Dalcetrapib Reduces Risk of New-Onset Diabetes in Patients With Coronary Heart Disease

Diabetes Care 2020;43:1077–1084 | https://doi.org/10.2337/dc19-2204

Gregory G. Schwartz,[1] Lawrence A. Leiter,[2] Christie M. Ballantyne,[3] Philip J. Barter,[4] Donald M. Black,[5] David Kallend,[6] Fouzia Laghrissi-Thode,[5] Eran Leitersdorf,[7] John J.V. McMurray,[8] Stephen J. Nicholls,[9] Anders G. Olsson,[10] David Preiss,[11] Prediman K. Shah,[12] Jean-Claude Tardif,[13] and John Kittelson[14]

OBJECTIVE

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.

RESEARCH DESIGN AND 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 on medical history, no use of antihyperglycemic medication, and hemoglobin A_{1c} 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 A_{1c} ≥6.5%, or a combination of at least two measurements of serum glucose ≥7.0 mmol/L (fasting) or ≥11.1 mmol/L (random).

RESULTS

At baseline, 10,645 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 5,326 patients (7.6%) assigned to dalcetrapib and in 516 of 5,319 (9.7%) assigned to placebo, corresponding to absolute risk reduction of 2.1%, hazard ratio of 0.77 (95% CI 0.68–0.88; $P < 0.001$), and a need to treat 40 patients for 3 years to prevent 1 incident case of diabetes. Considering only those with prediabetes at baseline, the number needed to treat for 3 years to prevent 1 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.

CONCLUSIONS

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

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 ~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 nonpharmacologic strategies to reduce incident type 2 diabetes.

[1]Cardiology Section, Veterans Affairs Medical Center, and University of Colorado School of Medicine, Aurora, CO
[2]Li Ka Shing Knowledge Institute, St Michael's Hospital, University of Toronto, Toronto, Canada
[3]Baylor College of Medicine, Houston, TX
[4]University of New South Wales, Sydney, Australia
[5]DalCor Pharmaceuticals, Zug, Switzerland
[6]The Medicines Company, Zurich, Switzerland
[7]Hadassah Hebrew University Medical Center, Jerusalem, Israel
[8]British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, Scotland, U.K.
[9]Monash Cardiovascular Research Centre, Monash University, Melbourne, Australia
[10]Linköping University, Linköping, Sweden
[11]Medical Research Council Population Health Research Unit, Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, U.K.
[12]Cedars-Sinai Heart Institute, Los Angeles, CA
[13]Montreal Heart Institute, Université de Montréal, Montreal, Canada
[14]University of Colorado School of Public Health, Aurora, CO

Corresponding author: Gregory G. Schwartz, gregory.schwartz@va.gov

Received 2 November 2019 and accepted 3 February 2020

Clinical trial reg. no. NCT00658515, clinicaltrials.gov

This article contains Supplementary Data online at https://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc19-2204/-/DC1.

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.

Cholesteryl ester transfer protein (CETP) inhibitors increase the concentration of HDL 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. Reductions in plasma glucose and insulin were noted in patients treated with torcetrapib (15), and an 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-C is purported to prevent β-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 a genetically instrumented elevation in HDL-C (18).

Dalcetrapib is a CETP inhibitor with modest effects on HDL-C and minimal effects on LDL-cholesterol (LDL-C) 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 6,000 patients with ACS (ClinicalTrials.gov reg. no. 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.

RESEARCH DESIGN AND 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 Functional Classification III or IV symptoms of heart failure or class II symptoms with left ventricular ejection fraction ≤40%, uncontrolled hypertension (systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg despite treatment), serum creatinine >2.2 mg/dL (194.5 μmol/L), or fasting triglycerides >400 mg/dL. Baseline laboratory testing included serum glucose and hemoglobin A_{1c}. Patients were instructed to report for study visits after an overnight fast; actual fasting or nonfasting 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 and then every 4 months and at the end of the trial. Hemoglobin A_{1c} was measured 6 and 12 months after randomization and then annually and at the end of the trial. Concurrent medications and medical conditions were determined, weight was measured, and 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, nonfatal 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 A_{1c} ≥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 A_{1c} ≥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 the risk of incident diabetes after month 3.

