Published in final edited form as:

J Hypertens. 2011 May ; 29(5): 863–868. doi:10.1097/HJH.0b013e3283450223.

Circulating Plasma Cholesteryl Ester Transfer Protein Activity and Blood pressure Tracking in the Community

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Abstract

Objective—Clinical trials using cholesteryl ester transfer protein (CETP) inhibitors to raise high-density lipoprotein cholesterol (HDL-C) concentrations reported an ‘off-target’ blood pressure (BP) raising effect. We evaluated the relations of baseline plasma CETP activity and longitudinal BP change.

Methods and Results—1307 Framingham Study participants free of CVD attending consecutive examinations 4 years apart (mean age 48 years) had baseline plasma CETP activity related to change in BP over the 4-year interval, adjusting for standard risk factors. Systolic BP increased (median +2 mm, 95% CI −16,+23 mm Hg), while diastolic BP decreased (median −3 mm, 95% CI −15,+11 mm Hg). Plasma CETP activity was not related to change in diastolic BP, but was inversely related to change in systolic BP that was borderline significant ($p=0.09$). On multivariable analyses, plasma CETP activity was inversely related to change in pulse pressure (PP; beta per SD increment=−0.71 mm Hg, $p=0.005$). When dichotomized at the median, plasma CETP activity above the median was associated with a 1 mm Hg lower PP on follow-up ($p=0.045$).

Conclusion—Decreasing plasma CETP activity was modestly related to increasing PP on follow-up in our community-based sample, suggesting that inhibition of intrinsic CETP activity itself is likely associated with minimal changes in BP.

Keywords

CETP; Blood pressure; prospective studies

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Conflict of Interest: none.

Accepted for Oral Presentation at American Heart Association High Blood Pressure Research Scientific Sessions October 2010

INTRODUCTION

Since the discovery of the association between elevated high density lipoprotein cholesterol (HDL-C) concentrations and lower risk of cardiovascular disease (CVD), considerable scientific effort has been directed at raising HDL-C levels.¹ Observational studies in humans with dyslipidemias, animal models, and in vitro assays emphasize the critical role of cholesterol ester transfer protein (CETP) in HDL-C metabolism, rendering inhibition of the activity of this enzyme a viable approach for raising HDL-C. Initial studies testing the effectiveness of CETP inhibition with an antagonist, torcetrapib, tempered enthusiasm about this strategy because of the findings of increased all-cause mortality, cardiovascular events, and atherosclerotic progression despite predictable and consistent elevations in HDL-C and reduction of LDL-C concentrations.^{2–4} Although the excess mortality in these initial studies was not solely attributable to cardiovascular disease, investigators have attributed the adverse effects at least in part to ‘off-target’ effects of torcetrapib on the adrenocortical axis, with a consequent elevation in systolic blood pressure (BP). Thus, these studies have focused greater attention on elucidating the role of HDL-C and CETP activity in cardiovascular disease and BP homeostasis.^{5–15}

The observed BP elevation caused by torcetrapib is believed to be an ‘off-target’ effect of tetrahydroquinoline (THQ) subclass of CETP inhibitors,^{5,6} given that non-THQ agents (such as anacetrapib) are not associated with BP elevation.^{5–8} While the molecular mechanisms by which THQ subclass CETP inhibitors raise BP remain incompletely understood,⁹ enhanced adrenal steroidogenesis seems a key potential pathway, and CETP inhibition does not seem directly implicated per se.^{5–8} Notwithstanding these mechanistic data, there is controversy as to whether the observed blood pressure changes were the result of torcetrapib related off-target effects, CETP inhibition effects, or if CETP itself affects blood pressure. We examined the relation of baseline plasma CETP activity itself to longitudinal BP tracking in a large community based sample not on CETP inhibitor treatment.

METHODS

Study sample

Children of the original Framingham Heart Study cohort participants and the spouses of these children were enrolled into the Framingham Offspring Study in 1971. Participants undergo regularly scheduled examinations at the Heart Study approximately every 4 years, when they have a physician-administered medical history and examination including BP measurements, as well as laboratory tests for vascular risk factors.¹⁶ A randomly selected sample of Offspring cohort participants who attended the fourth examination cycle (1987–1990) had plasma CETP activity measurements.¹⁵ For the present investigation, participants were eligible if they attended examination cycle 4 and were not hypertensive (systolic BP<140 mm Hg and diastolic BP<90 mm Hg, and not using antihypertensive medications), had plasma CETP activity measurements and BP, and they attended the fifth examination cycle (1991–1995) when BP was remeasured (N=1352). We excluded 45 participants with missing clinical or laboratory data, leaving 1307 participants in the analysis. The study complies with the Declaration of Helsinki, was approved by the Institutional Review Board at the Boston Medical Center, and all participants provided written informed consent.

