

Cholesteryl Ester Transfer Protein, Coronary Calcium, and Intima-Media Thickness of the Carotid Artery in Middle-Age Japanese Men

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The relation between cholesteryl ester transfer protein (CETP) levels and atherosclerosis is controversial. We examined whether the serum CETP levels were associated with subclinical atherosclerosis, independent of its most common gene variant, in a sample of Japanese men. A population-based cross-sectional study of 250 Japanese men aged 40 to 49 years was conducted to assess the intima-media thickness of the carotid artery, coronary artery calcium, serum CETP levels, and the CETP D442G gene variant. Compared with the lowest CETP quartile, the multivariate adjusted odds ratio for coronary artery calcium was 0.77 (95% confidence interval 0.18 to 3.36), 0.96 (95% confidence interval 0.27 to 3.40), and 3.49 (95% confidence interval 1.05 to 11.6) with increasing CETP quartiles. The serum CETP quartiles were also positively associated with the intima-media thickness of the carotid artery (adjusted mean 602, 616, 615, and 646 μm for the lowest to top quartile, respectively). The findings remained unchanged after additional adjustment for the CETP D442G gene variant. No significant difference was found in the prevalence of coronary artery calcium or in the mean intima-media thickness of the carotid artery between participants with and without the CETP D442G gene variant. © 2009 Elsevier Inc. All rights reserved. (Am J Cardiol 2009;104:818–822)

The cholesteryl ester transfer protein (CETP) plays a major role in exchanging cholesteryl esters in high-density lipoprotein (HDL) particles and triglycerides (TG) in apolipoprotein B-containing lipoproteins.¹ The purpose of the present study was to examine the relation between the serum CETP levels and subclinical atherosclerosis, such as coronary calcium and the carotid intima-media thickness (IMT), in a Japanese population with much lower prevalence of coronary heart disease (CHD) than that of Western populations.^{2,3} Our a priori hypothesis was that the serum

CETP levels would be positively associated with subclinical atherosclerosis, irrespective of the CETP D442G missense mutation, which is common in the Japanese.⁴ Therefore, we performed a cross-sectional study of Japanese men in a narrow age range who were randomly selected from a surveyed community.

Methods

The participants of the present study were Japanese men from a cross-sectional study comparing subclinical atherosclerosis findings between the United States and Japan.^{5–8} A total of 313 Japanese men aged 40 to 49 years (from Kusatsu City, Shiga, Japan) were randomly selected from resident registration of the city office. The exclusion criteria were (1) clinical cardiovascular disease, (2) type 1 diabetes, (3) cancer, except for previous skin cancer, (4) renal failure, (5) genetic familial hyperlipidemia. Of the 313 participants, 63 were excluded for the following reasons: informed consent for genetic analysis outside of Japan was not obtained ($n = 14$), genotype failure because of technical problems or a lack of blood samples ($n = 46$), and missing information ($n = 3$). Thus, we analyzed the data from 250 participants, all of whom provided informed consent. The institutional review boards of Shiga University of Medical Science and the University of Pittsburgh approved the present study.

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This research was supported by Grants R01 HL68200 and HL071561 from the National Institutes of Health, Bethesda, Maryland; by a Grant-in-Aid for Scientific Research, Grants C18590595 and C20590670, from the Japan Society for the Promotion of Science, Tokyo, Japan; and by a Grant-in-Aid for Scientific Research, Grant A13307016, by the Japanese Ministry of Education, Culture, Sports, Science and Technology, Tokyo, Japan.

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Table 1

Risk characteristics stratified by cholesteryl ester transfer protein quartile in 250 Japanese men aged 40 to 49 years, Kusatsu City, Shiga, Japan, 2002–2004