Many patients with ACS have hemoglobin A_{1c} or fasting glucose values that lie near dichotomous boundaries used to define diabetes, and intraindividual variability in these measurements may be considerable. We therefore performed a sensitivity analysis restricting the subgroup considered to be without diabetes at baseline to those with baseline hemoglobin A_{1c} <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

Patients were classified as having prediabetes at baseline if hemoglobin A_{1c} was at least 5.7% but <6.5%, or if fasting serum glucose was at least 5.6 mmol/L but <7 mmol/L, without fulfillment of any criterion for diabetes. Patients who did not meet criteria for prediabetes or diabetes were considered normoglycemic. Progression from normoglycemia to prediabetes was defined by normoglycemia at baseline and at least two postrandomization measurements of hemoglobin A_{1c} of at least 5.7% but <6.5% or two measurements of fasting serum glucose of at least 5.6 mmol/L but <7 mmol/L, without

fulfillment of any criteria for new-onset diabetes. Regression from diabetes to a nondiabetic state was defined by diabetes at baseline, the last two available measurements of hemoglobin A_{1c} of $<6.5\%$, and the last two available measurements of serum glucose of <7 mmol/L (if fasting) or <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 for 1,293 patients assigned to treatment with dalcetrapib and for 1,288 patients assigned to treatment with placebo and at month 3 for 1,071 patients assigned to dalcetrapib treatment and 1,197 patients assigned to placebo treatment, excluding patients who initiated treatment with antihyperglycemic medication prior to month 3. At each time point, HOMA of insulin resistance (HOMA-IR) was calculated as (23):

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

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% CI. Progression from normoglycemia to prediabetes or regression from diabetes to prediabetes or from diabetes to a nondiabetic 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 the 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 postrandomization 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, two-sided *P* values <0.05 were considered statistically significant.

RESULTS

Baseline Characteristics

At baseline using base-case criteria, 5,141 patients (32.5%) were classified with diabetes (dalcetrapib, 2,573; placebo, 2,568) and 10,645 (67.1%) without diabetes (dalcetrapib, 5,326; placebo, 5,319). Diagnostic criteria were missing for 85 patients (0.5%). Among those without diabetes, 6,695 (62.9%) were classified as prediabetic and 3,950 (37.1%) as normoglycemic. Baseline characteristics of patients in each category are reported in Table 1. The sensitivity analysis that used more restrictive criteria to define absence of diabetes at baseline placed 9,646 patients (60.8%) in that category, with characteristics reported in Supplementary Table 1.

Cardiovascular Outcomes, 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 end point 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 adverse effect profile. Adverse events of hypertension, diarrhea, and insomnia were reported more frequently in the dalcetrapib group than in the placebo group.

Hemoglobin A_{1c}, Fasting Glucose, and Concurrent Medication Use With Dalcetrapib or Placebo

Supplementary Table 2 reports changes in median hemoglobin A_{1c} and glucose levels over the course of the trial among patients without diabetes at baseline censored at first use of an antihyperglycemic medication. Hemoglobin A_{1c} levels were slightly lower with dalcetrapib at 6, 12, 24, and 36 months, 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, β-blockers, or diuretics (data not shown).

Incidence of 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 reported in Supplementary Table 3.

