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Original article

Therapy with cholesteryl ester transfer protein (CETP) inhibitors and diabetes risk

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ABSTRACT

Background. – Cholesteryl ester transfer protein (CETP) inhibitors are a class of drugs that targets the CETP enzyme to significantly increase serum high-density lipoprotein cholesterol (HDL-C) and decrease low-density lipoprotein cholesterol (LDL-C) levels. As HDL-C has potential antidiabetic properties, and the beneficial effects of CETP drugs on glucose homoeostasis have not been sufficiently studied, the aims of this study were: (1) to evaluate the effect of CETP inhibitors on the incidence of diabetes; and (2) to assess the association between CETP inhibitor-induced changes in HDL-C levels and incidence of diabetes.
Methods. – A meta-analysis was performed of randomized controlled clinical trials of CETP inhibitor therapy, either alone or combined with other lipid-lowering drugs, reporting data from new cases of diabetes with a minimum of 6 months of follow-up, after searching the PubMed/MEDLINE, Embase and Cochrane Controlled Trials databases. A fixed-effects meta-regression model was then applied.
Results. – Four eligible trials of CETP inhibitors, involving a total of 73,479 patients, were considered for the analyses, including 960 newly diagnosed cases of diabetes in the CTEP inhibitor group *vs* 1086 in the placebo group. CETP inhibitor therapy was associated with a significant 12% reduction in incidence of diabetes (OR: 0.88, 95% CI: 0.81–0.96; $P = 0.005$). Assessment of the relationship between on-treatment HDL-C and the effect of CETP inhibitors showed a statistically non-significant trend ($Z = -1.13$, $P = 0.26$).
Conclusion. – CETP inhibitors reduced the incidence of diabetes. The improvement in glucose metabolism may have been related, at least in part, to the increase in HDL-C concentration.

Introduction

Cardiovascular diseases are responsible for approximately one-third of all global deaths in both the developing and developed countries [1]. The impact of lipid-lowering drugs such as statins on cardiovascular risk has been clearly demonstrated, despite the fact that they can also increase the risk of type 2 diabetes (T2D) [2]. Cholesteryl ester transfer protein (CETP) inhibitors are a class of drugs targeting the CETP enzyme [3], a glycoprotein synthesized mainly in the liver that plays a prominent role in the bidirectional transfer of cholesterol esters and triglycerides between lipoproteins. Cholesterol esters are thereby transferred from cardioprotective high-density lipoprotein (HDL) particles to potentially atherogenic non-HDL particles [very low-density lipoproteins (VLDL), particles called 'chylomicron remnants' and low-density lipoproteins (LDL)] [4]. The very first CETP inhibitor, torcetrapib, was discontinued due to an increase in cardiovascular events attributed to off-target adverse effects [5]. More recently, two other CETP inhibitors, dalcetrapib and evacetrapib, failed to reduce cardiovascular morbidity and mortality despite not having the

Abbreviations: ABCA1, ATP-binding cassette subfamily A member 1; ABCG1, ATP-binding cassette subfamily G member 1; AMPK, AMP-activated protein kinase; CETP, cholesteryl ester transfer protein; CI, confidence interval; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homoeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio.

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off-target side-effects of torcetrapib [6,7]. Finally, another new CETP inhibitor, anacetrapib, reduced cardiovascular events in patients with atherosclerotic vascular disease with no significant increase in adverse events [8].

CETP inhibitors significantly increase serum HDL cholesterol (HDL-C) levels while reducing LDL-C and apolipoprotein B (apoB) levels. HDL has potential antidiabetic properties, with evidence *in vitro* that it increases glucose uptake by skeletal muscle, and stimulates synthesis and secretion of insulin from pancreatic β cells [9,10]. In fact, it has been shown that β-cell function and insulin secretion can be improved by depleting cholesterol from β cells [11]. As HDL is the predominant acceptor of cell cholesterol, it could be important for maintaining normal β-cell function and insulin secretion. Furthermore, the increase in HDL-C that accompanies genetic CETP deficiency is associated with a decrease in levels of plasma glucose [12]. Nevertheless, other than the impact of CETP drugs on cardiovascular events, their potential beneficial effects on glucose homoeostasis have not been sufficiently studied.

