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Cholesteryl ester transfer protein therapy and diabetes risk.A Meta-analysis.

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Abbreviations:

ABCA1: ATP-binding cassette, sub-family A, member 1.

ABCG1: ATP-binding cassette, sub-family G, member 1.

CETP: Cholesteryl ester transfer protein.

CI: Confidence interval.

HDL: High-density lipoprotein

HDL-C:High-density lipoprotein cholesterol

OR: Odds Ratio

ABSTRACT

Background: Cholesteryl ester transfer protein (CETP) inhibitors are a drug class that target the enzyme CETP, increasing significantly serum high-density lipoprotein-cholesterol level (HDL-C). Since HDL-C has potential antidiabetic properties and this beneficial effect of these drugs on glucose homeostasis has 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 inhibitors-induced changes in HDL-C levels and the incidence of diabetes.

Methods: We performed a meta-analysis including randomized, controlled clinical trials of CETP inhibitors therapy, alone or combined with other lipid-lowering drugs, reporting new cases of diabetes data with a minimum of 6 months of follow-up, searching in PubMed/Medline, EMBASE and Cochrane Clinical Trials databases. The fixed-effects model and meta-regression were performed.

Results: Four eligible trials of CETP inhibitors including 73479 patients were taken into account for the analysis and 960 new cases of diabetes in CTEP inhibitors group vs. 1086 in placebo group were diagnosed. CETP inhibitors therapy was associated with a significant 12% reduction in the incidence of diabetes (OR: 0.88; 95%CI: 0.81 to 0.96; p = 0.005). The assessment of the relationship between on-treatment HDL-C and the effect of CETP inhibitors showed a statistically not significant trend.

Conclusions: CETP inhibitors reduced the incidence of diabetes. This improvement in glucose metabolism may have been related, at least in part, to the increase in HDL-C concentration.

Keywords: Cholesteryl ester transfer protein inhibitors, high-density lipoprotein cholesterol, new onset-diabetes, meta-analysis.

INTRODUCTION

Cardiovascular diseasesare responsible for approximately one-third of global deaths both in 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 increase the risk of developing type 2 diabetes [2]. Cholesteryl ester transfer protein (CETP) inhibitors are adrug class targeting the enzyme CETP [3]. CETP is a glycoprotein synthesized mainly in the liver, which plays a prominent role in the bidirectional transfer of cholesterol esters and triglycerides between lipoproteins. The cholesterol esters are thus transferred from the cardioprotective high-density lipoprotein (HDL) particles to the potentially atherogenic non-HDL particles (very low-density lipoproteins, chylomicrons remnant particles and low-density lipoproteins) [4]. The first CETP inhibitor, torcetrapib, was discontinued due to an increase in cardiovascular events that was attributed to off-target adverse effects [5]. The two other CETP inhibitors, dalcetrapib and evacetrapib, were not able toreduce cardiovascular morbidity and mortality despite not having the off-target side effects of torcetrapib [6-7]. Another new CETP inhibitor, anacetrapib, reduced cardiovascular events in patients with atherosclerotic vascular disease without any significant increase of adverse events [8].

CETP inhibitors significantly increase serum high-density lipoprotein cholesterol (HDL-C) levels. HDL have potential antidiabetic properties, with evidence in vitro

that they increase the uptake of glucose by skeletal muscle and stimulate the synthesis and secretion of insulin from pancreatic ß-cells [9-10]. It has been shown that ß-cell function and insulin secretion can be improved by depleting cholesterol from the ß-cells [11]. HDL being the predominant acceptors of cell cholesterol, they might be important for maintaining normal ß-cell function and insulin secretion. Furthermore, the increase of HDL-C accompanying genetic CETP deficiency is associated with decreased level of plasma glucose [12].

Beyond the impact of these drugs on cardiovascular events, the potential beneficial effect on glucose homeostasis has not been sufficiently studied.

