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Single Nucleotide Polymorphisms in Cholesteryl Ester Transfer Protein Gene And Recurrent Coronary Heart Disease or Mortality in Patients with Established Atherosclerosis

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Abstract

It is not known whether genetic variants in the cholesteryl-ester-transfer-protein (CETP) gene are associated with recurrent coronary heart disease events or mortality in secondary prevention patients. Among 3717 acute coronary syndrome (ACS) or coronary artery bypass grafting (CABG) patients enrolled in a prospective genetic registry; we evaluated whether CETP gene variants previously shown to be associated with reduced CETP activity and high-density-lipoprotein-cholesterol increase (“A” allele for both *TaqIB* [rs708272] and rs12149545) are associated with a reduction in recurrent myocardial infarction [MI], recurrent revascularization or death. At 4.5 years of follow-up; 439 recurrent MI, 698 recurrent revascularizations and 756 deaths occurred. Using an additive model of inheritance, the “A” allele for rs708272 was not associated with recurrent MI (HR 0.95, 95% CI 0.78-1.17 for AG; HR 0.89, 95% CI 0.67-1.19 for AA; compared with GG genotype), recurrent revascularization (HR 1.13, 95% CI 0.95-1.33 for AG; HR 1.05, 95% CI 0.84-1.32 for AA) or mortality (HR 1.02, 95% CI 0.86-1.19 for AG; HR 1.11, 95% CI 0.91-1.37 for AA) in the overall cohort. Similar results were seen for the “A” allele

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for rs12149545. In the CABG subgroup, AG genotype for rs708272 was associated with an increased mortality (HR 1.38, 95% CI 1.06-1.79) compared to GG genotype. Results remained consistent using dominant model of inheritance. In conclusion, genetic CETP variants were not associated with recurrent MI or recurrent revascularization in overall cohort with a possible mortality increase in CABG patients.

Keywords

Cholesteryl-ester-transfer-protein; *TaqIB*; recurrent events; mortality

INTRODUCTION

Cholesteryl-ester-transfer-protein (CETP) inhibition has been suggested to be an important therapeutic target with several drugs in development [1]. Most of these trials have targeted patients with established atherosclerosis [2,3]. Two of these CETP inhibitors (torcetrapib, dalcetrapib) failed to show an improvement in cardiovascular (CV) outcomes with an increase in adverse outcomes with torcetrapib [4,5]. Several reasons have been postulated to explain these findings for e.g., increase in blood pressure [4] and possibly, differences in the high-density lipoprotein cholesterol (HDL-C) raising or low-density-lipoprotein cholesterol (LDL-C) lowering efficacy of these drugs [6]. Some have also questioned whether CETP inhibition itself is a viable therapeutic option [7]. Mendelian randomization studies have been shown to explain whether an increased risk of coronary heart disease (CHD) events seen with a risk marker is indeed causal [8]. Because the inheritance of a genetic trait is independent of environmental and behavioral factors, the associations seen in these studies are more robust compared with classic epidemiological studies where confounding and reverse causation remain a concern. Genotypic polymorphisms leading to an alteration in the level of a risk marker and CV outcomes are more likely to indicate a causal association. Therefore, using principles of mendelian randomization, we evaluated whether single nucleotide polymorphisms (SNPs) shown to be associated with lower levels of CETP and increased HDL-C levels [9-17] are associated with a decreased incidence of recurrent myocardial infarction (MI), recurrent revascularization or mortality in patients with established atherosclerosis (those presenting with acute coronary syndrome [ACS] or those undergoing coronary artery bypass grafting [CABG]).

METHODS

TexGen is a prospective, collaborative genetic registry enrolling patients with atherosclerotic CHD who seek care at multiple institutions within the Texas Medical Center [18,19]. For the current analyses, we restricted our patient population to those patients presenting with ACS or those undergoing CABG (with or without concomitant valve surgery) enrolled in the TexGen registry between September 2001 through September 2008. Pre-operative, intra-operative and postoperative characteristics of these patients were obtained through a clinical research database maintained at the St. Luke's Episcopal Hospital [20]. The variables used for our analyses included age, gender, history of hypertension, diabetes mellitus, smoking, presence of renal insufficiency, New York Heart Association (NYHA) functional class, and the use of aspirin, beta blockers, or statins.