Therefore, the objectives of the present meta-analysis were: (1) to evaluate the effect of CETP inhibitors on diabetes incidence; and (2) to assess the association between CETP inhibitor-induced changes in HDL-C and LDL-C levels and incidence of diabetes.

Materials and methods

Data extraction and quality assessment

Our meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews [13]. A literature search was performed that identified clinical trials of CETP inhibitor therapy either alone or combined with other lipid-lowering drugs, and published between January 1980 and October 2017 in English. Two independent reviewers searched the electronic PubMed/MEDLINE, Embase and Cochrane Controlled Trials databases using the following terms: 'cholesteryl ester transfer protein'; 'CETP'; 'torcetrapib'; 'anacetrapib'; 'dalcetrapib'; and 'evacetrapib'. Eligible studies were randomized controlled trials (RCTs) reporting data from new diabetes cases with a minimum follow-up of 6 months. The following variables were also collected from the retrieved articles: description of treatment and control arms; baseline and on-treatment plasma levels of HDL-C; differences in on-treatment lipid levels between study arms; and incidence of newly diagnosed cases of diabetes.

The Jadad scale was used to assess the quality of the trial designs. Studies were scored (ranging from 0 to 5 points) according to the presence of three key methodological features: randomization; blinding; and withdrawal/dropout rates. Studies with a Jadad score >2 points were considered high quality, while those scoring ≤2 points were deemed poor quality.

Meta-analysis and meta-regression analyses

The summary effect of CETP inhibitors on the endpoint of new cases of diabetes was estimated. Exploratory meta-regression analyses were performed to examine the potential associations between differences in HDL-C levels between trial arms and the effect sizes of CETP inhibitors on new diabetes cases. However, no multivariate meta-regression model was constructed due to the small number of RCTs included.

Statistical analysis

Measures of effect size were expressed as odds ratios (ORs), and the I^2 statistic was calculated to quantify between-trial heterogeneity and inconsistency. Because studies did not differ in their lipid-modifying regimens and effect sizes, a fixed-effects model was chosen. However, to assess the relationship between differences in on-treatment lipid levels and variations in natural log-transformed ORs of new cases of diabetes, a fixed-effects meta-regression model was performed. To compare mean effects between subgroups, a Z test was used. Statistical analyses were performed using Comprehensive Meta-Analysis Program Version 3 software. The level of statistical significance was set at a two-tailed alpha of 0.05.

Analysis of publication bias

A funnel plot using the standard error (SE) for log OR was created, and Begg and Mazumdar rank correlation and Egger's regression of intercept tests were also performed.

Results

Four eligible trials of CETP inhibitors, involving a total of 73,479 patients, were identified and considered eligible for analysis. A total of 36,734 subjects were allocated to receive CETP inhibitors while 36,745 subjects were allocated to the respective control arms. A flow diagram of the study screening process is presented in Fig. 1. All studies were RCTs of excellent quality (Jadad scores ≥3 points for each eligible trial). Most of the studies included patients with stable vascular disease, although one included patients with acute coronary syndrome. Median follow-up duration ranged from 18 to 49 (mean: 31.6 ± 13) months. Descriptions of the trials selected for our analysis are summarized in Table 1.

The present meta-analysis reveals that CETP inhibitor therapy is associated with a significant reduction in new cases of diabetes [OR: 0.88, 95% confidence interval (CI): 0.81–0.96; $P = 0.005$, I^2: 0%; Fig. 2].

Table 2 presents the differences in on-treatment HDL-C and LDL-C levels between study arms included in the meta-regression analysis. Assessment of the relationship between on-treatment HDL-C and the effects of CETP inhibitors found a statistically non-significant trend, most probably due to the small number of RCTs included in the analysis ($Z = -1.13$, $P = 0.26$; Fig. 3).