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

MATERIAL AND METHODS

Data extraction and quality assessment: the meta-analysis was performed according to The PRISMA statement for reporting systematic reviews [13]. We performed a literature search that identified clinical trials of CETP inhibitor therapy, alone or combined with other lipid-lowering drugs, published between January 1980 and October 2017 in English. Two independent reviewers searched in the electronic databases PubMed/Medline, EMBASE and Cochrane Clinical Trials using the following terms: "cholesteryl ester transfer protein", "CETP", "torcetrapib", "anacetrapib", "dalcetrapib" and "evacetrapib". Eligible studies were randomized, controlled studies reporting data of new diabetes cases with a minimum of 6

months of follow-up. The following variables were collected from the published articles: description of the treatment and control arms, baseline and on-treatment plasma levels of HDL-C, on-treatment lipid level differences between study arms, and the occurrence of new cases of diabetes.

Jadad´s scale was used to assess the quality of the trials design. Studies were scored according to the presence of three key methodological features: randomization, blinding and withdrawals/dropouts, ranging from 0 to 5 points. Studies with a Jadad´s score more than 2 points were considered of high quality, while those that scored 2 point or less were judged as 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 examining potential associations between differences in HDL-C levels between trial arms and the effect size of CETP inhibitors on new cases of diabetes. We did not perform a multivariate meta-regression model, due to the small number of studies included.

Statistical Analysis: Measures of effect size were expressed as odds ratios (ORs). The I2 statistic was calculated to quantify between-trial heterogeneity and inconsistency. Because studies did not differed in lipid-modifying regimens and effect sizes, a fixed-effects model was chosen. To assess the relationship between on-treatment lipid level differences and the variation in the natural log-transformed OR of new cases of diabetes, a fixed-effects model meta-regression was performed. To compare the mean effect between subgroups, we used a Z-test. Statistical analyses were performed using the Comprehensive Meta-Analysis

Program Version 3. The statistical significance level was set at the 2-tailed alpha of 0.05.

Analysis of publication bias: Funnel plot of standard error by Log odds ratio was displayed and Begg and Mazumdar rank correlation and Egger's regression intercept tests were done.

RESULTS

Four eligible trials of CETP inhibitors, including 73479 patients, were identified and considered eligible for the analyses. There was a total of 36734 subjects allocated to receive CETP inhibitors and 36745 subjects allocated to the respective control arms. A flow diagram of the study's screening process is shown in **Fig. 1**.

All studies were randomized and showed excellent quality (≥ 3 points of Jadad´s score for each eligible trial).

Most studies included patients with stable vascular disease, but one study included patients with acute coronary syndrome. Follow-up ranged from 18 to 49 months. Description of trials selected for this analysis is summarized in **Table 1**.

This meta-analysis showed that CETP inhibitors therapy was associated with a significant reduction in new cases of diabetes (OR: 0.88; 95%CI: 0.81 to 0.96; p= 0.005; I^2=0%, **Fig. 2**).

Table 2 shows on-treatment HDL-C levels differences between studies arms included in meta-regression analysis. The assessment of the relationship between on-treatment HDL-C and the effect of CETP inhibitor showed a statistically not significant trend probably due to the small number of clinical trials included in the analysis **(Fig. 3).**

The funnel plot of standard error by Log OR of new cases of diabetes does not suggest publication bias **(Fig. 4)**. In the same way, Begg and Mazumdar´s test for rank correlation gave a p-value of 0.31 and Egger´s test for a regression intercept a p-value of 0.48, not indicating possible publication bias.

DISCUSSION

We performed the first meta-analysis that assessed the risk of new cases of diabetes with CETP inhibitors. Our main result showed that this class of drugs decreased the incidence of diabetes.