Cardiovascular Risk Factors	CETP Quartile (mg/L)				p for Trend
	Q1 (≤ 1.9 ; n = 56)	Q2 (2.0–2.1; n = 56)	Q3 (2.2–2.5; n = 73)	Q4 (≥ 2.6 ; n = 65)	
CETP (stratum mean) (mg/L)	1.72 \pm 0.20	2.05 \pm 0.05	2.31 \pm 0.11	2.86 \pm 0.29	
Age (years)	45.1 \pm 2.6	44.3 \pm 2.6	45.8 \pm 2.7	45.0 \pm 2.8	0.47
Body mass index (kg/m ²)	23.5 \pm 3.1	23.6 \pm 3.5	24.4 \pm 2.9	23.7 \pm 3.1	0.49
Waist (cm)	84.8 \pm 8.1	84.7 \pm 9.4	87.1 \pm 7.4	84.8 \pm 8.8	0.27
LDL cholesterol (mmol/L)	2.96 \pm 0.68	2.96 \pm 0.85	3.72 \pm 0.82	3.71 \pm 0.96	<0.01
HDL cholesterol (mmol/L)	1.50 \pm 0.40	1.42 \pm 0.36	1.31 \pm 0.28	1.37 \pm 0.30	<0.01
Triglycerides* (mmol/L)	1.49	1.58	1.61	1.63	0.27
Hypertension	18 (32%)	18 (32%)	22 (30%)	13 (20%)	0.14
Diabetes	4 (7.1%)	2 (3.6%)	4 (5.5%)	5 (7.7%)	0.78
Metabolic syndrome	12 (21%)	12 (21%)	20 (27%)	14 (22%)	0.80
Current smoker	34 (61%)	31 (55%)	35 (48%)	28 (43%)	0.04
Current alcohol drinker	46 (82%)	44 (79%)	45 (62%)	34 (52%)	<0.01
Lipid-lowering medication use	1 (1.8%)	3 (5.4%)	4 (5.5%)	1 (1.5%)	0.93
CETP D442G mutation	11 (20%)	1 (1.8%)	0 (0%)	2 (3.1%)	0.01
Intima-media thickness (μ m)					
Common carotid artery	602 \pm 77	611 \pm 67	624 \pm 85	640 \pm 81	0.05
Average (μ m)	605 \pm 78	603 \pm 54	622 \pm 77	635 \pm 71	0.21
Plaque in carotid artery	2 (3.6%)	0 (0%)	4 (5.5%)	6 (9.2%)	0.06
Coronary artery calcium	5 (8.9%)	4 (7.1%)	8 (11.0%)	14 (21.5%)	0.03

Data are presented as mean \pm SD for continuous variables or numbers (%) for categorical variables.

* Geometric mean.

CETP = cholesteryl ester transfer protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; Q = quartile.

The samples for CETP measurement were shipped on dry ice to 1 laboratory in Japan (SRL, Tokyo, Japan). Serum CETP were measured by an enzyme-linked immunosorbent assay with 2 different monoclonal antibodies.⁹ The inter-assay coefficient of variation was 4.41% and the intra-assay coefficient of variation was 2.57%. Other samples were shipped to the Heinz Laboratory at the University of Pittsburgh (Pittsburgh, Pennsylvania), where the serum total cholesterol, low-density-lipoprotein cholesterol, HDL cholesterol, TG, and glucose were measured. Diabetes was defined as a fasting blood glucose level of ≥ 7.0 mmol/L (≥ 126 mg/dl) or the use of diabetic medications, or both.

Blood pressure was measured using an automated sphygmomanometer (BP-8800, Colin Medical Technology, Komaki, Japan). Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, the use of antihypertensive medications, or any combination of these. The body mass index was calculated as the weight in kilograms divided by the square of the height in meters. The waist circumference was measured at the umbilical level. The metabolic syndrome was defined according to the modified National Cholesterol Education Program-Adult Treatment Panel III criteria.¹⁰ Current smoking and drinking were assessed by a self-administered questionnaire. Current drinkers were defined as those who consumed alcohol ≥ 2 times/wk.

Genotyping was completed using genomic DNA prepared from buffy coats. The CETP D442G missense mutation (rs2303790) was genotyped using the fluorogenic 5'-nuclease TaqMan allelic discrimination assay (Applied Biosystems, Foster City, California). The assays were performed under standard conditions on a 7900HT real-time polymerase chain reaction instrument, with probes and re-

agents purchased from Applied Biosystems (Foster City, California). The allele and genotype counts were in Hardy-Weinberg equilibrium.

