Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors and Incident Type 2 Diabetes: A Systematic Review and Meta-analysis With Over 96,000 Patient-Years

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OBJECTIVE

Like mutations with loss of function in the proprotein convertase subtilisin/kexin type 9 (PCSK9) gene, inhibitors of PCSK9 (PCSK9i) may potentially favor the manifestation of diabetes.

RESEARCH DESIGN AND METHODS

A meta-analysis of phase 2/3 randomized clinical trials (RCTs) assessed PCSK9i versus placebo in the primary hypercholesterolemia setting. Statins and ezetimibe were used in 98.4% of these studies and balanced between PCSK9i and placebo. We calculated relative risks (RRs) and 95% CIs using random- and fixed-effect models.

RESULTS

We included 68,123 participants (20 RCTs) with median follow-up of 78 weeks. PCSK9i increased fasting blood glucose (weighted mean difference 1.88 mg/dL [95% CI 0.91–2.68]; I^2 = 0%; $P < 0.001$) and HbA_{1c} (0.032% [0.011–0.050]; I^2 = 15.5%; $P < 0.001$) when compared with placebo. This effect was not sufficient to increase incidence of diabetes (RR 1.04 [0.96–1.13]; I^2 = 0%; $P = 0.427$). Exploratory meta-regression analyses indicated an association between the increased risk of diabetes and the potency ($P = 0.029$) and duration ($P = 0.026$) of PCSK9i treatment.

CONCLUSIONS

In the short term, PCSK9i therapy favors a small but significant increase in plasma glycemia and HbA_{1c}.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a circulating protein that binds to the LDL receptor (LDLR), directing it to lysosome degradation pathways (1). Anti-PCSK9 monoclonal antibody (MAb) therapy reduces LDL cholesterol (LDL-C) by 50–60% in several clinical settings and over the maximal dose of statins plus ezetimibe, with a satisfactory safety profile (2).

Meanwhile, both Mendelian randomization and randomized clinical trials (RCTs) suggest an inverse association between plasma PCSK9 availability and the incidence of type 2 diabetes (3). Gain-of-function mutation on the *LDLR* gene impairs insulin secretion capacity by pancreatic β-cells (4). By inference, it is plausible that the

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improvement in LDLR turnover and functionality after PCSK9 MAb underlies a decline in β-cell function favoring type 2 diabetes manifestation. Hence, we conducted a systematic review and meta-analysis of RCTs with PCSK9 inhibitors (PCSK9i) in order to explore the existence and magnitude of this metabolic interaction.

RESEARCH DESIGN AND METHODS

Cochrane guidelines and Preferred Reporting Items for Systematic Reviews and Meta-Analyses statements were used to conduct the meta-analysis and report our findings. A detailed description of all procedures is included in the Supplementary Data. Briefly, MEDLINE (PubMed), Cochrane Library, and ClinicalTrials.gov databases were searched for original articles from inception to 19 March 2017 to identify all RCTs using PCSK9i therapy. Original trials were eligible for the present meta-analysis if they met the following criteria: *1*) phase 2 or 3 RCT; *2*) participants with familial or nonfamilial hypercholesterolemia; *3*) participants in the treatment group received PCSK9i versus control group, who received placebo with or without other lipid-lowering therapy, irrespective of balanced use of statin or ezetimibe across treatment arms; and *4*) treatment duration ≥12 weeks. Two investigators independently abstracted data by using prespecified forms and independently appraised the accuracy of the abstractions and resolved any discrepancies by consensus after discussion with the third investigator. Baseline data were obtained by weighted calculation. To identify potential effects of PCSK9i therapy on incident diabetes, we calculated an overall relative risk (RR) with both random- and fixed-effect model meta-analyses. Odds ratios and risk ratios were universally identical during data analysis. Further details regarding data analysis can be found in the Supplementary Data. For the summary treatment effect estimate, a two-tailed *P* value <0.05 was considered statistically significant. We analyzed data with Stata 13.

RESULTS

Using MEDLINE/PubMed, Cochrane Library databases, and ClinicalTrials.gov, we identified 133 citations using the previously defined search terms. Our search flow diagram can be found in Supplementary Fig. 1*A* and our network profile in Supplementary Fig. 1*B*.

For our coprimary outcome meta-analysis, we included 20 RCTs (5–19) with 68,123 patients. Baseline study characteristics can be found in Supplementary Table 1*A*. Baseline patient characteristics can be found in Supplementary Tables 2 and 3.