In recent years, studies have suggested that the use of some lipid-lowering drugs might be associated with the increase of new cases of diabetes. In a meta-analysis of 13 studies on statins including over 90000 individuals, the risk of developing diabetes was increased by 9% in the statins group compared to the placebo group [2]. A subsequent meta-analysis showed that intensive statin therapy was associated with increased risk of type 2 diabetes compared with moderate therapy [14]. The mechanism by which statins may increase the incidence of diabetes could be mediated by the inhibition of β-cell glucose transporters, inhibition of calcium channel-dependent insulin secretion and the β-cell apoptosis [15-16]. Similarly, in the HPS2-THRIVE trial, the analysis of the 17374 participants who did not have diabetes at the time of randomization, showed that the niacin-laropiprant treated group had a 32% increased risk of diabetes compared to the placebo group [17]. Indeed, niacin-laropiprant therapy had a significant negative impact on insulin

resistance by chronic elevation of circulating fatty acids and increased postprandial glucose, leading potentially to new cases of diabetes [18].

The highlighting of the anti-diabetogenic effect of CETP inhibitors, has led to several hypotheses to explain the mechanisms. A recent study suggests that cholesterol accumulation compromises ß-cell function and reduces insulin secretion and that this effect can be alleviated by depleting the cells of cholesterol [11]. In our study, we observed a clear trend in the negative association between the increase of the HDL-C levels and the risk of new-onset diabetes on-treatment. However, probably due to the small number of trials incorporated into the analysis, this association was not statistically significant.

Several mechanisms have been proposed to explain the relationship between HDL-C level and glucose metabolism [19-20]. Pancreatic lipid accumulation and lipotoxicity have been well documented to inhibit insulin production and secretion [11]. It has been previously reported that impairment of glucose stimulated insulin secretion induced by oxidized low-density lipoproteins can be countered by native HDL treatment [9]. Fryirs et al. showed that HDLs and their main apolipoproteins, apolipoprotein A-I and apolipoprotein A-II, increased the insulin secretory capacity of pancreatic ß-cells [21]. These effects on ß-cell function might be mediated by the bioactive lipid sphingosine-1-phosphate, which is primarily carried within HDL particles and is known to independently promote glucose stimulated insulin secretion [22]. The HDL transporters ATP-binding cassette, sub-family A, member 1 (ABCA1) and ATP-binding cassette, sub-family G, member 1 (ABCG1) have both been implicated in HDL-mediated effects on insulin secretion [23-24]. HDL may also influence insulin secretion via mechanisms other than cholesterol depletion,

including its action on insulin transcription [23]. Finally, the ability of HDL to inhibit ß-cell apoptosis could be another important mechanism by which HDL may improve beta cell dysfunction [26-27].

The beneficial effect on glucose homeostasis was also observed in patients with diabetes. In the ILLUMINATE trial, diabetic patients who received the combination of atorvastatin plus torcetrapib had lower levels of both plasma glucose and glycated hemoglobin levels than those receiving only atorvastatin, indicating that treatment with torcetrapib, compared with placebo, resulted in an improvement in diabetes control [28]. In DEFINE trial, among patients with diabetes, there was a trend toward a lower glycated hemoglobin level with anacetrapib at 24 weeks and at 76 weeks in comparison to placebo [29]. Similarly, Drew et al. reported that infusing supraphysiological doses of discoidal reconstituted HDLs into humans with type 2 diabetes increased plasma insulin levels and reduced plasma glucose levels [9].

Recently, the REVEAL study showed that CETP inhibition was associated with a significant reduction in cardiovascular events [8]. Our findings suggest that the additional effect linked to the reduction in the incidence of diabetes. In the on-treatment group could play a role in the decrease of major coronary events compared with the placebo group. Moreover, the beneficial effect of CETP inhibitors on glucose homeostasis, could probably counteract the pro-diabetogenic effect of other lipid-lowering drugs such as statin or niacin therapy. Thus, this class of drugs could emerge as a new therapeutic option in high-risk patients with dyslipidemia and glucose metabolism anomalies, but further studies are needed to clarify this point.