Heart scanning was performed using a GE-Imatron C150 EBCT scanner (GE Medical Systems, South San Francisco, California) to obtain 30 to 40 contiguous 3-mm-thick transverse images from the level of the aortic root to the apex of the heart. The images were obtained during a maximal breath hold using electrocardiographic triggering (60% of RR interval) so that each 100 ms exposure was obtained during the same phase of the cardiac cycle. One trained reader at the Cardiovascular Institute, University of Pittsburgh, read the images, using a Digital Imaging and Communications in Medicine workstation and software from AccuImage (AccuImage Diagnostic, San Francisco, California). The software program implements the widely accepted Agatston scoring method.¹¹ The reproducibility of the EBCT scans had an intraclass correlation of 0.98.^{5–8} In the present study, coronary artery calcium (CAC) was defined as absent for a coronary calcium score of < 10 and present for a coronary calcium score of ≥ 10 .

The carotid scanning procedures have been previously described.^{5,8} Before the study began, sonographers received a 3-day training session for carotid scanning provided by the Ultrasound Research Laboratory, University of Pittsburgh. We also applied continuous quality assessment programs developed by the laboratory to ensure the scanning quality.¹² Using these programs, the certified sonographers scanned and the certified reader read the scanned images. A Toshiba 140A scanner equipped with a 7.5-MHz linear array imaging probe was used. The sonographers scanned the right and left common carotid arteries, carotid bulbs, and internal carotid arteries. The trained readers digitized the

Table 2

Age and multivariate-adjusted ORs (95% CIs) for coronary calcification (coronary calcium score ≥ 10) comparing top 3 quartiles and bottom quartile of serum cholesteryl ester transfer protein (CETP) in 250 Japanese men aged 40 to 49 years, Kusatsu City, Shiga, Japan, 2002–2004

Variable	Q1 (≤ 1.9 ; Referent)	Q2 (2.0–2.1)		Q3 (2.2–2.5)		Q4 (> 2.6)		1-mg/L Increase
		OR	95% CI	OR	95% CI	OR	95% CI	
Japanese men (n)	56	56		73		65		
Age-adjusted	1.00	0.90	0.23–3.60	1.09	0.33–3.61	2.89	0.96–8.75	2.57 (1.14–5.79)
Multivariate adjusted								
Model 1*	1.00	0.77	0.18–3.36	0.96	0.27–3.40	3.49	1.05–11.6	3.07 (1.22–7.72)
Model 2 [†]	1.00	0.79	0.18–3.57	1.01	0.26–3.87	3.64	1.03–12.9	3.26 (1.28–8.34)

* Adjusted for age, body mass index, hypertension, diabetes, triglycerides (log-transformed), current smoking, current drinking, and use of lipid-lowering medications.

[†] Further adjusted for CETP D442G mutation.

CI = 95% confidence interval; OR = odds ratio; Q = quartile.

Table 3

Age and multivariate-adjusted associations of serum cholesteryl ester transfer protein (CETP) levels with intima-media thickness of common carotid artery in 250 Japanese men aged 40 to 49 years, Kusatsu City, Shiga, Japan, 2002–2004

Variable	CETP Quartiles				p for Trend
	Q1 (≤ 1.9 ; n = 56)	Q2 (2.0–2.1; n = 56)	Q3 (2.2–2.5; n = 73)	Q4 (≥ 2.6 ; n = 65)	
Age adjusted	602 (10)	616 (10)	619 (9)	641 (9)	0.05
Multivariate adjusted					
Model 1*	602 (10)	616 (10)	615 (9)	646 (9)	0.01
Model 2 [†]	600 (10)	616 (10)	617 (9)	646 (9)	0.01

Data in parenthesis are standard errors.

* Adjusted for age, body mass index, hypertension, diabetes, triglycerides (log-transformed), current smoking, current drinking, and lipid-lowering medication use.

[†] Further adjusted for CETP D442G mutation.