The funnel plot with the SE for log OR of new cases of diabetes suggests no publication bias (Fig. 4). In the same way, Begg and Mazumdar's test for rank correlation gave a P value of 0.31, while Egger's test for a regression intercept resulted in $P = 0.48$, thus again indicating no possible publication bias.

Discussion

This was the first-ever meta-analysis to assess the risk of new cases of diabetes with CETP inhibitor treatment. In fact, our main result was that this class of drugs decreases the incidence of diabetes.

In recent years, studies have suggested that the use of some lipid-lowering drugs might be associated with an increase in the number of new cases of diabetes. In a meta-analysis of 13 studies of statins including >90,000 individuals, the risk of developing diabetes was increased by 9% in the statin groups compared with the placebo groups [2]. A subsequent meta-analysis showed that intensive statin therapy compared with moderate therapy was associated with an increased risk of T2D [14]. The mechanism by which statins can increase the incidence of diabetes could be mediated by inhibition of β-cell glucose transporters, inhibition of calcium channel-dependent insulin secretion and β-cell apoptosis [15,16]. Similarly, in the Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE),

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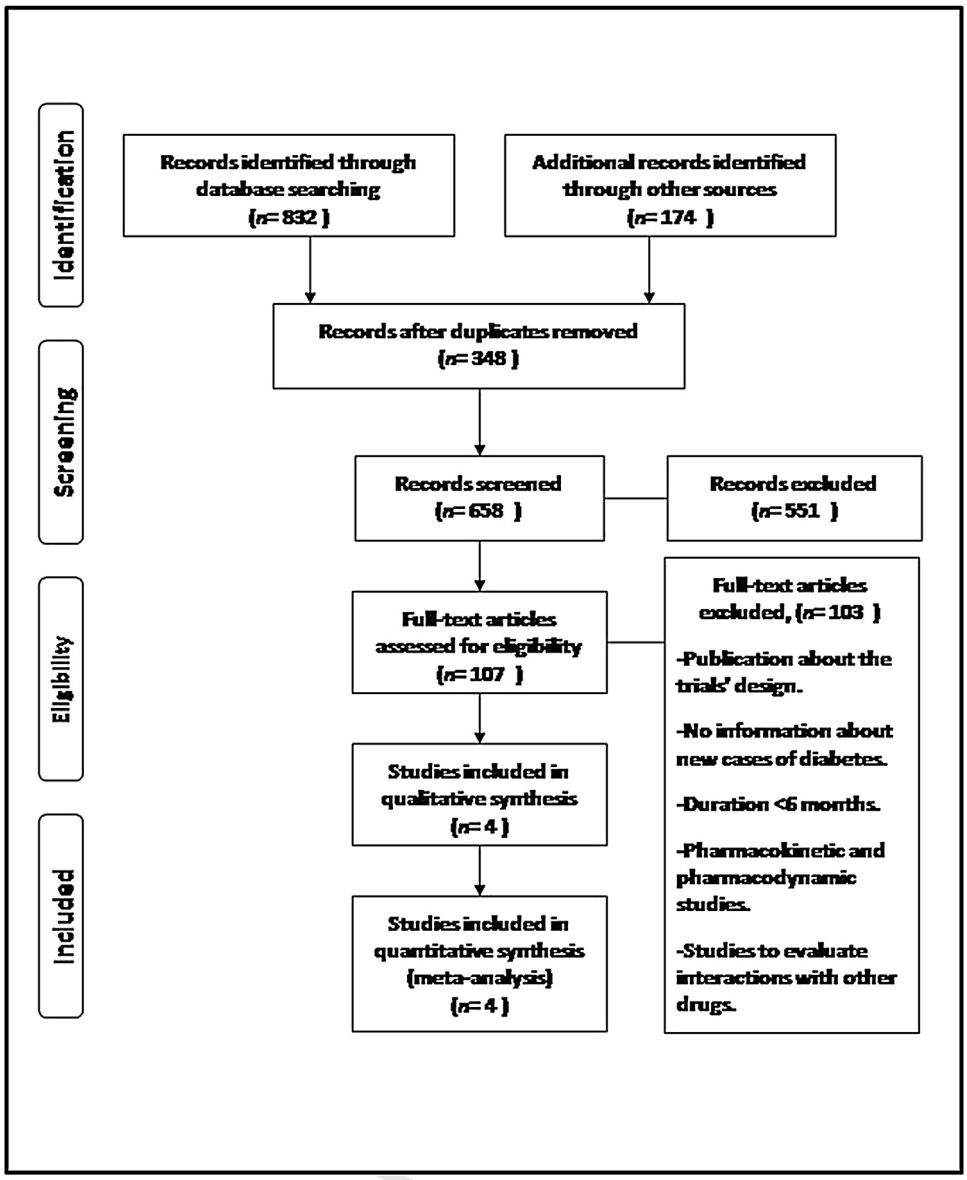