Dalcetrapib treatment reduced incident diabetes (Table 2 and Fig. 1*A*). As determined from base-case criteria, incident diabetes developed in 403 of 5,326 patients (7.6%) in the dalcetrapib group and in 516 of 5,319 patients (9.7%) in the placebo group, 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 1 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 3,394 patients (10.7%) in the dalcetrapib group and in 473 of 3,301 patients (14.3%) in the placebo group, corresponding to a HR of 0.74 (95% CI 0.65–0.85, $P < 0.001$) (Table 2 and Fig. 1*B*) and a need to treat 25 patients for 3 years to prevent 1 incident case. Restricting the analysis further to 3,371 patients with impaired fasting glucose (100–125 mg/dL) at baseline, incident diabetes developed in 251 of 1,681 patients (14.9%) in the dalcetrapib group compared with 321 of 1,690 (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 4,602 patients (5.5%) in the dalcetrapib group and

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

	Normoglycemia (N = 3,950)		Prediabetes (N = 6,695)		Diabetes (N = 5,141)	
Characteristic	Dalcetrapib n = 1,932	Placebo n = 2,018	Dalcetrapib n = 3,394	Placebo n = 3,301	Dalcetrapib n = 2,573	Placebo n = 2,568
Age, years*†‡	58.6 (8.7)	58.6 (8.8)	59.9 (9.1)	60.0 (9.0)	61.8 (9.1)	61.4 (9.2)
Male sex (%)*†‡	82.9	84.2	80.7	81.7	77.4	78.0
White race (%)*†‡	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 myocardial infarction (%)*†	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
Blood pressure, mmHg						
Systolic*†‡	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	76.8 (9.6)	76.6 (9.8)	76.9 (9.8)	77.0 (9.6)	77.1 (9.9)	76.8 (9.6)
BMI, kg/m^2*†‡	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 A_{1c}, %*†‡	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†‡	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*†‡	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*†‡	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*†‡	123 (69)	122 (62)	132 (71)	132 (74)	145 (78)	143 (80)
eGFR, mL/min/1.7 m^2*†	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
β-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

Data are mean (SD) unless otherwise indicated. All characteristics were balanced between the dalcetrapib and placebo groups ($P > 0.05$). BMI 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 A_{1c} data to determine baseline glycemic status and are not included in this table or in the analyses. ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate. *$P < 0.05$ 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.

in 324 of 4,602 patients (7.0%) 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 the 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 mean (SD) change 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-to-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

Table 2—Transitions in glycemic status

Model	Dalcetrapib, n/N (%)	Placebo, n/N (%)	HR*	95% CI	P value
New-onset diabetes					
Base case (prediabetes or normoglycemia at baseline)	403/5,326 (7.6)	516/5,319 (9.7)	0.77	0.67–0.89	<.001
Prediabetes to diabetes	364/3,394 (10.7)	473/3,301 (14.3)	0.74	0.65–0.85	<.001
Normoglycemia to diabetes	39/1,932 (2.0)	43/2,018 (2.1)	0.95	0.61–1.47	.80
Sensitivity analysis (prediabetes or normoglycemia at baseline)	254/4,602 (5.5)	324/4,602 (7.0)	0.78	0.66–0.92	.003
Normoglycemia to prediabetes	711/1,846 (38.5)	826/1,915 (43.1)	0.83*	0.73–0.94	.004
Diabetes to no diabetes	325/2,354 (13.8)	271/2,393 (11.3)	1.25*	1.06–1.49	.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 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 ORs.

