

Cholesteryl Ester Transfer Protein Inhibitors: New Concept of Cardiovascular Event Prevention?

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ABSTRACT

Cholesteryl ester transfer protein (CETP) ensures transfers of cholesteryl esters and triglycerides between circulating high-density (HDL) and low-density (LDL) lipoproteins. Previous clinical studies have shown that CETP inhibitors had positive impact on the lipid profile, biomarkers of inflammation and oxidative stress, fasting glucose, but it was associated with several adverse effects, such as

increase in blood pressure, electrolyte abnormalities, and serum levels of aldosterone. The HDL-target therapy had been discussed as promising among patients at higher risk of cardiovascular (CV) events and disease, because CETP inhibitor monotherapy and in combination with statins had exhibited a superiority in lipid profile improvement when compared with placebo or statins. However, the results of the clinical studies reading CV benefits of CETP inhibitors (torcetrapib, dalcetrapib, anacetrapib, evacetrapib) appeared to be controversial. The aim of the editorial is to summarize the clinical benefits of the CETP inhibitors in patients with CV disease and events prevention. The role of the CETP gene polymorphisms and other genetic variants are discussed to explain the results of previous clinical trials dedicated HDL-target therapy with the CETP inhibitors.

Key words: Cholesteryl ester transfer protein inhibitors; High-density lipoprotein target therapy; Cardiovascular outcomes; Adverse effects; single nucleotide genetic polymorphism

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INTRODUCTION

Cholesteryl ester transfer protein (CETP) was previously found a circulating transporter of the neutral lipids, such as triglycerides and cholesteryl esters, between high-density lipoprotein (HDL) and apolipoprotein B100-containing lipoproteins^[1]. The main biological function of CETP is to facilitate exchange of cholesteryl esters between HDL and low-density (LDL) / very low-density lipoproteins (VLDL) and transfer triglycerides from LDL/VLDL to HDL through bent-to-linear conformation changes of the CETP molecule^[2]. This turn-over effect was called "tunnel mechanism" and single nucleotide polymorphism (SNPs) in CETP gene (i.e., A373P and R451Q) was found to be essential for effective transformation of the CETP molecule when cholesteryl esters moves through the tunnel^[3,4]. Previous clinical studies have yielded twenty and more SNPs in

CETP gene which were responsible for lower risk of cardiovascular (CV) disease and events including myocardial infarction and ischemic stroke that was associated with higher circulating levels of HDL cholesterol, lower triglycerides and non-HDL cholesterol^[5,6]. Indeed, The Copenhagen City Heart Study has been reported A373P/R451Q SNP in CETP related to decreases in HDL cholesterol and possibly was associated with a paradoxical 36% decrease in the risk of ischemic heart disease in women^[5]. Additionally, it has been suggested that a reduction of LDL cholesterol by 2-3 mmol/L among individuals with dyslipidemia would reduce CV risk by about 40-50%^[7]. Thus, it has become obvious that the CETP activity can relate to a lower risk of CV disease and that pharmacological inhibition of CETP may be beneficial because elevated HDL cholesterol may potentially prevent a manifestation CV disease via restoring lipid profile^[8]. Although CETP inhibitors were not associated with the incidence of major CV events (MACE), they remain to be promising drugs to improve CV outcomes in vulnerable populations due to established positive impact on the lipid profile and glucose tolerance. The aim of the editorial is to summarize the clinical benefits of the CETP inhibitors in CV disease and events prevention.

CETP INHIBITORS AND SURROGATE END POINTS

In early the dal-VESSEL trial dalcetrapib reduced CETP activity and increased HDL-C levels without affecting NO-dependent endothelial function, blood pressure (BP), or markers of inflammation and oxidative stress among patients at risk of coronary artery disease (CAD)^[9]. Additionally, in the dal-PLAQUE trial dalcetrapib did not influence on atherosclerosis progression and atherosclerosis-related events, but hyperaldosteronism and electrolyte disturbances were found as side effects of the drug^[10]. Evacetrapib has yielded positive effects on lipid profile regardless statin use that was related to increased HDL cholesterol levels and decreased LDL cholesterol levels in patients with established dyslipidemia^[11]. In contrast to dalcetrapib, evacetrapib and torcetrapib, anacetrapib in monotherapy in wide range of doses (10, 40, 150, and 300 mg) did not increase in systolic or diastolic BP and was well tolerated, while produced significant reductions in LDL cholesterol and increase in HDL cholesterol levels^[12,13]. Importantly, 2-year extensive treatment with anacetrapib was associated with well toleration and good safety profile similar to placebo^[13,14]. New CETP inhibitor CKD-519 is a clinical candidate being developed for further treatment of dyslipidemia, because it has revealed well toleration and high inhibition of CETP activity^[15,16].

CETP INHIBITORS AND CLINICAL BENEFITS

The Cochrane Library of Clinical Trials consists of data for four placebo-controlled randomized controlled trials (RCTs) that examined the effect of CETP inhibitors (torcetrapib, dalcetrapib, anacetrapib, evacetrapib) on all-cause mortality and major CV events^[17]. The CV effects of the CETP inhibitors are listed in the Table 1. Torcetrapib in the ILLUMINATE study ($n = 15067$) has revealed an increase of 72.1% in HDL cholesterol and a decrease of 24.9% in LDL cholesterol that was associated with an increase in systolic blood pressure by 5.4 mm Hg and risk of CV events (hazard ratio [HR] = 1.25; 95% confidence interval [CI] = 1.09-1.44; $p = 0.001$) and all-cause mortality (HR = 1.58; 95% CI = 1.14-2.19; $p = 0.006$) among patients with known stable coronary artery disease (CAD)^[18].