Fig. 1. Flow diagram of the screening process for eligible studies.

Table 1
Characteristics of the selected randomized controlled trials (RCTs) for analysis.

RCT	Total sample (*n*)	Treatment arm	Control arm	Population description	Median follow-up (months)
Illuminate	15,067	Torcetrapib	Placebo	Diabetes or history of cardiovascular disease for 30 days to 5 years prior to screening	18.1
Dal-outcomes	15,871	Dalcetrapib	Placebo	Acute coronary syndrome	31.0
Accelerate	12,092	Evacetrapib	Placebo	High cardiovascular risk (acute coronary syndrome within the past 30–365 days, cerebrovascular atherosclerotic disease, peripheral vascular arterial disease, diabetes with coronary artery disease)	28.0
HPS3/TIMI 55–REVEAL	30,449	Anacetrapib	Placebo	History of myocardial infarction, cerebrovascular atherosclerotic disease, peripheral artery disease, diabetes with symptomatic coronary heart disease	49.2

analysis of the 17,374 participants free of diabetes at the time of randomization showed that the niacin-laropiprant-treated group had a 32% higher risk of diabetes compared with the placebo group [17]. Indeed, niacin-laropiprant therapy had a significant negative impact on insulin resistance through chronic elevation of circulating fatty acids and increased postprandial glucose, thereby potentially leading to new cases of diabetes [18].

In addition, studies investigating the relationships between genetic variants of the *CETP* gene and risk of diabetes have shown: (1) a reduction in plasma glucose levels or no effect on diabetes risk

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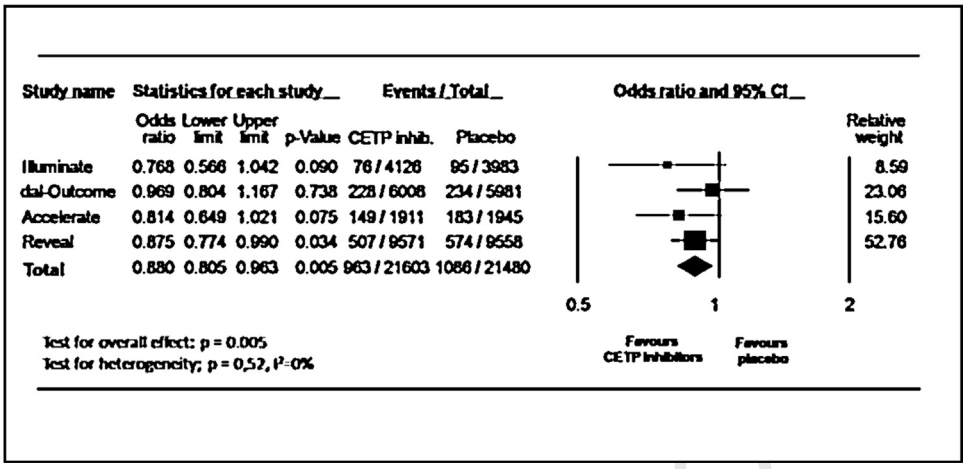

Fig. 2. Effects of cholesteryl ester transfer protein (CETP) inhibitors on diabetes incidence: fixed effects, odds ratios, 95% confidence intervals (CI) and I^2 statistics.