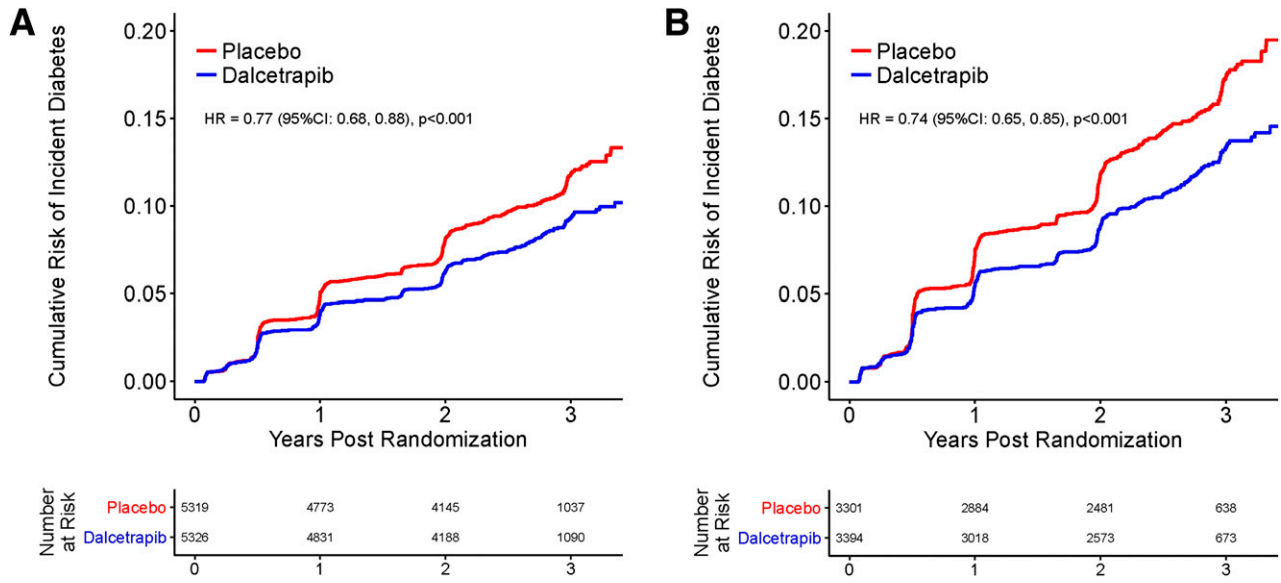

Figure 1—Cumulative incidence of new-onset diabetes in the dalcetrapib and placebo groups among all patients without diabetes at baseline (*A*) and among patients with prediabetes at baseline (*B*).

change 0.98, 95% CI 0.97–0.99, $P < 0.001$).

Progression From Normoglycemia to Prediabetes, Regression From a Diabetic to a Nondiabetic State, and Modification of These Transitions by Dalcetrapib

Dalcetrapib reduced the likelihood of progression from normoglycemia to prediabetes (Fig. 2). Among 3,761 patients who were normoglycemic at baseline and were evaluable for glycemic status at their last two study visits, prediabetes developed in 711 of 1,846 (38.5%) assigned to dalcetrapib compared with 826 of 1,915 (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 a diabetic to a nondiabetic state (Fig. 2). Among 4,747 patients with diabetes at baseline who were evaluable for subsequent glycemic status, 325 of 2,354 (13.8%) assigned to dalcetrapib had improved to a state of prediabetes or normoglycemia at their two final study visits compared with 271 of 2,393 (11.3%) assigned to placebo, corresponding to an OR of 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 the treatment groups 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 ~0.2 kg/m^2 was sustained through month 36 (Supplementary Table 2). 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 adjustments for baseline and month 12 change in BMI, the HR for new-onset diabetes with dalcetrapib relative to placebo (HR 0.80, 95% CI 0.70– 0.92, $P = 0.001$) was equivalent to the unadjusted HR.

Effect of Dalcetrapib on Insulin Resistance

Supplementary Table 4 reports data for patients without diabetes at baseline who had concurrent measurements of fasting glucose and insulin at randomization ($n = 2,581$) and at month 3 ($N = 2,168$). At baseline, median (IQR) fasting glucose was 5.3 (4.9–5.7) mmol/L, insulin was 8.3 (5.5–12.4) μU/mL, and HOMA-IR was 1.9 (1.3–3.0), without differences between treatment groups. At month 3, median fasting glucose was unchanged, and fasting insulin increased slightly in both groups. However, dalcetrapib had no effect on the change in these measurements from randomization to month 3, nor did dalcetrapib have a discernible effect on new-onset diabetes at month 3.