We evaluated one SNP in the *TaqIB* polymorphism from intron 1 (rs708272) and one SNP in the promoter region G-2708A (rs12149545) of the CETP gene. These SNPs in the CETP gene have been known to be associated with HDL-C levels in prior studies [9-17]. Genotyping (details provided as supplemental text) was performed in a multiplex reaction using the MassARRAY system and iPLEX Gold Complete Genotyping Reagent Set

(Sequenom, Inc.). Both SNPs had a missing rate of 2.7%. QC concordance for 37 replicated samples that were randomly distributed multiple times throughout the plate set was 100%. Prospective follow-up of outcomes in the TexGen registry includes annual follow-up phone calls by the research nurses and annual surveys mailed to each patient. In addition, any hospitalization for patients enrolled in the database is also verified using hospitalization records. Our primary outcome of interest was the incidence of recurrent MI in the entire cohort (those presenting with ACS or those undergoing CABG). Our secondary outcomes included the need for recurrent revascularization procedures (recurrent percutaneous coronary intervention or recurrent CABG after the index ACS event or CABG surgery) and all-cause mortality. We included all-cause death as one of the secondary outcomes because some of the patients experiencing MI may suffer a sudden arrhythmic death and could possibly be miss-classified if only recurrent MI was used as the outcome measure.

Recurrent MI was defined as new ST-segment elevation in 2 contiguous leads in the setting of ischemic symptoms, or new horizontal or down-sloping ST depression ≥ 0.05 mV in 2 contiguous leads; and/or T wave inversions ≥ 0.1 mV in 2 contiguous and serum TnI >99 th percentile of the upper normal limit. In-hospital MI following CABG was defined as the increased levels of creatine kinase-MB isoenzyme with appearance of new Q waves on electrocardiogram, a new regional wall motion abnormality (other than paradoxical septal motion), or the presence of MI at autopsy. Recurrent revascularization was defined as the receipt of another PCI or CABG after the index ACS event or CABG surgery. Vital status was ascertained on patients using data from the Texas State Bureau of Vital Statistics.

Each of the two SNPs were studied separately. Our hypothesis was that the presence of genetic polymorphisms associated with reduced CETP activity (and higher HDL-C levels) will be associated with a lower risk of recurrent CHD events and mortality. We initially performed a log rank test to evaluate the univariate association between each of the two SNPs (rs708272 and rs12149545) and the risk of recurrent MI. Cox proportional-hazards regression models (adjusting for age, gender, hypertension, diabetes mellitus, current smoking, renal insufficiency, NYHA functional class, and aspirin, beta blocker, and statin use) were subsequently performed to determine whether “A” allele for each of the two SNPs (known to be associated with a reduced CETP activity, and therefore, increased HDL-C levels) was independently associated with a reduction in the incidence of recurrent MI. Cox regression analyses were also performed to study whether the “A” for each of the SNPs was also associated with a reduction in the recurrent revascularization or mortality. We initially used an additive model of inheritance as the risk ratios in prior studies followed an additive genetic pattern [9-17], although, results are also presented using a dominant genetic model as supplemental material. Analyses were also performed separately for TexGen patients presenting with ACS or those who underwent CABG. Finally, although SNPs in the CETP gene have shown to be associated with HDL-C levels in ethnicities other than Whites (for e.g. Blacks [15] or Asians [16,17]), we also performed analyses in those TexGen participants who self-identified their race as White.

Statistical analyses were performed using SAS statistical software version 9.1 (SAS Institute, Inc.; Cary, NC). All analyses were performed using two-tailed tests for significance. Because we evaluated SNPs affecting a CETP locus with future risk of MI, revascularization, or death on an *a priori* basis and did not perform a genome wide association, adjustments were not made for multiple testing. The study protocol was approved by the Institutional Review Board at Baylor College of Medicine. The authors are solely responsible for the design and conduct of the study, all analyses, the drafting and editing of the manuscript, and its final contents.

RESULTS

We included 3,717 patients who either presented with ACS or underwent CABG. Out of this cohort, 2,926 patients presented with ACS and 1,569 patients underwent CABG during the index hospitalization. Table 1 describes the baseline characteristics of the study cohort. Mean age was 62.5 years with a predominance of males (73%). Diabetes and hypertension were prevalent in 34.3% and 78.7% of patients, respectively. Sixteen percent of the patients had history of renal insufficiency and 50.6% had NYHA functional class III/IV symptoms.