CETP = cholesteryl ester transfer protein; Q = quartile.

best image for scoring and then measured the average IMT across 1-cm segments of the near and far walls of the common carotid arteries and the far wall of the carotid bulb and internal carotid arteries on both sides. The readers were unaware of the participant's characteristics and the study center. The correlation coefficient of the IMT between the sonographers and between the readers was 0.96 and 0.99, respectively.¹²

The Statistical Package for Social Sciences, version 14.0J (SPSS Japan, Tokyo, Japan) was used for statistical analysis. For a comparison of the risk factors across the CETP quartiles, tests for trend were done using generalized linear models and chi-square tests. Fisher's exact test was used to compare frequencies for medication. Logistic regression analyses were used to examine the contribution of serum CETP to CAC with adjustment for age, and further adjustment for body mass index, hypertension, diabetes, TG (log-transformed), current smoking, current drinking, and using lipid lowering medication (model 1) with additional adjustment for CETP D442G variant (model 2). General linear model analyses were used to examine the contribution of serum CETP to IMT. All probability values were 2-tailed, and all confidence intervals were estimated at the 95% level.

Results

The range of serum CETP was 1.1 to 4.2 mg/L. The mean value of serum CETP was 2.26 ± 0.45 . Of the 250

participants, 14 were heterozygous for the CETP D442G missense variant (5.6%) and no homozygotes. The mean CETP level was significantly lower in those with participants than in those without the D442G variant: 1.79 ± 0.56 and 2.29 ± 0.43 mg/L, respectively ($p < 0.01$).

Table 1 lists the cardiovascular risk characteristics for the participants in each CETP quartile. Among the characteristics, the LDL cholesterol levels increased with an increasing concentration of CETP and the HDL cholesterol levels decreased with increasing CETP. The prevalence of the metabolic syndrome was almost similar in each CETP quartile. The mean IMT of the common carotid arteries was greater in the higher CETP quartiles. The prevalence of CAC showed a positive relation with the CETP quartile. The prevalence of the D442G missense variant was greatest in the lowest CETP quartile.

Table 2 lists the age-adjusted and multivariate-adjusted odd ratios for CAC in which comparisons were made between the top 3 CETP quartiles and the bottom quartile as a reference. The odds ratio for CAC in the highest CETP quartile was about 3 to 4 times greater than that in the bottom quartiles in all models.

Table 3 lists the age-adjusted and multivariate-adjusted IMT of the common carotid arteries among the CETP quartiles. In all models, the IMT of the common carotid arteries was positively associated with increasing serum CETP. Similar patterns were also observed when we used the average IMT of the whole or part of the carotid artery

(common carotid arteries or internal carotid artery and bulb), or when we excluded participants with plaque (data not shown).

Similar results were observed among those with normal (<1.7 mmol/L, 150 mg/dl, n = 148) and high TG levels (\geq 1.7 mmol/L, n = 102). The odds ratio for CAC with a 1-mg/L increase of serum CETP was 2.35 (95% confidence interval 0.52 to 10.6) in the normal TG group and 4.05 (95% confidence interval 1.05 to 15.7) in the high TG group (model 2). The serum CETP quartiles were also positively associated with the IMT of the common carotid arteries in both the normal TG group (model 2, adjusted mean 589, 606, 624, and 634 μ m, p = 0.09) and the high TG group (model 2, adjusted mean 603, 636, 615, and 659 μ m, p = 0.04).

No significant difference was found in the prevalence of CAC between participants with and without the CETP D442G variant (14.3% and 12.3%, respectively, p = 0.69). The age-adjusted IMT of the common carotid arteries was also similar in participants with and without the D442G variant (619 μ m [SE 21] and 620 μ m [SE 5], respectively; p = 0.94).

Discussion

This is the first community-based study to investigate the relation between serum CETP levels and subclinical atherosclerosis in Japan. The serum CETP levels in middle-age Japanese men were positively associated with CAC and IMT, independent of the presence of the CETP D442G missense variant. Furthermore, the increase in CAC prevalence and IMT seemed to be evident between the third and fourth (highest) quartile, at a CETP level of 2.6 mg/L.