In the study Dal-OUTCOMES the patients ($n = 15871$) were randomly allocated to receive dalcetrapib (600 mg daily) or matching placebo running 4 to 12 weeks after acute coronary syndrome (unstable angina or myocardial infarction)^[19,20]. Although dalcetrapib have significantly positive impact the lipid profile, the drug did not decline a risk of the cumulative ischemia event rate (HR=1.04; 95% CI=0.93-1.16; $p = 0.52$) and did not have a significant effect on any component of total mortality^[19]. Additionally, investigators found that dalcetrapib declined the number of patients who progressed from euglycemia to pre-diabetes and increased the number who regressed from diabetes mellitus to no diabetes mellitus^[20].

The ACCELERATE study were enrolled 12092 patients with recent acute coronary syndrome or having cerebrovascular atherosclerotic disease, peripheral vascular arterial disease, or diabetes mellitus with established CAD^[21]. Patients were allocated either evacetrapib at a dose of 130 mg or matching placebo for 26 months. The primary composite end point was CV death, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina. The results of the study have shown that evacetrapib was not better than placebo in decrease in a risk of the composite end point (HR=1.01; 95% CI=0.91-1.11; $p = 0.91$). Moreover, among patients with diabetes mellitus having dyslipidemia there was no benefits of treatment with evacetrapib on clinical outcomes despite a favorable increase in HDL cholesterol and decrease in LDL cholesterol and HbA1c levels^[21].

The results of the TIMI55-REVEAL have shown that among patients with atherosclerotic vascular disease anacetrapib treatment influenced a lower incidence of major CV events when compared with placebo (HR=0.91; 95% CI=0.85-0.97; $p = 0.004$)^[23]. Investigators did not find significant differences between groups in the risk of death, cancer, or other serious adverse outcomes. Unfortunately, anacetrapib has not been approved by manufacturer regardless of the positive results of the REVEAL Study due to received evidence for accumulation of the drug in adipose tissue during the treatment period^[24].

The meta-analysis of 11 RCTs ($n = 62,431$), which included 4 RCTs with dalcetrapib ($n = 16,612$), 6 RCTs with anacetrapib ($n = 33,682$), and 1 RCT with evacetrapib ($n = 12,092$), has revealed that dalcetrapib and anacetrapib were better than evacetrapib in raising HDL cholesterol levels (100% and 130% versus 30% respectively when compared with baseline)^[14]. Anacetrapib and evacetrapib have demonstrated ability to significantly decrease in LDL cholesterol by approximately 30%, but dalcetrapib did not reduce the LDL cholesterol level. Despite positive effect on lipid profile, all CETP inhibitors were not strongly associated with the incidence of MACE (relative risk [RR]=0.97; 95% CI=0.91-1.04). However, there was a trend to decrease the risks of non-fatal myocardial infarction (RR=0.93; 95% CI=0.87-1.00) and CV death (RR=0.92; 95% CI=0.83-1.01)^[14]. Thus, dalcetrapib and new CKD-519 remain the CETP inhibitors within this area still in clinical investigation.

CV BENEFITS OF CETP INHIBITORS AND GENETIC POLYMORPHISM OF KEY GENES

There is a hypothesis that the CV effects of CETP inhibitors may be pharmacogenetically determined and that an optimal benefit-risk ratio could be received among patients with specific genotype, because genetic associations had been scaled to 10% reduction in relative risk of CAD. In fact, the AA SNP (rs1967309) in the adenylate cyclase type 9 (ADCY9) gene was found to be predictor of fewer number of CV events, whereas the GG SNP of the ADCY9 gene was associated

with an increased frequency of CV events in the Dal-OUTCOMES trial. The heterozygous AG genotype patients treated with dalcetrapib did not yield a significant difference in CV risk when compared with placebo^[20]. These facts required a reconsideration of the role of CETP in patients at higher CV risk and having established CV disease. The Dal-GenE study has been designed as pharmacogenetic trial to confirm whether an effect of dalcetrapib on the composite of CV death, myocardial infarction or stroke in the dal-Outcomes study could relate to a polymorphism in the ADCY9 gene^[25]. Additionally, CETP exists of full-length and exon 9-deleted isoforms, which regulates the secretion of full-length form of CETP^[26]. The next expectations relate to the role of the SNP in the ATP-binding cassette transporter A1 (ABCA1)-gene. Previously HDL-targeted clinical studies had revealed the effect of CETP inhibitor on an increase in the number of HDL particles in connection with ABCA1-mediated cholesterol efflux^[27,28]. Probably, SNP in genes of CETP isoforms could associate with genetic inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase^[29] and this is an explanation why the clinical trials dedicated the CV benefits of CETP inhibitors had failed. Whether CETP inhibitors alter cellular triglyceride metabolism and a transfer of HDL particles depending on CETP isoforms genetic polymorphisms of is not fully understood and required to be investigated in the future.

Conclusions: Although CETP inhibitors provides insufficient CV benefit amid patients at higher CV risk and known CV disease, there are promising findings that can explain the role of HDL-target therapy for routine use. Large clinical trials are required to investigate clinical significance of genetic inhibition of CETP in dislipidemic individuals.

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