Laboratory Measurements of Plasma CETP Activity

At examination cycle 4, blood was drawn after an overnight fast, immediately centrifuged to separate plasma, and plasma was stored at –80 °C until biomarkers were assayed. CETP activity was determined on plasma samples (previously unfrozen) utilizing the Roar CETP assay kit.¹⁵ The intra-assay and interassay coefficients of variation were both <3%.¹⁵ The

Roar CETP Activity Assay Kit detects the CETP mediated transfer of neutral lipid, in this case cholesteryl esters, from a fluorescently labeled emulsion of neutral lipid with non-ApoA1 lipoprotein to excess endogenous acceptor, specifically VLDL. This non-ApoA1 donor is a preferred substrate of CETP over endogenous HDL-C, negating competition with endogenous HDL. Several in vitro and in vivo studies have demonstrated the linearity of the assay across the physiologic range of CETP activity levels, correlation of this assay with radioisotopic measurements of CETP activity, and the proportionality of CETP activity with CETP mass concentrations, as well as an expected decrease in CETP mass and activity in response to HMG-CoA (statin) therapy.^{17–23}

Blood pressure measurements

At each Heart Study examination participants undergo BP measurements using a standardized protocol with rigorous attention to certification of observers and quality control. Briefly, BP was measured on the left arm of seated participants by a physician, using a mercury-column sphygmomanometer, a cuff of appropriate size and a standardized protocol. Participants had rested in a chair for five minutes before BP was measured, and the average of two physician-obtained readings was considered the examination BP. Hypertension was defined as systolic BP ≥ 140 mm Hg, or diastolic BP ≥ 90 mm Hg or use of blood-pressure lowering medications.

Statistical Analysis

We assessed the relations between baseline plasma CETP activity (at examination cycle 4) to the changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP) from examination cycle 4 to examination cycle 5 using multivariable linear regression. Plasma CETP activity was modelled as a continuous variable, and as a binary variable dichotomized at the median (separate models for each). Additionally, we used generalized additive models to plot the relations of plasma CETP activity (continuous) to the change in BP measures on follow-up. To assess the possibility of a nonlinear association between CETP activity and BP, we also built models utilizing CETP activity squared and CETP activity cubed.

To account for treatment with antihypertensive medications at the follow-up examination, we used an imputation method (previously described²⁴) to estimate BP on follow up among individuals who were treated with BP lowering medications at the follow-up examination (cycle 5). Separate analyses were conducted for changes in SBP, DBP and for changes in PP. Clinical covariates included in the models were age, sex, baseline (examination cycle 4) body mass index, baseline SBP and DBP for SBP and DBP analyses, baseline PP for PP analysis, smoking, and high density lipoprotein cholesterol (HDL-C) concentration, and percent weight change on follow-up (between examination cycles 4 and 5). We adjusted for these covariates to be consistent with prior studies demonstrating that these variables influence longitudinal changes in BP.^{25–27} A two-sided p-value below 0.05 was considered statistically significant.

RESULTS

The characteristics of our non-hypertensive study sample at the baseline examination cycle 4 are detailed in Table 1. Characteristics of the cohort at follow-up are listed in Supplementary Table 1 (Supplementary Data Content 1). Distribution of CETP activity is illustrated in Supplementary Figure 1 (Supplementary Data Content 1).

Relations of Plasma CETP activity to Change in Blood Pressure on Follow-up

On follow-up (mean 3.6 ± 0.4 years) SBP increased, with a median change of +2 mm Hg, 95% CI -16 to +23 mm Hg; DBP decreased with a median change of -3 mm Hg, 95% CI -15 to +11 mmHg; and PP increased with a median change of 5 mm Hg, 95% CI -11 to +22 mm Hg. Only 20 individuals (1.5%) were on BP-lowering treatment at follow-up.