Table 2
Differences between baseline and on-treatment high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels between study arms included in meta-regression analyses.

Randomized clinical trials	Baseline HDL-C (mg/dL)	On-treatment HDL-C (mg/dL)	Difference (mg/dL)	On-treatment HDL-C differences between study arms (mg/dL)	Baseline LDL-C (mg/dL)	On-treatment LDL-C (mg/dL)	Difference (mg/dL)	On-treatment LDL-C differences between study arms (mg/dL)
Illuminate, placebo	48.5	49.0	0.5	28.5	79.9	80.5	0.6	21.2
Illuminate, torcetrapib	48.6	77.5	28.9		79.7	59.3	20.4	
Dal-outcomes, placebo	42.2	43.9	1.7	11.8	75.8	78.8	3.0	21.3
Dal-outcomes, dalcetrapib	42.5	55.7	13.2		76.4	100.1	23.7	
Accelerate, placebo	45.3	45.6	0.3	58.5	81.6	86.5	4.9	30.6
Accelerate, evacetrapib	45.3	104.6	59.3		81.1	55.9	25.2	
HPS3/TIMI 55–REVEAL, placebo	40.0	42.0	2.0	43.0	61.0	64.0	3.0	26.0
HPS3/TIMI 55–REVEAL, anacetrapib	40.0	85.0	45.0		61.0	38.0	23.0	

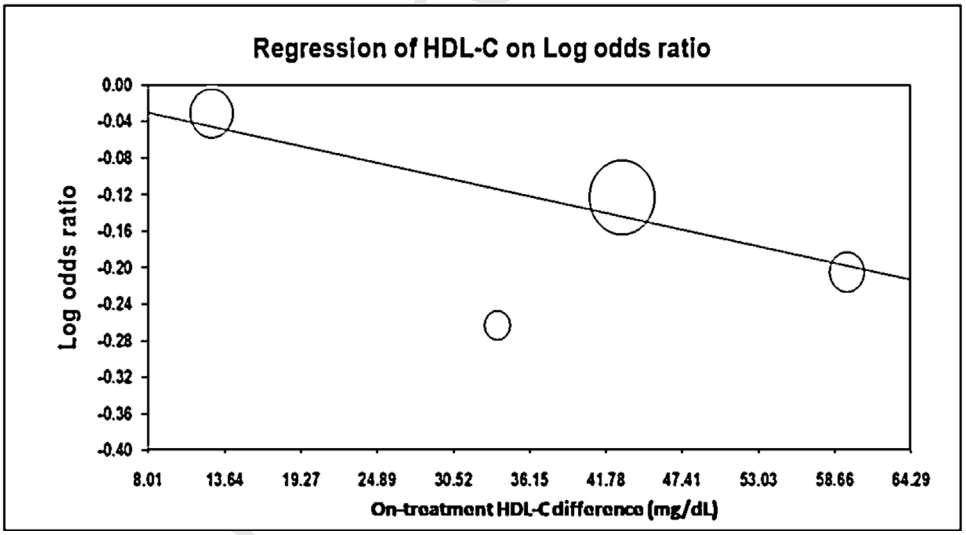

Fig. 3. Fixed-effects meta-regression analyses: association between differences in on-treatment high-density lipoprotein cholesterol (HDL-C) levels between study arms and new cases of diabetes.