PCSK9i and Glycemic Levels

The changes in both fasting blood glucose (FBG) and HbA_{1c} from baseline to follow-up were compared in patients randomized to PCSK9i or placebo. Only trials with background statin were included in this analysis because no trials with restricted statin use or open-label statins reported glycemic parameters. Patients treated with PCSK9i had an absolute increase (weighted mean difference) of 1.88 mg/dL (95% CI 0.91–2.68), which was significantly different from placebo (Fig. 1*A*) (standardized mean difference 0.166% [95% CI 0.143–0.188; I^2 = 0%; $P < 0.001$). Regarding HbA_{1c} levels, compared with baseline, patients treated with PCSK9i had a weighted mean difference of 0.032% (0.011–0.050) (Fig. 1*B*) (standardized mean difference 0.096% [0.074–0.119]; I^2 = 15.5%; $P < 0.001$). As shown in Supplementary Fig. 2*A* and *B* and Supplementary Table 4, there was no significant publication bias in funnel plots and no significant small study bias according to the Egger tests. In addition, even after excluding the results of the SPIRE-1 and SPIRE-2 trials, HbA_{1c} and FBG significantly increased with PCSK9i in comparison with placebo. Additional sensitivity analyses are available in the Supplementary Data.

PCSK9i and Incident Diabetes

In most of the included RCTs, the use of statins and ezetimibe was reported to be balanced between PCSK9i and control arms, except in the following trials: GAUSS, ODYSSEY OPTIONS I, ODYSSEY COMBO II, and ODYSSEY MONO (1.6% of the total sample size).

As seen in Supplementary Fig. 4*A* and *B*, PCSK9i did not significantly increase the incidence of diabetes (RR 1.045 [95% CI 0.954–1.135]; I^2 = 0%; *P* = 0.345) or the compound end point of incident or worsening diabetes (RR 1.035 [95% CI 0.949–1.128]; I^2 = 0%; *P* = 0.429) after 78 weeks (1.50 years). When limiting the analysis to studies with follow-up of ≥48 weeks (Supplementary Fig. 4*C*), there was no significant increase in the risk of diabetes. As shown in Supplementary Fig. 2*C* and *D* and Supplementary Table 4, there was no significant publication bias in funnel plots and no small study bias by the Egger test.

Across anti-PCSK9 MAbs—alirocumab, evolocumab, and bococizumab—no difference was found to the propensity of favoring incident or worsening type 2 diabetes, as shown in Supplementary Fig. 3*A* and *B*. Exploratory meta-regression analyses indicated the association between the magnitude and duration of LDL-C lowering and the risk of worsening diabetes or new onset (Supplementary Fig. 5).

CONCLUSIONS

Consistently with observational and mechanistic data, this meta-analysis reveals the existence of a small albeit significant increase in plasma levels of glucose and HbA_{1c} after a short-term (1.5-year) treatment with PCSK9i; this effect was proportional to the decrease in plasma LDL-C. In this cohort of patients and under such a short period of time, this increase was not sufficient to impact on incident diabetes. These findings are strengthened by the very low heterogeneity among trials in both continuous and dichotomous end points and the scrutiny of robust sensitivity analysis.

In line with our findings, a meta-analysis including 91,140 patients followed during ~4 years found a 9% increased risk for incident diabetes with statins (20). This incidence was amplified by intensive statin therapy and in the individuals with greater decrease in LDL-C (≥50%). Concurrently, observational studies using Mendelian randomization approach observed an inverse association between genetically determined cholesterol levels and incident diabetes (21). An inverse association was also described between the severity of LDLR dysfunction in patients with familial hypercholesterolemia and propensity to develop diabetes (3). In parallel, in vitro and in vivo models indicate LDLR and intracellular cholesterol content as key regulators of pancreatic β-cell homeostasis (4). Altogether, our findings and these prior studies support the concept of an inverse and dose-dependent effect of LDL-C levels on plasma glucose levels.

As seen with statins, heterogeneity of this lipid-lowering effect on glucose homeostasis is clearly influenced by duration of treatment. Indeed, the meta-regression analyzes obtained in our study indicated a progressively greater imbalance in glucose homeostasis as the duration of treatment increases. As the follow-up period