CONCLUSIONS

This analysis demonstrates that dalcetrapib, a CETP inhibitor, reduces incident diabetes by ~23% (absolute reduction 2.1%) over a median follow-up of 30 months in patients with ACS who do not have diabetes at baseline. On the basis of Kaplan-Meier incidences at 3 years, 40 patients would have to be treated with dalcetrapib to prevent 1 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 a diabetic to a nondiabetic 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

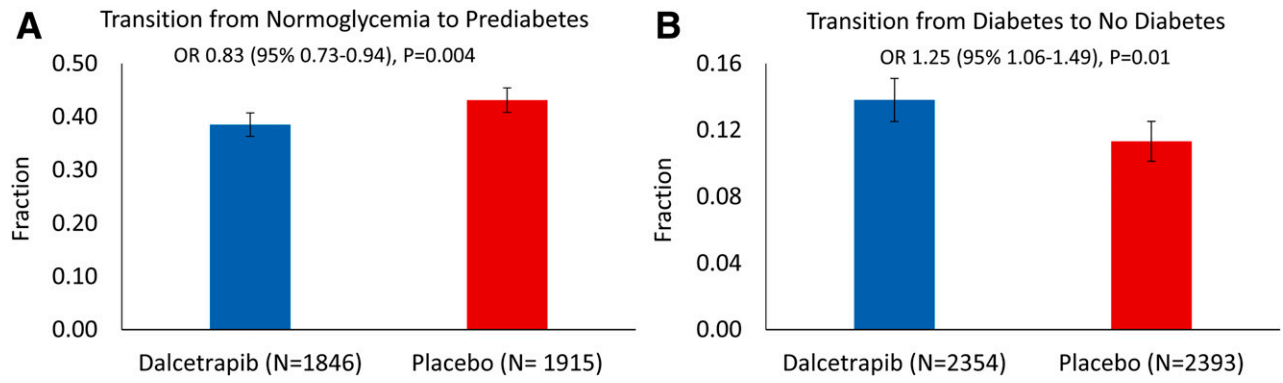

Figure 2—*A*: Proportion of patients with normoglycemia at baseline who progressed to prediabetes after randomization. *B*: Proportion of patients with diabetes at baseline who regressed to no diabetes after randomization. Definitions of transitions are provided in the text.

prior ACS. Among potential mechanisms, HDL-C, possibly through its component apolipoprotein A-I, may improve β-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-C 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 A_{1c} between 6 and 36 months after randomization. An effect on postprandial 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, 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 for insulin measurement in a case-control design rather than with random sampling or in the entire study cohort. Further targeted studies to assess β-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-C (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 monitored 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 (HR 0.89, 95% CI 0.79–1.00, $P = 0.05$) (14). In an analysis of 3,856 patients with acute or chronic coronary heart disease without diabetes at baseline and with a median follow-up 30 months (the same duration as in the current analysis), diabetes developed in 176 of 1,911 patients (9.2%) treated with the CETP inhibitor evacetrapib compared with 200 of 1,945 patients (10.3%) treated with placebo (OR 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). Therefore, 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-C 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 A_{1c} value >6.5%. In contrast, the present analysis used all of the above criteria as well as measurements of fasting or random glucose. Therefore, absolute incidence rates for new-onset diabetes should not be compared directly among studies, but comparison of ORs for active treatment versus placebo may be reasonable.

Considering all available laboratory data, there were relatively small changes in median fasting glucose and hemoglobin A_{1c} over time within and between treatment groups (Supplementary Table 2). 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 A_{1c} or glucose. However, in a sensitivity analysis that restricted the analysis cohort to patients with baseline hemoglobin A_{1c} 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 after 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 nonfasting 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 Effect of Dalcetrapib vs. Placebo on CV Risk in a Genetically Defined Population With a Recent ACS (dal-GenE) trial (20). Moreover, there could be a long-term cardiovascular benefit of preventing diabetes with dalcetrapib, only becoming apparent with a longer observation period than the median 30 months in the current analysis. Dalcetrapib does not share the risks of fluid retention and heart failure, weight gain, and bone fractures associated with thiazolidinediones, the hemodynamic and electrolyte effects with valsartan, or the 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.