The relation between the blood CETP levels and atherosclerosis is controversial. CETP transfers cholesteryl esters from antiatherogenic HDL cholesterol classes toward proatherogenic lipoproteins of lower density classes in exchange for TG.^{1,13} Thus, a high transfer of cholesteryl esters from HDL to apolipoprotein B-containing lipoproteins might be involved in the development of atherosclerosis. Alternatively, CETP could inhibit atherosclerosis by accelerating the rate of reverse cholesterol transport, by which excess cholesterol in peripheral tissues is finally transported to the liver by way of the low-density lipoprotein receptor.^{13,14}

Plasma CETP mass was associated with incident CHD in healthy participants in a United Kingdom community-based population, especially with high serum TG.¹⁵ Another study showed a positive correlation between the plasma CETP concentration and carotid artery IMT.¹⁶ CETP concentrations were significantly greater in 117 survivors of myocardial infarction and 110 patients with stroke compared to 335 healthy controls in Chinese subjects.¹⁷ In middle-age men with CHD, high CETP levels were associated with faster progression of coronary atherosclerosis.¹⁸ However, Colhoun et al¹⁹ did not find any support for the hypothesis that increased plasma CETP activity levels were atherogenic in type 1 diabetic and nondiabetic controls using CAC as a measure of coronary atherosclerosis in a United Kingdom sample. de Vries et al²⁰ also suggested that no independent

relation existed between the plasma CETP mass and IMT in type 2 diabetic and nondiabetic controls in a Dutch sample.

A recent clinical trial of the CETP inhibitor torcetrapib combined with atorvastatin was terminated because of excess deaths in the intervention group.²¹ Torcetrapib treatment produced a substantial increase in HDL cholesterol and decrease in LDL cholesterol; however, it was also associated with an increase in blood pressure. Similar results were observed in other clinical trials targeting coronary atherosclerosis measured by ultrasonography²² and increases in the maximum IMT.^{23,24} No epidemiologic study has indicated a blood pressure increase in participants with genetic CETP mutations.^{4,25–27} Furthermore, a recent analysis showed that regression of coronary atherosclerosis by torcetrapib was at least observed in the top quartile of HDL cholesterol change.²⁸ We believe more evidence from observational epidemiologic studies might help to better understand these results.

In the present study, we focused on the common CETP D442G gene variant. In epidemiologic studies of the CETP gene variants in Japanese and Japanese Americans, a relation between the CETP genotype, mainly the D442G gene variant, and CHD was not consistently observed.^{4,25–27} Only 1 prospective study²⁵ showed a low risk of CHD in participants with high HDL cholesterol (\geq 60 mg/dl) in Japanese descendants in Hawaii, irrespective of their CETP genotype. The results of this prospective study were consistent with ours.

The present study had some limitations. The study was cross-sectional and, as such, could not prove a causal relation. Second, the blood CETP concentration is not always consistent with CETP activity, because a positive interaction exists between the plasma CETP concentration and TG on plasma cholesteryl ester transport, which underscores the contribution of the plasma CETP concentration.¹ However, the plasma CETP level itself also affects cholesteryl ester transport,²⁰ and some studies have indicated that the CETP concentration is strongly correlated with CETP activity.²⁹ We observed similar results in those with normal TG and high TG in the present study. Third, we did not test for other CETP gene variants. Fourth, with a relatively small sample size, it was difficult to compare the men with and without the D442G variant. Fifth, residual confounding factors might have been present such as socioenvironmental and behavioral factors. Finally, a study confined to men aged 40 to 49 might limit the generalization of the results to older men and women.

1. Tall AR. Plasma cholesteryl ester transfer protein. *J Lipid Res* 1993; 34:1255–1274.
2. Rumana N, Kita Y, Turin TC, Murakami Y, Sugihara H, Morita Y, Tomioka N, Okayama A, Nakamura Y, Ueshima H. Seasonal pattern of incidence and case fatality of acute myocardial infarction in a Japanese population (from the Takashima AMI Registry, 1988–2003). *Am J Cardiol* 2008;102:1307–1311.
3. Okamura T, Kokubo Y, Watanabe M, Higashiyama A, Miyamoto Y, Yoshimasa Y, Okayama A. Low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol and the incidence of cardiovascular disease in an urban Japanese cohort study: the Suita study. *Atherosclerosis* 2009;203:587–592.
4. Inazu A, Jiang XC, Haraki T, Yagi K, Kamon N, Koizumi J, Mabuchi H, Takeda R, Takata K, Moriyama Y, Doi M. Genetic cholesteryl ester transfer protein deficiency caused by two prevalent mutations as a