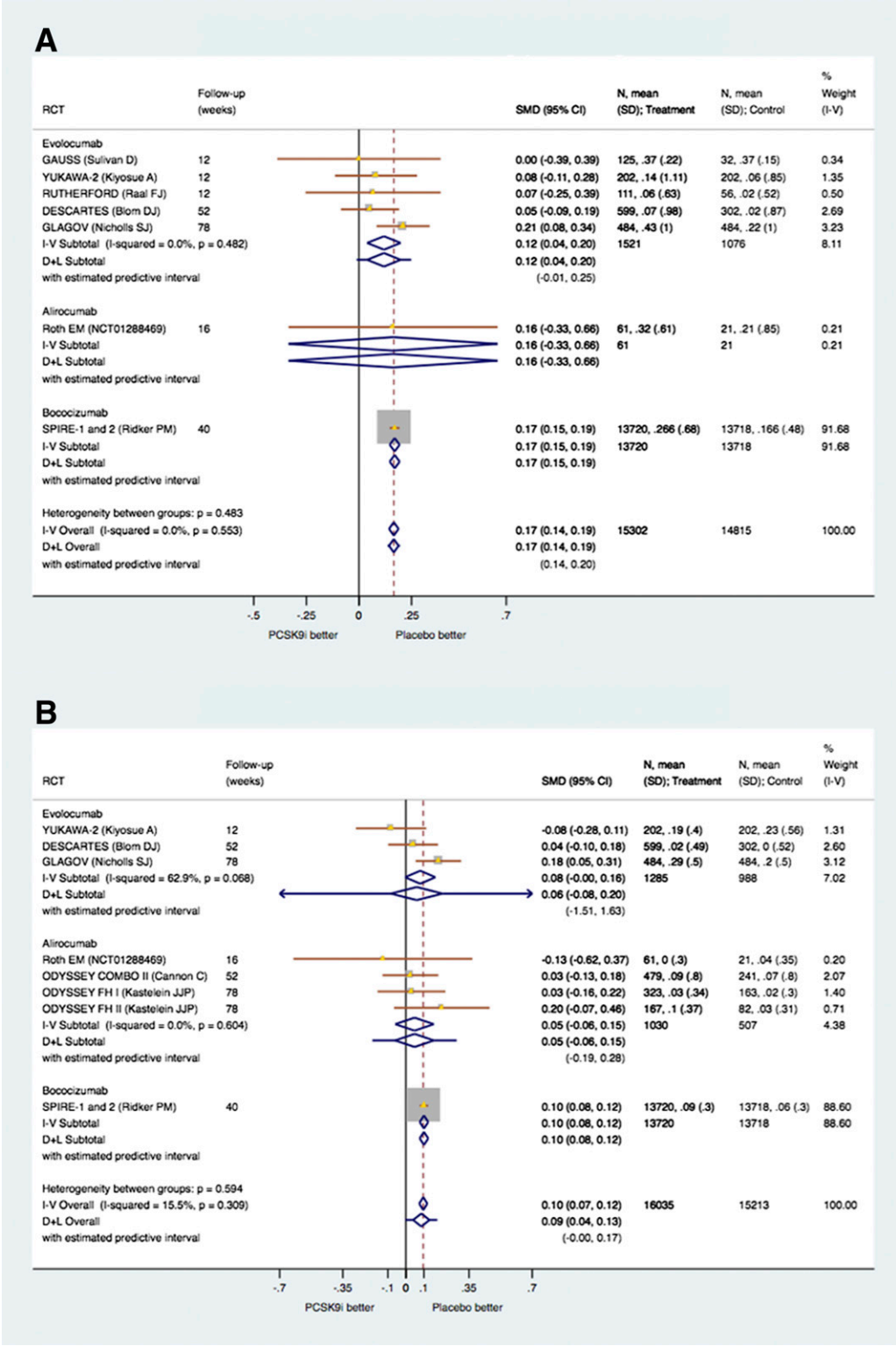

Figure 1—Meta-analysis of studies assessing the effect of PCSK9i vs. placebo on FBG change (*A*) and HbA_{1c} change (*B*). Yellow boxes are the center of the estimate for each study. The odds ratio for each study is indicated by a gray box, and the maroon horizontal lines show the corresponding 95% CI. Combined estimates are indicated by blue diamonds (there is no comparison between them). The dashed vertical line points to the center of estimates with the combined trials. The I^2 (heterogeneity) for bococizumab can be calculated only if SPIRE-1 and SPIRE-2 trials (22) are separated; however, these data are not published separately but only in combination. Thus, I^2 for bococizumab and alirocumab on FBG and for bococizumab on HbA_{1c} are excluded. For the GLAGOV trial, see ref. 23. D+L Subtotal/Overall, random-effect meta-analysis; I-V Subtotal/Overall, fixed-effects meta-analysis; SMD, standardized mean difference.

is restricted to 114 weeks, it was not possible to foresee the long-term nature of this effect curve shape. In this meta-analysis, although the incidence of diabetes may have been minimized by the short follow-up period, the achieved statistical power ($1 - \beta$) was 97% for both FBG and HbA_{1c}, which reinforces that our estimates might be close to the actual impact of blood cholesterol reduction on blood glucose homeostasis.

Main limitations that must be borne in mind in this meta-analysis are study-level nature, the rarity of the clinical outcome, the inclusion of unbalanced trials with ezetimibe versus PCSK9i (1.6% of sample size), and the lack of information on the concomitant use and up- or down-titration of antidiabetes medications. Pooling raw data from PCSK9i RCTs would be the best approach to unveil the particularities of this metabolic interaction under a great robustness. Besides that, the data presented in this study are the best approximation available for glimpsing the relationship between blood cholesterol and glucose.

In conclusion, the current study indicates that treatment with PCSK9i is associated with increased blood glucose at mean follow-up of 1.50 years. The effect on diabetes risk is only apparent among individuals who achieved very low levels of LDL-C after treatment.

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