In the overall cohort, the frequencies of GG, AG, and AA genotypes for rs708272 were 33%, 50%, and 17%, respectively. For rs12149545, the prevalence of GG, AG, and AA genotypes was 52%, 41%, and 7%, respectively. Overall, 67% of the patients carried at least one copy of the “A” for rs708272 and 48% of the patients carried at least one copy of the “A” allele for rs12149545. The association between rs708272 and the primary and secondary outcomes for the entire cohort at a mean follow-up of 4.5 years from the index ACS event or CABG surgery is shown in Table 2. A total of 1,893 (51%) patients suffered an adverse CHD event (439 [11.8%] had recurrent MIs, 698 [18.8%] underwent recurrent revascularization, and 756 [20.3%] died). Using additive model of inheritance, the presence of AG or AA genotype for rs708272 was not associated with a significantly lower incidence of recurrent MI compared with GG genotype in adjusted models. In addition, AG and AA genotypes were not associated with a lower incidence of recurrent revascularization or mortality compared with the GG genotype. Similar non-significant results were seen for the AG or AA genotypes (compared with GG genotype) for rs12149545 for either the primary or the secondary outcomes.

We also evaluated the association between rs708272 or rs12149545 and the primary or secondary outcomes in the subgroup of patients admitted with ACS or those undergoing CABG. AG or AA genotypes for rs708272 or rs12149545 were not associated with recurrent MI or the need for recurrent revascularization in patients who presented with ACS (Table 3) or those who underwent CABG (Table 4) in fully adjusted models. Contrary to our hypothesis, AG phenotype for rs708272 was associated with an increased risk of mortality (HR 1.38, 95% CI 1.06-1.79) compared to GG genotype in the CABG subgroup (Table 4). No significant association between CETP genotypes and increased mortality was seen for patients in the ACS subgroup.

Associations between rs708272 or rs12149545 and the primary or secondary outcomes using dominant model of inheritance (GG vs. AG or AA genotype) are described in Supplemental Tables 1-3. The “A” allele for rs708272 and rs12149545 was not associated with either primary or secondary outcomes in the overall cohort (Supplemental Table 1) or in those who presented with ACS (Supplemental Table 2). In the CABG subgroup (Supplemental Table 3), the “A” allele for rs708272 was associated with a significantly increased risk of mortality (HR 1.36, 95% CI 1.06-1.74 in the fully adjusted model). Directionally similar results were seen for the association between the “A” allele for rs12149545 and mortality (HR 1.16, 95% CI 0.93-1.45), although, the confidence interval crossed unity. We also performed subgroup analyses among patients who self-identified their race as White. These results (data not shown) were consistent with the results shown in Tables 2-4, and Supplemental Tables 1-3.

DISCUSSION

Our analyses show that SNPs in the CETP gene shown in prior studies to be associated with reduced CETP activity and higher HDL-C levels were not associated with a lower incidence of recurrent MI or the need for recurrent revascularization. In the CABG subgroup, the “A” allele for rs708272 was associated with a significantly increased risk of mortality. Our study

results are in contrast to the findings of some earlier studies that predominantly included primary prevention population [13,14,21], but are consistent with other studies either showing no effect [12] or an increased risk of CHD events in carriers of CETP genotypes associated with lower CETP activity [22,23]. This could be due to several reasons. First, the association between CETP polymorphisms and CHD events in primary prevention studies reflects a lifelong reduction in CETP levels, which likely has more impact on the time to first event compared to the time to a recurrent CHD event. Similarly, the use of statins, beta blockers and angiotensin converting enzyme inhibitors in our secondary prevention population could have blunted a beneficial effect of CETP variants that was seen in primary prevention studies. Our study results complement earlier observations showing that CETP inhibition may not be useful and in fact be detrimental in patients on statin therapy who have low levels of endogenous CETP activity [24,25]. Supporting this hypothesis, a recent study also showed that statin therapy decreases ATP-binding Cassette A1 transporter (ABCA1) expression and consequently, cholesterol efflux via this transporter [26]. Second, it is possible that modulation of HDL-C levels itself may not be effective in a secondary prevention setting. This observation is supported by results of The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) [27] and the recently concluded Heart Protection Study 2-Treatment of HDL to Reduce Incidence of Vascular Events (HPS-2 THRIVE) trials [28], where HDL-C increase using niacin therapy (with or without laropiprant) was not associated with a reduction in CV disease outcomes in well treated predominantly secondary prevention populations. It is important to note that in the statin treated arm of the primary prevention JUPITER trial [29] or the statin treated secondary prevention population of dal-OUTCOMES trial [5], no relationship between baseline HDL-C levels and subsequent events was seen. Third, it is possible that although CETP inhibition raises HDL-C levels, this raise in HDL-C may not be associated with a corresponding improvement in HDL functionality or the reverse cholesterol transport capacity of the HDL particle. In this regard, a prior study using a CETP inhibitor (torcetrapib) did not show a significant change in the fecal sterol excretion which is a marker of efficiency of the reverse cholesterol transport process [7].