with *CEPT* gene variations resulting in decreased CETP activity and increased HDL-C levels [12,19]; and (2) an increased risk of diabetes with *CETP* polymorphisms associated with increased CETP activity and decreased HDL-C levels [20]. This highlighting of the antidiabetogenic effects of CETP inhibitors has led to several hypotheses to explain the underlying mechanisms. One recent study suggested that cholesterol accumulation compromises β-cell function and reduces insulin secretion, and that this effect can be alleviated by depleting cells of cholesterol [11]. In our present study, a clear trend of a negative association was observed between the increase in HDL-C levels and risk of new-onset diabetes while on treatment. However, as this was most likely due

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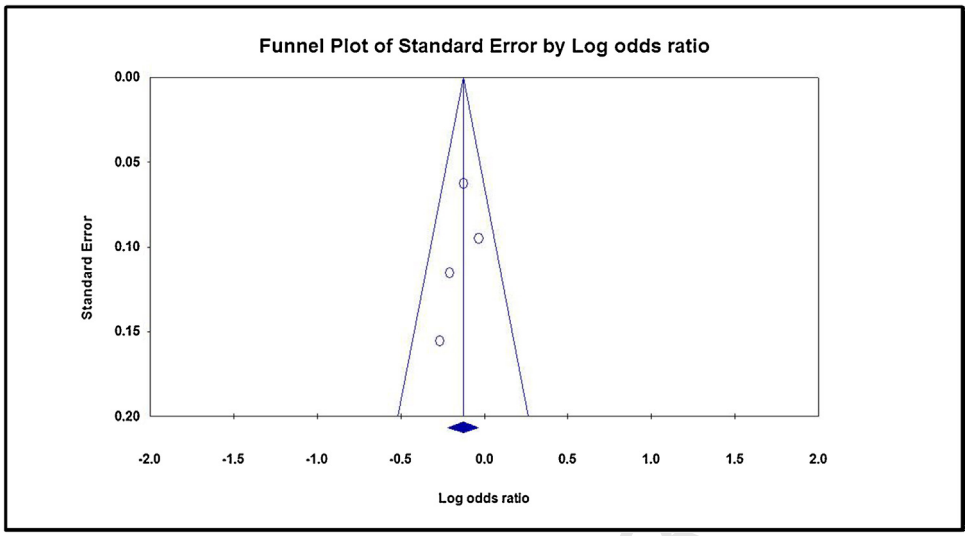

Fig. 4. Funnel plot using standard error for log odds ratio of new diabetes cases.

to the small number of RCTs included in the analysis, this association was not statistically significant. In contrast, two Mendelian randomization studies showed a significant association between HDL-C increases and a lower risk of diabetes [21,22].

Several mechanisms have been proposed to explain the relationship between HDL-C levels and glucose metabolism [23,24]. Pancreatic lipid accumulation and lipotoxicity have been well documented to inhibit insulin production and secretion [11]. It has also been previously reported that impaired glucose-stimulated insulin secretion induced by oxidized LDL can be countered by native HDL treatment [9]. Fryirs et al. [25] showed that HDL and its main apolipoproteins apoA-I and apoA-II increased insulin secretory capacity of pancreatic β cells. Such effects on β-cell function could be mediated by the bioactive lipid sphingosine-1-phosphate, which is primarily carried within HDL particles and known to independently promote glucose-stimulated insulin secretion [26]. The HDL transporters ATP-binding cassette subfamily A member 1 (ABCA1) and ATP-binding cassette subfamily G member 1 (ABCG1) have both been implicated in HDL-mediated effects on insulin secretion [27,28]. HDL could also influence insulin secretion *via* mechanisms other than cholesterol depletion, including its action on insulin transcription [27].