- major determinant of increased levels of high density lipoprotein cholesterol. *J Clin Invest* 1994;94:1872–1882.
5. Sekikawa A, Ueshima H, Kadowaki T, El-Saed A, Okamura T, Takamiya T, Kashiwagi A, Edmundowicz D, Murata K, Sutton-Tyrrell K, Maegawa H, Evans RW, Kita Y, Kuller LH. Less subclinical atherosclerosis in Japanese men in Japan than in white men in the United States in the post-World War II birth cohort. *Am J Epidemiol* 2007; 165:617–624.
 6. Okamura T, Kadowaki T, Sekikawa A, Murata K, Miyamatsu N, Nakamura Y, El-Saed A, Kashiwagi A, Maegawa H, Nishio Y, Takamiya T, Kanda H, Mitsunami K, Kita Y, Edmundowicz D, Tamaki S, Tsujita Y, Kuller LH, Ueshima H. Alcohol consumption and coronary artery calcium in middle-aged Japanese men. *Am J Cardiol* 2006;98: 141–144.
 7. Nakamura Y, Ueno Y, Tamaki S, Kadowaki T, Okamura T, Kita Y, Miyamatsu N, Sekikawa A, Takamiya T, El-Saed A, Sutton-Tyrrell K, Ueshima H. Fish consumption and early atherosclerosis in middle-aged men. *Metabolism* 2007;56:1060–1064.
 8. Sekikawa A, Curb JD, Ueshima H, El-Saed A, Kadowaki T, Abbott RD, Evans RW, Rodriguez BL, Okamura T, Sutton-Tyrrell K, Nakamura Y, Masaki K, Edmundowicz D, Kashiwagi A, Willcox BJ, Takamiya T, Mitsunami K, Seto TB, Murata K, White RL, Kuller LH; ERA JUMP (Electron-Beam Tomography, Risk Factor Assessment Among Japanese and U.S. Men in the Post-World War II Birth Cohort) Study Group. Marine-derived n-3 fatty acids and atherosclerosis in Japanese, Japanese Americans, and whites: a cross-sectional study. *J Am Coll Cardiol* 2008;52:417–424.
 9. Sasai K, Okumura-Noji K, Hibino T, Ikeuchi R, Sakuma N, Fujinami T, Yokoyama S. Human cholesteryl ester transfer protein measured by enzyme-linked immunosorbent assay with two monoclonal antibodies against rabbit cholesteryl ester transfer protein: plasma cholesteryl ester transfer protein and lipoproteins among Japanese hypercholesterolemic patients. *Clin Chem* 1998;44:1466–1473.
 10. Kokubo Y, Okamura T, Yoshimasa Y, Miyamoto Y, Kawanishi K, Kotani Y, Okayama A, Tomoike H. Impact of metabolic syndrome components on the incidence of cardiovascular disease in a general urban Japanese population: the Suita study. *Hypertens Res* 2008;31: 2027–2035.
 11. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;15:827–832.
 12. Thompson T, Sutton-Tyrrell K, Wildman R. Continuous quality assessment programs can improve carotid duplex scan quality. *J Vasc Technol* 2001;25:33–39.
 13. Barter PJ, Brewer HB Jr, Chapman MJ, Hennekens CH, Rader DJ, Tall AR. Cholesteryl ester transfer protein: a novel target for raising HDL and inhibiting atherosclerosis. *Arterioscler Thromb Vasc Biol* 2003; 23:160–167.
 14. Hirano K, Yamashita S, Nakajima N, Arai T, Maruyama T, Yoshida Y, Ishigami M, Sakai N, Kameda-Takemura K, Matsuzawa Y. Genetic cholesteryl ester transfer protein deficiency is extremely frequent in the Omagari area of Japan: marked hyperalphalipoproteinemia caused by CETP gene mutation is not associated with longevity. *Arterioscler Thromb Vasc Biol* 1997;17:1053–1059.
 15. Boekholdt SM, Kuivenhoven JA, Wareham NJ, Peters RJ, Jukema JW, Luben R, Bingham SA, Day NE, Kastelein JJ, Khaw KT. Plasma levels of cholesteryl ester transfer protein and the risk of future coronary artery disease in apparently healthy men and women: the prospective EPIC (European Prospective Investigation into Cancer and nutrition)-Norfolk population study. *Circulation* 2004;110:1418–1423.