Our results showing a significant association between the “A” allele for *Taq1B* and mortality in CABG patients are consistent with a prior study [22] which showed an increased mortality associated with B2 (A) allele of *Taq1B* in men with prior CHD. This study [22] showed a pharmacogenomic interaction between CETP polymorphism and statin therapy whereby, although *Taq1B* AA genotype was associated with better CHD outcomes in trials with low baseline use of statin therapy, it was paradoxically associated with an increased risk of adverse outcomes in trials where 50% or more of the participants were on statin therapy. Although these associations could be real, there remains a possibility that our results showing increased mortality in patients who underwent CABG represent a chance finding as a result of performing multiple comparisons. This is supported by the observation that the increased mortality noted was statistically significant only in patients who underwent CABG (and not ACS), and that no dose effect was seen when evaluating the risk ratios for mortality in those who were homozygous (AA) versus heterozygous (AG) for the “A” allele of *Taq1B*.

Our study has limitations. First, we did not have lipid data available, and therefore, could not establish whether the SNPs described in the CETP gene were associated with an increase in HDL-C in our cohort. Although this is a potential limitation, the “A” allele of the SNPs studied has consistently been shown to be associated with an increase in HDL-C levels in several prior studies [9-17]. Second, it is possible that the magnitude of increase in HDL-C levels with these polymorphisms (for e.g., between 4.5% increase in HDL-C per “A” allele for *Taq1B* [13,14]) may not be significant enough to alter outcomes. This could have led to

a decrease in the statistical power to show an association. Although this is a possibility, we did not see a directionally consistent pattern across various study outcomes. For example, although the overall association with “A” allele for both SNPs and recurrent MI was that of a protective association (albeit non-significant); an increased risk of recurrent revascularization and mortality was seen with the same minor allele. Third, because the studied CETP polymorphisms predominantly affect HDL-C levels with minimal effect on other lipid parameters (0.9% and 2% decrease in LDL-C and triglycerides, respectively [14]); our results may not account for the efficacy of CETP inhibition attributable to LDL-C or triglyceride reduction. Lastly, given our analyses were performed from a preexisting genetic registry, our results cannot account for any unmeasured or unknown confounders. The strengths of our study include a large number of events (439 recurrent MI, 698 recurrent revascularizations, and 756 deaths, total events = 1,893 [51% of the cohort]) which allowed us to confidently evaluate the studied outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Barter PJ, Rye KA. Cholesteryl ester transfer protein inhibition as a strategy to reduce cardiovascular risk. *J Lipid Res.* 2012; 53:1755–1766. [PubMed: 22550134]
2. Randomized Evaluation of the Effects of Anacetrapib Through Lipid-Modification (REVEAL).. [2/19/2013] NCT01252953 Clinical trials.gov
3. A Study of Evacetrapib in High-Risk Vascular Disease (ACCELERATE). [2/19/2013] NCT01687998 Clinical trials.gov
4. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, Lopez-Sendon J, Mosca L, Tardif JC, Waters DD, Shear CL, Revkin JH, Buhr KA, Fisher MR, Tall AR, Brewer B; ILLUMINATE Investigators. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med.* 2007; 357:2109–2122. [PubMed: 17984165]
5. Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J, Chaitman BR, Holme IM, Kallend D, Leiter LA, Leitersdorf E, McMurray JJ, Mundl H, Nicholls SJ, Shah PK, Tardif JC, Wright RS, dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med.* 2012; 367:2089–2099. [PubMed: 23126252]
6. Kathiresan S. Will cholesteryl ester transfer protein inhibition succeed primarily by lowering low-density lipoprotein cholesterol? Insights from human genetics and clinical trials. *J Am Coll Cardiol.* 2012; 60:2049–2052. [PubMed: 23083775]
7. Brousseau ME, Diffenderfer MR, Millar JS, Nartsupha C, Asztalos BF, Welty FK, Wolfe ML, Rudling M, Björkhem I, Angelin B, Mancuso JP, Digenio AG, Rader DJ, Schaefer EJ. Effects of cholesteryl ester transfer protein inhibition on high-density lipoprotein subspecies, apolipoprotein A-I metabolism, and fecal sterol excretion. *Arterioscler Thromb Vasc Biol.* 2005; 25:1057–1064. [PubMed: 15761191]
8. Smith GD, Ebrahim S. “Mendelian randomization”: can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol.* 2003; 32:1–22. [PubMed: 12689998]