CONCLUSION

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

Conflicts of interest: none

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REFERENCES

[1] Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics-2016 update: A report from the American Heart Association. Circulation 2016;133:e38–360.

[2] Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomized statin trials. Lancet. 2010;375:735-42.

[3] Filippatos TD, Klouras E, Barkas F, Elisaf M. Cholesteryl ester transfer protein inhibitors: challenges and perspectives. Expert Rev Cardiovasc Ther. 2016;14:953-62.

[4] Barter PJ, Rye KA. Cholesteryl ester transfer protein inhibition as a strategy to reduce cardiovascular risk. J Lipid Res. 2012;53:1755-66.

[5] 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.

[6] 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.

[7] 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.

[8] Bowman L, Hopewell JC, Chen F, Wallendszus K, Stevens W, Collins R, et al. Effects of anacetrapib in patients with atherosclerotic vascular disease. N Engl J Med. 2017;377:1217-27.

[9] Drew BG, Duffy SJ, Formosa MF, Natoli AK, Henstridge DC, Penfold SA, et al. High-density lipoprotein modulates glucose metabolism in patients with type 2 diabetes mellitus. Circulation. 2009;119:2103-11.

[10] Stenkula KG, Lindahl M, Petrlova J, Dalla-Riva J, Goransson O, Cushman SW, et al. Single injections of apoA-I acutely improve in vivo glucose tolerance in insulin-resistant mice. Diabetologia. 2014;57:797-800.

[11] Hao M, Head WS, Gunawardana SC, Hasty AH, Piston DW. Direct effect of cholesterol on insulin secretion: a novel mechanism for pancreatic beta-cell dysfunction. Diabetes. 2007;56:2328-38.

[12] Zhong S, Sharp DS, Grove JS, Bruce C, Yano K, Curb JD, et al. Increased coronary heart disease in Japanese-American men with mutation in the cholesteryl ester transfer protein gene despite increased HDL levels. J Clin Invest. 1996;97:2917-23.

[13] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of

studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.

[14] Preiss D, Seshasai SR, Welsh P, Murphy SA, Ho JE, Waters DD, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA. 2011;305:2556-64.

[15] Sattar N, Taskinen MR. Statins are diabetogenic--myth or reality? Atheroscler Suppl. 2012;13:1-10.

[16] Sampson UK, Linton MF, Fazio S. Are statins diabetogenic? Curr Opin Cardiol. 2011;26:342-7.

[17] Landray MJ, Haynes R, Hopewell JC, Parish S, Aung T, Tomson J, et al. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med. 2014;371:203-12.

[18] Aye MM, Kilpatrick ES, Afolabi P, Wootton SA, Rigby AS, Coady AM, et al. Postprandial effects of long-term niacin/laropiprant use on glucose and lipid metabolism and on cardiovascular risk in patients with polycystic ovary syndrome. Diabetes Obes Metab. 2014;16:545-52.

[19] Siebel AL, Heywood SE, Kingwell BA. HDL and glucose metabolism: current evidence and therapeutic potential. Front Pharmacol. 2015;6:258.

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

[21] Fryirs MA, Barter PJ, Appavoo M, Tuch BE, Tabet F, Heather AK, et al. Effects of high-density lipoproteins on pancreatic beta-cell insulin secretion. Arterioscler Thromb Vasc Biol. 2010;30:1642-48.

[22] Cantrell Stanford J, Morris AJ, Sunkara M, Popa GJ, Larson KL, Ozcan S. Sphingosine 1-phosphate (S1P) regulates glucose-stimulatedinsulin secretion in pancreatic beta cells. J Biol Chem. 2012;287:13457-64.

[23] Kruit JK, Wijesekara N, Westwell-Roper C, Vanmierlo T, De Haan W, Bhattacharjee A, et al. Loss of both ABCA1 and ABCG1 results inincreased disturbances in islet sterol homeostasis, inflammation, and impaired beta-cell function. Diabetes Metab Res Rev. 2012;61:659-64.