 16. Föger B, Luef G, Ritsch A, Schmidauer C, Doblinger A, Lechleitner M, Aichner F, Patsch JR. Relationship of high-density lipoprotein subfractions and cholesteryl ester transfer protein in plasma to carotid artery wall thickness. *J Mol Med* 1995;73:369–372.
 17. Zhuang Y, Wang J, Qiang H, Li Y, Lui X, Li L, Chen G. Serum cholesteryl ester transfer protein concentrations in healthy Chinese subjects and cardio-cerebrovascular disease patients. *Clinica Chim Acta* 2001;305:19–25.
 18. Klerkx 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.
 19. Colhoun HM, Scheek LM, Rubens MB, Van Gent T, Underwood SR, Fuller JH, Van Tol A. Lipid transfer protein activities in type 1 diabetic patients without renal failure and nondiabetic control subjects and their association with coronary artery calcification. *Diabetes* 2001;50:652–659.
 20. de Vries R, Perton FG, Dallinga-Thie GM, van Roon AM, Wolffenbuttel BH, van Tol A, Dullaart RP. Plasma cholesteryl ester transfer is a determinant of intima-media thickness in type 2 diabetic and non-diabetic subjects: role of CETP and triglycerides. *Diabetes* 2005;54: 3554–2559.
 21. 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.
 22. Nissen SE, Tardif JC, Nicholls SJ, Revkin JH, Shear CL, Duggan WT, Ruzyllo W, Bachinsky WB, Lasala GP, Tuzcu EM; ILLUSTRATE Investigators. Effect of torcetrapib on the progression of coronary atherosclerosis. *N Engl J Med* 2007;356:1304–1316.
 23. Bots ML, Visseren FL, Evans GW, Riley WA, Revkin JH, Tegeler CH, Shear CL, Duggan WT, Vicari RM, Grobbee DE, Kastelein JJ; RADIANCE 2 Investigators. Torcetrapib and carotid intima-media thickness in mixed dyslipidaemia (RADIANCE 2 study): a randomised, double-blind trial. *Lancet* 2007;370:153–160.
 24. Vergeer M, Bots ML, van Leuven SI, Basart DC, Sijbrands EJ, Evans GW, Grobbee DE, Visseren FL, Stalenhoef AF, Stroes ES, Kastelein JJ. Cholesteryl ester transfer protein inhibitor torcetrapib and off-target toxicity: a pooled analysis of the rating atherosclerotic disease change by imaging with a new CETP inhibitor (RADIANCE) trials. *Circulation* 2008;118:2515–2522.
 25. Curb JD, Abbott RD, Rodriguez BL, Masaki K, Chen R, Sharp DS, Tall AR. A prospective study of HDL-C and cholesteryl ester transfer protein gene mutations and the risk of coronary heart disease in the elderly. *J Lipid Res* 2004;45:948–953.
 26. Hirano K, Yamashita S, Nakajima N, Arai T, Maruyama T, Yoshida Y, Ishigami M, Sakai N, Kameda-Takemura K, Matsuzawa Y. Genetic cholesteryl ester transfer protein deficiency is extremely frequent in the Omagari area of Japan: marked hyperalphalipoproteinemia caused by CETP gene mutation is not associated with longevity. *Arterioscler Thromb Vasc Biol* 1997;17:1053–1059.
 27. Moriyama Y, Okamura T, Inazu A, Doi M, Iso H, Mouri Y, Ishikawa Y, Suzuki H, Iida M, Koizumi J, Mabuchi H, Komachi Y. A low prevalence of coronary heart disease among subjects with increased high-density lipoprotein cholesterol levels, including those with plasma cholesteryl ester transfer protein deficiency. *Prev Med* 1998; 27(5 Pt 1):659–667.
 28. Nicholls SJ, Tuzcu EM, Brennan DM, Tardif JC, Nissen SE. Cholesteryl ester transfer protein inhibition, high-density lipoprotein raising, and progression of coronary atherosclerosis: insights from ILLUSTRATE (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation). *Circulation* 2008;118:2506–2514.
 29. 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.