9. Chen SN, Cilingiroglu M, Todd J, Lombardi R, Willerson JT, Gotto AM Jr, Ballantyne CM, Marian AJ. Candidate genetic analysis of plasma high-density lipoprotein-cholesterol and severity of coronary atherosclerosis. *BMC Med Genet.* 2009; 10:111. [PubMed: 19878569]
10. McCaskie PA, Beilby JP, Chapman CM, Hung J, McQuillan BM, Thompson PL, Palmer LJ. Cholesteryl ester transfer protein gene haplotypes, plasma high-density lipoprotein levels and the risk of coronary heart disease. *Hum Genet.* 2007; 121:401–411. [PubMed: 17287950]
11. Boekholdt SM, Thompson JF. Natural genetic variation as a tool in understanding the role of CETP in lipid levels and disease. *J Lipid Res.* 2003; 44:1080–1093. [PubMed: 12639975]
12. Klerkx AH, Tanck MW, Kastelein JJ, Molhuizen HO, Jukema JW, Zwinderman AH, Kuivenhoven JA. Haplotype analysis of the CETP gene: not TaqIB, but the closely linked -629C-->A polymorphism and a novel promoter variant are independently associated with CETP concentration. *Hum Mol Genet.* 2003; 12:111–123. [PubMed: 12499392]
13. Boekholdt SM, Sacks FM, Jukema JW, Shepherd J, Freeman DJ, McMahon AD, Cambien F, Nicaud V, de Grooth GJ, Talmud PJ, Humphries SE, Miller GJ, Eiriksdottir G, Gudnason V, Kauma H, Kakko S, Savolainen MJ, Arca M, Montali A, Liu S, Lanz HJ, Zwinderman AH, Kuivenhoven JA, Kastelein JJ. Cholesteryl ester transfer protein TaqIB variant, high-density lipoprotein cholesterol levels, cardiovascular risk, and efficacy of pravastatin treatment: individual patient meta-analysis of 13,677 subjects. *Circulation.* 2005; 111:278–287. [PubMed: 15655129]
14. Thompson A, Di Angelantonio E, Sarwar N, Erqou S, Saleheen D, Dullaart RP, Keavney B, Ye Z, Danesh J. Association of cholesteryl ester transfer protein genotypes with CETP mass and activity, lipid levels, and coronary risk. *JAMA.* 2008; 299:2777–2788. [PubMed: 18560005]
15. Nettleton JA, Steffen LM, Ballantyne CM, Boerwinkle E, Folsom AR. Associations between HDL-cholesterol and polymorphisms in hepatic lipase and lipoprotein lipase genes are modified by dietary fat intake in African American and White adults. *Atherosclerosis.* 2007; 194:e131–140. [PubMed: 17157861]
16. Tai ES, Ordoas JM, Corella D, Deurenberg-Yap M, Chan E, Adiconis X, Chew SK, Loh LM, Tan CE. The TaqIB and -629C>A polymorphisms at the cholesteryl ester transfer protein locus: associations with lipid levels in a multiethnic population. The 1998 Singapore National Health Survey. *Clin Genet.* 2003; 63:19–30. [PubMed: 12519368]
17. Tsujita Y, Nakamura Y, Zhang Q, Tamaki S, Nozaki A, Amamoto K, Kadowaki T, Kita Y, Okamura T, Horie M, Ueshima H. The association between high-density lipoprotein cholesterol level and cholesteryl ester transfer protein TaqIB gene polymorphism is influenced by alcohol drinking in a population-based sample. *Atherosclerosis.* 2007; 191:199–205. [PubMed: 16674961]
18. Virani SS, Brautbar A, Lee VV, MacArthur E, Morrison AC, Grove ML, Nambi V, Frazier L, Wilson JM, Willerson JT, Boerwinkle E, Ballantyne CM. Chromosome 9p21 Single Nucleotide Polymorphisms are Not Associated with Recurrent Myocardial Infarction in Patients with Established Coronary Artery Disease. *Circ J.* 2012; 76:950–956. [PubMed: 22322877]
19. Virani SS, Brautbar A, Lee VV, Elayda M, Sami S, Nambi V, Frazier L, Wilson JM, Willerson JT, Boerwinkle E, Ballantyne CM. Usefulness of Single Nucleotide Polymorphism in Chromosome 4q25 to Predict In-Hospital and Long Term Development of Atrial Fibrillation and Survival in Patients Undergoing Coronary Artery Bypass Grafting. *Am J Cardiology.* 2011; 107:1504–1509.
20. Virani SS, Nambi V, Polsani VR, Lee VV, Elayda M, Kohsaka S, Pan W, Reul RM, Wilson JM, Petersen LA, Willerson JT, Ballantyne CM. Preoperative statin therapy decreases risk of postoperative renal insufficiency. *Cardiovasc Ther.* 2010; 28:80–86. [PubMed: 20398096]
21. Johannsen TH, Frikke-Schmidt R, Schou J, Nordestgaard BG, Tybjaerg-Hansen A. Genetic inhibition of CETP, ischemic vascular disease and mortality, and possible adverse effects. *J Am Coll Cardiol.* 2012; 60:2041–2048. [PubMed: 23083790]
22. Regieli JJ, Jukema JW, Grobbee DE, Kastelein JJ, Kuivenhoven JA, Zwinderman AH, van der Graaf Y, Bots ML, Doevendans PA. CETP genotype predicts increased mortality in statin-treated men with proven cardiovascular disease: an adverse pharmacogenetic interaction. *Eur Heart J.* 2008; 29:2792–2799. [PubMed: 18957472]
23. Borggreve SE, Hillege HL, Wolffenbuttel BH, de Jong PE, Zuurman MW, van der Steege G, van Tol A, Dullaart RP. PREVEND Study Group. An increased coronary risk is paradoxically associated with common cholesteryl ester transfer protein gene variations that relate to higher