Table 2 displays the relations of plasma CETP activity and longitudinal changes in BP measures. CETP activity had a borderline statistically significant inverse relation to change in SBP ($p=0.09$ for continuous CETP) but was not related to change in DBP. However, CETP activity was inversely related to changes in pulse pressure. When modeled as a continuous variable, each 1 standard deviation increment in plasma CETP activity was inversely related to PP (beta -0.72; CI-1.23,0.22; $p=0.005$). Individuals with CETP activity above the median experienced a 1 mm lower PP increase on follow-up. Squared and cubed CETP activity was not associated with BP changes and did not substantially alter the association between CETP and BP. Figure 1 (**Panels A-C**) displays the relations of continuous CETP and changes in BP measures based on the results of generalized additive models. These models confirmed the inverse relations of plasma CETP activity and changes in PP. When analyses were repeated only on individuals not on antihypertensive medications on follow-up ($n=1287$) or on individuals who remained non-hypertensive on follow-up ($n=1169$), the inverse association of continuous CETP and change in PP was maintained ($p=0.006$ and 0.049 , respectively).

DISCUSSION

The present investigation is the first study, to our knowledge, to evaluate the potential relations of plasma CETP enzymatic activity and longitudinal changes in BP in a community-based sample. In our longitudinal study of middle-aged nonhypertensive participants free of CVD, we observed an inverse association between plasma CETP activity at baseline and pulse pressure change on follow-up. Plasma CETP activity was not related to changes in DBP, and only demonstrated a borderline statistically significant inverse association with changes in SBP. Of note, the observed effect size for PP-CETP relations was exceedingly modest, on the order of 1 mm Hg difference (for individuals with CETP activity above the median versus below), leaving the clinical significance of this association unclear, especially given the larger change in PP observed in clinical trials involving torcetrapib.⁴

Large clinical trials including ILLUMINATE, RADIANCE, and ILLUSTRATE demonstrated that the addition of CETP inhibitor torcetrapib to baseline atorvastatin therapy increased HDL-C concentration, decreased LDL-C concentration, but did not cause atheroma regression, and was in fact associated with increased all cause mortality and cardiovascular events.²⁻⁴ In ILLUMINATE, this increase mortality was attributed to a slight increase in BP (5.4 ± 13.2 mm Hg systolic, 2.0 ± 8.1 mmHg diastolic) in the treatment arm, along with a significant relation between death and decreased serum potassium concentration and increased serum bicarbonate concentration in the torcetrapib arm.⁵ These observations suggested a potential 'off-target' effect linking torcetrapib to the adrenal steroid biosynthetic pathways. Experimental data now suggests that torcetrapib-related BP increases were likely related to increased aldosterone and corticosterone production, and are not mediated by mechanisms involving direct effects on smooth muscle cells, adrenoreceptor, angiotensin 2, or endothelin.⁸ Preliminary data also suggest these BP raising effects are likely a CETP inhibitor subclass phenomenon that are independent of actual CETP inhibition, and are absent in the newer CETP inhibitors.⁵⁻⁹ To our knowledge, the relationship between baseline, untreated CETP activity and long-term BP tracking in the community has not been previously studied.

In our study, lower plasma CETP activity was associated with greater increase in PP on follow-up. One mechanism by which CETP activity may be related to BP change is via HDL-C levels. Higher HDL-C levels have been associated with lower BP on follow-up.²⁷ However, if lower CETP activity is associated with higher HDL-C, one would expect a lesser increase in PP on follow-up in individuals with lower baseline CETP activity levels if indeed the principal mediating mechanism is related to alterations in HDL-C levels. Our data did not find a significant difference in HDL-C concentrations in those with CETP activity above the median versus below the median, making it difficult to assign HDL-C mass as the explanatory actor of the observed greater PP change with lower baseline CETP activity. In addition to changing the quantity of circulating HDL-C, higher CETP activity also changes the quality of HDL-C in the blood by creating more mature, more dense HDL-C particles, such as HDL-C 3b. HDL-C 3b interacts with scavenger receptor BI (sr-BI) to activate endothelial nitric oxide synthase (eNOS).³³ Increased nitric oxide (NO) from higher eNOS activity has been linked to lower arterial stiffness.^{35,36} Thus, greater CETP activity may be associated with lower arterial stiffness, and vice versa. Thus, our data are consistent with the notion that lower plasma CETP activity may be associated with greater PP increase on follow-up, possibly because of greater vascular stiffness (due to lower dense HDL-C levels). Since we did not measure either arterial stiffness or assay HDL-C subparticles, this explanation remains speculative at best. Furthermore, the magnitude of the observed changes in PP in our study was so modest that it is unlikely to explain the effect of torcetrapib on blood pressure. Overall, our observations are consistent with the notion that the observed BP change in ILLUMINATE was likely the result of a combination of CETP inhibition effects and 'off-target' effects.³⁴