Funding. G.G.S. has received research support from the Medical Research Service of the U.S. Department of Veterans Affairs. C.M.B. has received research support from the National Institutes of Health (grants R01HL134320 and R01HL098839), the American Heart Association (grant AHA16GRNT30410012), and the American Diabetes Association (grant 1-17-IBS-082). P.J.B. has received research support from the National Health and Medical Research Council of Australia. D.P. is supported by a University of Oxford British Heart Foundation Centre of Research Excellence Senior Transition Fellowship (RE/13/1/30181).

Duality of Interest. F. Hoffmann-La Roche funded the dal-OUTCOMES trial. G.G.S., through his institution, has received research support from Resverlogix, Roche, Sanofi, and The Medicines Company. L.A.L. has received research funding from Amgen, AstraZeneca, Esperion, Kowa, The Medicines Company, and Regeneron/Sanofi, and has acted as a consultant to or provided continuing medical education on behalf of Amgen, AstraZeneca, HLS, Merck, and Regeneron/Sanofi. C.M.B. has received research support from Abbott Diagnostics, Amarin, Amgen, Eli Lilly, Esperion, Novartis, Pfizer, Otsuka, Regeneron, Roche Diagnostic, Sanofi-Synthelabo, and Takeda. P.J.B. has received research support from Merck and Pfizer and has received honoraria from Amgen, AstraZeneca, CSL Behring, Eli Lilly, Merck, Novartis, Pfizer, and Sanofi-Regeneron. D.M.B. and F.L.-T. are employees of DalCor. D.K. was an employee of F. Hoffmann-La Roche when the dal-OUTCOMES study was performed. E.L. is consulting for Novartis, AstraZeneca, Sanofi, and Amgen. J.J.V.M. has received funding through his institution from AbbVie, Amgen, Cardiorentis, GSK, Novartis, Pfizer, Roche, and Sanofi. S.J.N. has received research support from Amgen, Anthera, Eli Lilly, Cerénis, AstraZeneca, Novartis, Resverlogix, and Sanofi-Regeneron, and is a consultant for Amgen, AstraZeneca, Boehringer Ingelheim, CSL Behring, Eli Lilly, Merck, Takeda, Roche, Pfizer, and Sanofi-Regeneron. A.G.O. has received research grants from Amgen, AstraZeneca, Karo Bio, Merck, Pfizer, Roche, and Sanofi and consultation fees from AstraZeneca, Merck Sharp & Dohme, Merck, Pfizer, and Roche. D.P. reports that the Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), University of Oxford, has a staff policy of not accepting honoraria or other payments from the pharmaceutical industry; CTSU coordinated the REVEAL trial, which was sponsored by the University of Oxford and funded by Merck Sharp and Dohme, the British Heart Foundation, and the Medical Research Council. J.-C.T. has received research support from Amarin, AstraZeneca, DalCor, Eli Lilly, Esperion, Hoffmann-LaRoche, Merck, Pfizer, Sanofi, and Servier and honoraria from Hoffmann-LaRoche, Pfizer, Sanofi, and Servier, and holds equity in DalCor. A patent was submitted based on the findings of genotype-dependent results of dalcetrapib on clinical outcomes, and J.-C.T. is mentioned as an author. J.K. has received consulting fees from Bayer Healthcare, Jansen, AMAG Pharmaceuticals, and Agile Therapeutics for advisory and steering committee activities, and has received consulting fees for work on data and safety monitoring committees from Cystic Fibrosis Foundation Therapeutics, Novo Nordisk, Pfizer, Genentech, and BioMarin Pharmaceuticals. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. G.G.S. researched the data, designed the analysis, and wrote the manuscript. L.A.L., C.M.B., P.J.B., E.L., J.J.V.M., S.J.N., A.G.O., P.K.S., and J.-C.T. researched the data and critically reviewed and edited the manuscript. D.M.B. and D.P. critically reviewed and edited the manuscript. D.K. and F.L.-T. supervised and managed the research and critically reviewed and edited the manuscript. J.K. performed statistical analysis and critically reviewed and edited the manuscript. G.G.S. and J.K. take full responsibility for the work as a whole, the study design, access to data, and the decision to submit and publish the manuscript. G.G.S. and J.K. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the European Society of Cardiology Congress, Paris, France, 31 August–4 September 2019.