- high-density lipoprotein cholesterol: a population-based study. *J Clin Endocrinol Metab.* 2006; 91:3382–3388. [PubMed: 16684835]
24. van Venrooij FV, Stolk RP, Banga JD, Sijmonsma TP, van Tol A, Erkelens DW, Dallinga-Thie GM, DALI Study Group. Common cholesteryl ester transfer protein gene polymorphisms and the effect of atorvastatin therapy in type 2 diabetes. *Diabetes Care.* 2003; 26:1216–1223. [PubMed: 12663600]
25. Klerx AH, de Grooth GJ, Zwinderman AH, Jukema JW, Kuivenhoven JA, Kastelein JJ. Cholesteryl ester transfer protein concentration is associated with progression of atherosclerosis and response to pravastatin in men with coronary artery disease (REGRESS). *Eur J Clin Invest.* 2004; 34:21–28. [PubMed: 14984434]
26. Niesor EJ, Schwartz G, Suchankova G, Benghozi R, Abt M, Kallend D. Statin-induced decrease in ABCA1 expression via MiR33 induction may counteract cholesterol efflux by high-density lipoprotein raised with the cholesteryl ester transfer protein modulator Dalcetrapib. *J Am Coll Cardio.* 2013; 61(10_S) [Abstr].
27. AIM-HIGH Investigators. Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, McBride R, Teo K, Weintraub W. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med.* 2011; 365:2255–2267. [PubMed: 22085343]
28. Treatment of HDL to Reduce the Incidence of Vascular Events HPS2-THRIVE. [2/20/2013] NCT00461630 Clinical trials.gov
29. Ridker PM, Genest J, Boekholdt SM, Libby P, Gotto AM, Nordestgaard BG, Mora S, MacFadyen JG, Glynn RJ, Kastelein JJ, JUPITER Trial Study Group. HDL cholesterol and residual risk of first cardiovascular events after treatment with potent statin therapy: an analysis from the JUPITER trial. *Lancet.* 2010; 376:333–339. [PubMed: 20655105]

Table 1

Baseline characteristics of the patients (n = 3,717) included in the analyses.

Characteristic	n (%)
Age, mean $\pm$ standard deviation (years)	62.51 $\pm$ 10.92
Male gender	2,712 (73%)
Family history of premature coronary artery disease	1,248 (33.6%)
Diabetes mellitus	1,274 (34.3%)
Hypertension (by history)	2,925 (78.7%)
Transient ischemic attacks or stroke	333 (9%)
Renal insufficiency	599 (16.1%)
Smoker	812 (21.9%)
New York Heart Association functional class III/IV symptoms	1,882 (50.6%)
Beta blocker use	2,779 (74.8%)
Statin use	2,708 (73%)
Aspirin use	3,144 (84.6%)
History of acute coronary syndrome	2,926 [*] (78.7%)
History of coronary artery bypass grafting	1,569 [*] (42.2%)

* numbers add up to > 3,717 as some patients with acute coronary syndrome underwent coronary artery bypass grafting.