STUDY LIMITATIONS

The predominant limitation of our investigation is its observational nature. While our study is observational, the temporal pattern of the association, i.e., plasma CETP activity measurements preceding PP change, is important to underscore. We did not have measures of vascular stiffness at either the baseline or at the follow-up examination. Therefore we are unable to positively demonstrate the possible link between CETP activity and arterial stiffness. Our observations may be confounded or mediated by unmeasured factors. For example, mineralocorticoids have been implicated in the blood pressure effects seen with THQ subclass CETP inhibitors. We did not have measures of serum aldosterone, plasma electrolytes, or biomarkers of systemic inflammation at baseline examination to assess if the observed association was in any way confounded or mediated by endogenous mineralocorticoid levels or by inflammation. Additionally, the Framingham Offspring cohort is predominantly white, which limits the generalizability of our findings to other ethnicities.

CONCLUSIONS

In our prospective study relating plasma cholesteryl ester transfer protein activity (measured via an in vitro assay using an exogenous substrate) to longitudinal BP change in nonhypertensive participants in a large community-based sample, we observed that plasma CETP activity was not significantly related to changes in SBP or DBP, but lower CETP activity was associated with greater PP change on follow-up. The magnitude of the PP change was insufficient to explain the BP change seen in recent CETP inhibitor torcetrapib trials, supporting the proposition that 'off-target' effects of torcetrapib likely mediated BP increase in those trials. Additional investigations are warranted to corroborate these findings and to explore possible mechanisms that may underlie the observed inverse association of plasma CETP activity and longitudinal changes in PP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of Support: This work was supported through contract N01-HC-25195 and T32 HL007572 (JPZ) from the National Heart Lung and Blood Institute

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Fig 1 a

Fig 1b.

Fig 1c.

Figure 1.

Regression spline curves demonstrating the relations between plasma CETP activity in nanomoles/mL/hr and mmHg change between baseline and follow-up: a) systolic blood pressure, b) diastolic blood pressure, and c) pulse pressure.

Table 1

Baseline characteristics by Plasma CETP activity below versus at or above the median

	Whole sample	Plasma CETP activity	
		<median	≥median
Number of participants	1307	628	679
Women, %	57	57	57
Age, years	48±9	49±9	48±9
Body mass index, kg/m ²	25.9±4.3	25.9±4.3	25.8±4.3
Systolic blood pressure, mm Hg	117±12	117±12	117±12
Diastolic blood pressure, mm Hg	75±8	75±8	75±8
Smoking, %	25	25	25
Diabetes, %	2	2	2
Percent change in weight	3	3	3
Total cholesterol, mg/dl	200±37	198±35	202±39
HDL-C, mg/dl	51±15	52±15	51±14
LDL-C, mg/dl	128±35	125±34	131±35
Lipid lowering drugs, %	1.4	1.8	1
Plasma CETP activity, nmol/mL/hr	1.6±0.99	0.8±0.29	2.3±0.8

Data are means±SD unless indicated.

Table 2

Association of Plasma CETP activity with longitudinal changes in blood pressure

Δ BP measure	Δ Systolic BP, mm Hg [*]		Δ Diastolic BP, mm Hg [*]		Δ Pulse Pressure, mm Hg [*]	
	beta (95% CI)	p	beta (95% CI)	p	beta (95% CI)	p
Plasma CETP activity $\geq$ median (<median as referent)	-0.80 (-2.03, 0.43)	0.2	0.33 (-0.45, 1.12)	0.4	-1.02 (-2.02, -0.02)	0.045
Plasma CETP activity per one standard deviation increment	-0.54 (-1.15, 0.08)	0.09	0.22 (-0.17, 0.61)	0.27	0.02 (-0.71, -1.21, -0.21)	0.005
Plasma CETP activity squared per one standard deviation increment	-0.17 (-1.00, 0.65)	0.7	-0.03 (-0.56, 0.50)	0.9	-0.17 (-0.84, 0.51)	0.6
Plasma CETP activity cubed per one standard deviation increment	0.02 (-0.19, 0.23)	0.9	0.005 (-0.13, 0.14)	0.9	0.02 (-0.14, 0.19)	0.8

 Δ = change.

* models adjust for age, sex, BMI, percent weight gain, HDL cholesterol, baseline blood pressure component.