke DC, Banerji M, Bray GA, Buchanan TA, et al. Pioglitazone for diabetes prevention in impaired glucose tolerance. *N Engl J Med* 2011; 364:1104-15.

28. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; 346:393-403.

29. Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, et al. Pioglitazone after Ischemic Stroke or Transient Ischemic Attack. *N Engl J Med* 2016; 374:1321-31.

Table 1: Baseline characteristics of patients according to glycemic category and treatment group

	Normoglycemia (N=3950)		Prediabetes (N=6695)		Diabetes (N=5141)	
Characteristic	**Dalcetrapib N=1932**	**Placebo N=2018**	**Dalcetrapib N=3394**	**Placebo N=3301**	**Dalcetrapib N=2573**	**Placebo N=2568**
Age (years, SD)*†‡	58.6 (8.7)	58.6 (8.8)	59.9 (9.1)	60.0 (9.0)	61.8 (9.1)	61.4 (9.2)
Sex (% male)*†‡	82.9	84.2	80.7	81.7	77.4	78.0
Race (% white)*†‡	92.5	92.0	89.1	89.2	83.9	84.5
History of hypertension (%)*†‡	58.6	60.8	62.3	63.0	80.3	81.2
Current smoking (%)‡	18.7	18.6	22.8	23.4	20.4	19.3
Prior MI (%)*†	12.0	11.6	14.5	14.0	21.2	19.4
Prior stroke (%)	2.6	2.7	2.6	2.6	4.8	5.1
Systolic blood pressure (mm Hg)*†‡	125.5 (16.6)	125.6 (16.7)	126.8 (16.9)	127.1 (16.6)	130.0 (17.1)	129.7 (17.1)
Diastolic blood pressure (mm Hg)	76.8 (9.6)	76.6 (9.8)	76.9 (9.8)	77.0 (9.6)	77.1 (9.9)	76.8 (9.6)
Body mass index (kg/m^2, SD)*†‡	27.5 (4.5)	27.4 (4.1)	28.1 (4.6)	28.2 (4.5)	30.1 (5.3)	30.2 (5.7)
Laboratory tests:						
Fasting serum glucose (mmol/L)*†‡	5.17 (0.53)	5.18 (0.53)	5.43 (0.60)	5.45 (0.59)	7.20 (2.40)	7.18 (2.32)
Hemoglobin A1c (%, SD)*†‡	5.34 (0.23)	5.35 (0.22)	5.85 (0.24)	5.84 (0.24)	6.82 (1.07)	6.80 (1.07)
Total cholesterol (mg/dL, SD)†‡	143.9 (30.6)	142.4 (31.5)	148.0 (33.6)	147.1 (31.9)	143.4 (34.0)	142.5 (33.5)

LDL-C (mg/dL, SD)*†‡	75.3 (24.1)	74.7 (24.8)	78.8 (27.1)	78.2 (24.9)	74.1 (26.8)	73.4 (27.6)
HDL-C (mg/dL, SD)*†‡	44.2 (12.6)	43.4 (12.2)	43.0 (11.4)	42.7 (11.2)	40.6 (11.2)	40.5 (11.2)
Triglycerides (mg/dL, SD)*†‡	123 (69)	122 (62)	132 (71)	132 (74)	145 (78)	143 (80)
eGFR (ml/min/1.7m^2, SD)*†	81.9 (16.6)	82.6 (17.4)	81.9 (17.0)	81.9 (17.2)	80.6 (21.5)	80.9 (20.4)
Medications (%):						
Aspirin or other antiplatelet agent†	99.2	99.3	99.2	99.6	98.8	98.9
ACE inhibitor or ARB*†‡	73.8	72.7	78.6	79.1	84.7	84.2
Beta blocker*†	86.6	87.1	86.8	87.1	88.4	88.7
Statin*†	97.5	98.1	97.6	97.8	96.7	96.8

All characteristics were balanced between dalcetrapib and placebo groups (P>0.05). * P<0.05 for difference between normoglycemia and diabetes; † P<0.05 for difference between prediabetes and diabetes; ‡ P<0.05 for difference between normoglycemia and prediabetes, comparing the aggregate of both treatment groups in each metabolic category. Body mass index data missing for 27 patients (0.7%) with normoglycemia, 33 patients (0.5%) with prediabetes, and 44 patients (0.9%) with diabetes. Some laboratory data missing for 5 patients (0.1%) with normoglycemia, 5 patients (0.1%) with prediabetes, and 40 patients (0.8%) with diabetes. An additional 85 patients (0.5%) had insufficient glucose and hemoglobin A1c data to determine baseline glycemic status and are not included in this Table or in analyses. MI, myocardial infarction; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker.

Table 2: Transitions in glycemic status

Model	Dalcetrapib n/N, (%)	Placebo n/N, (%)	Hazard ratio*	95% CI	P-value
New onset diabetes					
Base case (prediabetes or normoglycemia at baseline)	403/5326 (7.6)	516/5319 (9.7)	0.77	0.67-0.89	<0.001
Prediabetes to diabetes	364/3394 (10.7)	473/3301 (14.3)	0.74	0.65-0.85	<0.001
Normoglycemia to diabetes	39/1932 (2.0)	43/2018 (2.1)	0.95	0.61-1.47	0.80
Sensitivity analysis (prediabetes or normoglycemia at baseline)	254/4602 (5.5)	324/4602 (7.0)	0.78	0.66-0.92	0.003
Normoglycemia to prediabetes	711/1846 (38.5)	826/1915 (43.1)	0.83*	0.73-0.94	0.004
Diabetes to no diabetes	325/2354 (13.8)	271/2393 (11.3)	1.25*	1.06-1.49	0.01

Base case uses standard criteria to define absence of diabetes at baseline and incident diabetes after randomization. Sensitivity analysis uses restrictive criteria to define absence of diabetes at baseline and standard criteria to define incident diabetes after randomization. Diabetes to no diabetes includes transitions from diabetes to either prediabetes or normoglycemia. See text for full descriptions of criteria for each transition. *Outcomes that were assessed at final study observation points are described with odds ratios.

FIGURE LEGENDS

Figure 1: Cumulative incidence of new onset diabetes in the dalcetrapib and placebo groups among all patients without diabetes at baseline (Panel A) and among patients with prediabetes at baseline (Panel B).

Figure 2: Proportion of patients with normoglycemia at baseline who progressed to prediabetes after randomization (Panel A). Proportion of patients with diabetes at baseline who regressed to no diabetes after randomization (Panel B). Definitions of transitions are provided in the text.