Likewise, the ability of HDL to inhibit β-cell apoptosis could be another important mechanism by which HDL may improve β-cell dysfunction [29,30]. CETP inhibitors could also have an effect on insulin sensitivity. In a model of insulin-resistant and dyslipidaemic hamsters, torcetrapib treatment compared with vehicle significantly reduced fasting plasma triglycerides, glycerol and free fatty acids by 60%, according to the homoeostasis model assessment of insulin resistance (HOMA-IR) index. Hamsters treated with torcetrapib showed higher glucose uptakes in soleus muscle linked to stimulation of AMP-activated protein kinase (AMPK) phosphorylation. Indeed, AMPK is known to regulate glucose uptake in tissues such as skeletal muscle, liver and heart [31]. Also, the higher apoA-I content of HDL observed in mice treated with torcetrapib compared with vehicle could be contributing to the improvement of insulin sensitivity through its effects on AMPK and acetyl-coenzyme A carboxylase (ACC) phosphorylation [32].

The beneficial effects on glucose homoeostasis were also observed in patients with diabetes. In the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE), diabetes patients who received the combination of atorvastatin plus torcetrapib had lower levels of both plasma glucose and glycated haemoglobin than those receiving atorvastatin alone, indicating that treatment with torcetrapib compared with placebo resulted in an improvement in diabetes control [33]. In the RCT by Cannon et al. [34], among patients with diabetes, there was a trend towards lower glycated haemoglobin levels with anacetrapib at 24 weeks and at 76 weeks compared with placebo. Similarly, Drew et al. [9] reported that infusing supraphysiological doses of discoidal reconstituted HDL into patients with T2D increased plasma insulin levels and reduced plasma glucose levels.

CETP inhibitors also reduced LDL-C levels (by up to 40%), whereas the increased risk of diabetes associated with the LDL-C decrease with statin therapy is now well established [2]. However, the reduction of diabetes risk with CETP inhibitors despite the LDL-C decrease could be due to the greater proportional increase in HDL-C and resultant beneficial effects on glucose metabolism. Most probably, though, the discrepancy between the similar LDL-C reduction effects with CETP inhibitors and statins, and their opposite effects on diabetes risk, may be explained by their different mechanisms of action. Indeed, two Mendelian randomization studies demonstrated the associations between variants of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR; the target of statins) or proprotein convertase subtilisin/kexin type 9 (PCSK9), decreased LDL-C and increased risk of diabetes [35,36]. In contrast, the risk of diabetes is decreased among patients with familial hypercholesterolaemia [*via* LDL receptor (LDLR) or apoB mutations] compared with their unaffected relatives [37].

These data suggest that the diabetogenic effect of statins is directly linked to activation of the LDLR pathway. Several animal studies *in vitro* and *in vivo* have suggested that the upregulation of LDLR by statins in pancreatic β cells can induce lipotoxicity mediated by the uptake of LDL-C, leading to a defect of insulin secretion [11,38,39]. Millar et al. [40] showed, in a human lipoprotein kinetic study, that LDL-C reduction with anacetrapib might be explained by increased LDL clearance due to a change in LDL lipid composition (increased triglyceride-to-cholesterol ratio due to CETP inhibition) and not upregulation of LDLR expression.

Recently, the Randomized Evaluation of the Effects of Anacetrapib Through Lipid Modification (REVEAL) study showed that CETP inhibition is associated with a significant reduction in cardiovascular events [8]. Our present findings suggest that the additional effect linked to a reduction in the incidence of diabetes with CETP treatment might also play a role in the reduction of major coronary events compared with placebo. However, this

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potential effect is thought to be minor, given the dramatic changes in lipid profiles and the less-than-expected effect of the drug on cardiovascular outcomes.

Moreover, the beneficial effect of CETP inhibitors on glucose homoeostasis could most probably counteract the pro-diabetogenic effects of other lipid-lowering drugs, such as statins and niacin therapy. Thus, the CETP class of drugs could emerge as a new therapeutic option for high-risk patients with dyslipidaemia and glucose metabolism anomalies, although further studies are now needed to clarify the possibilities.

Conclusion

In our present meta-analysis, CETP inhibitors reduced the incidence of diabetes. This effect on glucose metabolism might, at least partly, be due to the increase in HDL-C in the treated subjects.

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Disclosure of interest

The authors declare that they have no competing interest.

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