References

1. Cannon CP, Blazing MA, Giugliano RP, et al.; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372:2387–2397

2. Schwartz GG, Steg PG, Szarek M, et al.; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379:2097–2107

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, et al. Recognition of incident diabetes mellitus during an acute myocardial infarction. Circ Cardiovasc Qual Outcomes 2015;8:260–267
5. Meisinger C, Beck J, Heier M, et al.; KORA Study Group. 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;159:258–263
6. Forbes JM, Cooper ME. Mechanisms of diabetic complications. Physiol Rev 2013;93:137–188
7. Bethel MA, Xu W, Theodorakis MJ. Pharmacological interventions for preventing or delaying onset of type 2 diabetes mellitus. Diabetes Obes Metab 2015;17:231–244
8. Carlsson LM, Peltonen M, Ahlin S, 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, et al. Long-term sustainability of diabetes prevention approaches: a systematic review and meta-analysis of randomized clinical trials. JAMA Intern Med 2017;177:1808–1817
10. McMurray JJ, Holman RR, Haffner SM, et al.; NAVIGATOR Study Group. Effect of valsartan on the incidence of diabetes and cardiovascular events. N Engl J Med 2010;362:1477–1490
11. Barter PJ, Caulfield M, Eriksson M, et al.; ILLUMINATE Investigators. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med 2007;357:2109–2122
12. Lincoff AM, Nicholls SJ, Riesmeyer JS, et al.; ACCELERATE Investigators. Evacetrapib and cardiovascular outcomes in high-risk vascular disease. N Engl J Med 2017;376:1933–1942
13. Schwartz GG, Olsson AG, Abt M, et al.; dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. N Engl J Med 2012;367:2089–2099
14. Bowman L, Hopewell JC, Chen F, et al.; HPS3/TIMI55–REVEAL Collaborative Group. Effects of anacetrapib in patients with atherosclerotic vascular disease. N Engl J Med 2017;377:1217–1227
15. Barter PJ, Rye KA, Tardif JC, 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;124:555–562
16. Menon V, Lincoff AM, Nicholls SJ, et al. Impact of evacetrapib on glyvemic control: results from the ACCELERATE trial. Eur Heart J 2017;38(Suppl. 1):ehx493.P5355.
17. von Eckardstein A, Widmann C. High-density lipoprotein, beta cells, and diabetes. Cardiovasc Res 2014;103:384–394
18. White J, Swerdlow DI, Preiss D, et al. Association of lipid fractions with risks for coronary artery disease and diabetes. JAMA Cardiol 2016;1:692–699
19. Tardif JC, Rhéaume E, Lemieux Perreault LP, et al. Pharmacogenomic determinants of the cardiovascular effects of dalcetrapib. Circ Cardiovasc Genet 2015;8:372–382
20. Tardif JC, Rhainds D, Rhéaume E, Dubé 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, et al.; dal-OUTCOMES Committees and Investigators. 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, 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;3:164–168
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;28:412–419
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, et al. Association between low-density lipoprotein cholesterol-lowering genetic variants and risk of type 2 diabetes: a meta-analysis. JAMA 2016;316:1383–1391
26. Niesor EJ. Different effects of compounds decreasing cholesteryl ester transfer protein activity on lipoprotein metabolism. Curr Opin Lipidol 2011;22:288–295
27. DeFronzo RA, Tripathy D, Schwenke DC, et al.; ACT NOW Study. Pioglitazone for diabetes prevention in impaired glucose tolerance. N Engl J Med 2011;364:1104–1115
28. Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. 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, et al.; IRIS Trial Investigators. Pioglitazone after ischemic stroke or transient ischemic attack. N Engl J Med 2016;374:1321–1331