Table 2

Association between single nucleotide polymorphisms in the CETP gene and the outcome of recurrent MI, need for recurrent revascularization or death in the overall TexGen cohort.

rs708272 (TaqIB) *			
Genotype (n)	Recurrent MI	HR (95% CI) (unadjusted)	HR (95% CI) †
GG (1259)	153 (12.2%)	<i>Referent</i>	<i>Referent</i>
AG (1840)	218 (11.9%)	0.95 (0.77-1.16)	0.95 (0.78-1.17)
AA (618)	68 (11%)	0.87 (0.66-1.16)	0.89 (0.67-1.19)
	Recurrent revascularization	HR (95% CI) (unadjusted)	HR (95% CI) †
GG (1259)	219 (17.4%)	<i>Referent</i>	<i>Referent</i>
AG (1840)	363 (19.8%)	1.13 (0.96-1.34)	1.13 (0.95-1.33)
AA (618)	116 (18.8%)	1.05 (0.84-1.31)	1.05 (0.84-1.32)
	Death	HR (95% CI) (unadjusted)	HR (95% CI) †
GG (1259)	247 (19.6%)	<i>Referent</i>	<i>Referent</i>
AG (1840)	367 (20%)	0.99 (0.84-1.16)	1.02 (0.86-1.19)
AA (618)	142 (23%)	1.12 (0.91-1.37)	1.11 (0.91-1.37)
rs12149545 *			
Genotype (n)	Recurrent MI	HR (95% CI) (unadjusted)	HR (95% CI) †
GG (1921)	240 (12.5%)	<i>Referent</i>	<i>Referent</i>
AG (1514)	171 (11.3%)	0.87 (0.72-1.06)	0.88 (0.72-1.07)
AA (282)	28 (9.9%)	0.77 (0.52-1.14)	0.81 (0.55-1.20)
	Recurrent revascularization	HR (95% CI) (unadjusted)	HR (95% CI) †
GG (1921)	341 (17.8%)	<i>Referent</i>	<i>Referent</i>
AG (1514)	301 (19.9%)	1.11 (0.95-1.29)	1.10 (0.94-1.29)
AA (282)	56 (19.9%)	1.07 (0.81-1.42)	1.10 (0.83-1.46)
	Death	HR (95% CI) (unadjusted)	HR (95% CI) †
GG (1921)	380 (19.8%)	<i>Referent</i>	<i>Referent</i>
AG (1514)	310 (20.5%)	1.02 (0.87-1.18)	1.02 (0.88-1.18)
AA (282)	66 (23.4%)	1.14 (0.88-1.48)	1.13 (0.87-1.47)

MI = myocardial infarction, HR = hazard ratio, CI = confidence interval

* A allele shown to be associated with reduced CETP activity and increase levels of HDL-C

† Adjusted for age, gender, hypertension, diabetes, current smoking, renal insufficiency, presence of New York Heart Association Functional Class III/IV symptoms, aspirin use, beta blocker use, and statin use

Table 3

Association between single nucleotide polymorphisms in the CETP gene and the outcome of recurrent MI, need for recurrent revascularization or death in the TexGen acute coronary syndrome cohort.

rs708272(TaqIB) *			
Genotype (n)	Recurrent MI	HR (95% CI) (unadjusted)	HR (95% CI)†
GG (1011)	133 (13.2%)	<i>Referent</i>	<i>Referent</i>
AG (1446)	191 (13.2%)	0.96 (0.77-1.23)	0.98 (0.79-1.22)
AA (469)	59 (12.6%)	0.91 (0.67-1.23)	0.92 (0.68-1.26)
	Recurrent revascularization	HR (95% CI) (unadjusted)	HR (95% CI)†
GG (1011)	199 (19.7%)	<i>Referent</i>	<i>Referent</i>
AG (1446)	328 (22.7%)	1.14 (0.96-1.36)	1.12 (0.94-1.34)
AA (469)	103 (22%)	1.06 (0.84-1.35)	1.06 (0.83-1.34)
	Death	HR (95% CI) (unadjusted)	HR (95% CI)†
GG (1011)	201 (19.9%)	<i>Referent</i>	<i>Referent</i>
AG (1446)	269 (18.6%)	0.90 (0.74-1.07)	0.96 (0.80-1.15)
AA (469)	111 (23.7%)	1.09 (0.86-1.37)	1.10 (0.87-1.39)
rs12149545 *			
Genotype (n)	Recurrent MI	HR (95% CI) (unadjusted)	HR (95% CI)†
GG (1522)	210 (13.8%)	<i>Referent</i>	<i>Referent</i>
AG (1179)	150 (12.7%)	0.88 (0.72-1.09)	0.90 (0.73-1.11)
AA (225)	23 (10.2%)	0.71 (0.46-1.09)	0.73 (0.47-1.12)
	Recurrent revascularization	HR (95% CI) (unadjusted)	HR (95% CI)†
GG (1522)	309 (20.3%)	<i>Referent</i>	<i>Referent</i>
AG (1179)	271 (23%)	1.11 (0.94-1.31)	1.10 (0.94-1.29)
AA (225)	50 (22.2%)	1.03 (0.77-1.39)	1.04 (0.78-1.41)
	Death	HR (95% CI) (unadjusted)	HR (95% CI)†
GG (1522)	296 (19.5%)	<i>Referent</i>	<i>Referent</i>
AG (1179)	234 (19.9%)	0.99 (0.84-1.18)	1.04 (0.88-1.24)
AA (225)	51 (22.7%)	1.09 (0.81-1.47)	1.15 (0.85-1.55)