[24] Sturek JM, Castle JD, Trace AP, Page LC, Castle AM, Evans-Molina C, et al. An intracellular role for ABCG1-mediated cholesterol transport in the regulated secretory pathway of mouse pancreatic beta cells. J Clin Invest. 2010;120:2575-89.

[25] Cochran BJ, Bisoendial RJ, Hou L, Glaros EN, Rossy J,Thomas SR, et al. Apolipoprotein A-I increases insulin secretion and production from pancreatic beta-cells via a G-protein-cAMP-PKA-FoxO1-dependent mechanism. Arterioscler Thromb Vasc Biol. 2014;34:2261-67.

[26] Petremand J, Bulat N, Butty AC, Poussin C, Rutti S, Au K, et al. Involvement of 4E-BP1 in the protection induced by HDLs on pancreatic beta-cells. Mol Endocrinol. 2009;23:1572-86.

[27] Rutti S, Ehses JA, Sibler RA, Prazak R, Rohrer L, Georgopoulos S, et al. Low and high density lipoproteins modulate function, apoptosis, and proliferation of primary human and murine pancreatic beta-cells. Endocrinology. 2009;150:4521-30.

[28] 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.

[29] Cannon CP, Shah S, Dansky HM, Davidson M, Brinton EA, Gotto AM, et al. Safety of anacetrapib in patients with or at high risk for coronary heart disease. N Engl J Med. 2010;363:2406-15.

Table 1. Characteristics of the selected trials.

Study	N	Treatment arm	Control arm	Population	Follow-up
ILLUMINATE[3]	15.067	Torcetrapib	Placebo	Diabetes or history of cardiovascular disease 30 days to 5 years before screening.	18,1 months
dal-OUTCOMES[4]	15.871	Dalcetrapib	Placebo	Acute coronary syndrome.	31,0 months
ACCELERATE[5]	12092	Evacetrapib	Placebo	High cardiovascular risk (acute coronary syndrome within the previous 30 to 365 days, cerebrovascular atherosclerotic disease, peripheral vascular arterial disease, or diabetes mellitus with coronary artery disease).	28,0 months
HPS3/TIMI55–REVEAL[6]	30449	Anacetrapib	Placebo	History of myocardial infarction, cerebrovascular atherosclerotic disease, peripheral-artery disease, or diabetes with symptomatic coronary heart disease.	49,2 months

Table 2. Baseline, on-treatment HDL-C and on-treatment HDL-C levels differences between study arms included in meta-regression-analyses.

Study	Baseline HDL-C (mg/dL)	On-treatment HDL-C (mg/dL)	Difference (mg/dL)	On-treatment HDL-C differences between study arms (mg/dL)
ILLUMINATE, placebo	48.5	49.0	0.5	28.5
ILLUMINATE, torcetrapib	48.6	77.5	28.9	
Dal-OUTCOMES, placebo	42.2	43.9	1.7	11.8
Dal-OUTCOMES, dalcetrapib	42.5	55.7	13.2	
ACCELERATE, placebo	45.3	45.6	0.3	58.5
ACCELERATE, evacetrapib	45.3	104.6	59.3	
HPS3/TIMI55-REVEAL, Placebo	40.0	42.0	2.0	43.0
HPS3/TIMI55-REVEAL, anacetrapib	40.0	85.0	45.0	

Foot of figures:

Figure 1. Flow diagram of the study screening process.

Figure 2. Effect of CETP inhibitorson the incidence of diabetes.Random effects, odds ratio, 95%confidence intervals (CI) and I^2 statistics.

Figure 3. Random-effects meta-regression analyses: association between on-treatment HDL-C levels differences between study arms and new cases of diabetes.

Figure 4. Funnel Plot of standard error by Log odds ratio.