MI = myocardial infarction, HR = hazard ratio, CI = confidence interval

* A allele shown to be associated with reduced CETP activity and increase levels of HDL-C

† Adjusted for age, gender, hypertension, diabetes, current smoking, renal insufficiency, presence of New York Heart Association Functional Class III/IV symptoms, aspirin use, beta blocker use, and statin use

Table 4

Association between single nucleotide polymorphisms in the CETP gene and the outcome of recurrent MI, need for recurrent revascularization or death in the TexGen coronary artery bypass grafting cohort.

rs708272(TaqIB) *			
Genotype (n)	Recurrent MI	HR (95% CI) (unadjusted)	HR (95% CI)†
GG (526)	52 (9.9%)	<i>Referent</i>	<i>Referent</i>
AG (770)	69 (8.9%)	0.91 (0.63-1.30)	0.90 (0.62-1.28)
AA (273)	20 (7.3%)	0.74 (0.44-1.24)	0.75 (0.45-1.25)
Recurrent revascularization			
Genotype (n)		HR (95% CI) (unadjusted)	HR (95% CI)†
GG (526)	45 (8.6%)	<i>Referent</i>	<i>Referent</i>
AG (770)	78 (10.1%)	1.22 (0.85-1.76)	1.21 (0.84-1.74)
AA (273)	28 (10.3%)	1.23 (0.77-1.97)	1.24 (0.77-1.99)
Death			
Genotype (n)		HR (95% CI) (unadjusted)	HR (95% CI)†
GG (526)	87 (16.5%)	<i>Referent</i>	<i>Referent</i>
AG (770)	171 (22.2%)	1.40 (1.08-1.82)	1.38 (1.06-1.79)
AA (273)	58 (21.3%)	1.33 (0.96-1.86)	1.32 (0.94-1.84)
rs12149545 *			
Genotype (n)	Recurrent MI	HR (95% CI) (unadjusted)	HR (95% CI)†
GG (792)	73 (9.2%)	<i>Referent</i>	<i>Referent</i>
AG (659)	58 (8.8%)	0.94 (0.67-1.33)	0.92 (0.65-1.29)
AA (118)	10 (8.5%)	0.90 (0.47-1.74)	0.91 (0.47-1.77)
Recurrent revascularization			
Genotype (n)		HR (95% CI) (unadjusted)	HR (95% CI)†
GG (792)	71 (9%)	<i>Referent</i>	<i>Referent</i>
AG (659)	70 (10.6%)	1.19 (0.86-1.66)	1.18 (0.85-1.64)
AA (118)	10 (8.5%)	0.90 (0.46-1.74)	0.91 (0.47-1.76)
Death			
Genotype (n)		HR (95% CI) (unadjusted)	HR (95% CI)†
GG (792)	146 (18.4%)	<i>Referent</i>	<i>Referent</i>
AG (659)	141 (21.4%)	1.18 (0.94-1.49)	1.14 (0.91-1.44)
AA (118)	29 (24.6%)	1.27 (0.86-1.90)	1.25 (0.84-1.87)

MI = myocardial infarction, HR = hazard ratio, CI = confidence interval

* A allele shown to be associated with reduced CETP activity and increase levels of HDL-C

† Adjusted for age, gender, hypertension, diabetes, current smoking, renal insufficiency, presence of New York Heart Association Functional Class III/IV symptoms, aspirin use, beta blocker use, and statin use