Common Cholesteryl Ester Transfer Protein Gene Polymorphisms and the Effect of Atorvastatin Therapy in Type 2 Diabetes

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OBJECTIVE — The cholesteryl ester transfer protein (CETP) plays a key role in the remodeling of triglyceride (TG)-rich and HDL particles. Sequence variations in the CETP gene may interfere with the effect of lipid-lowering treatment in type 2 diabetes.

RESEARCH DESIGN AND METHODS — We performed a 30-week randomized double-blind placebo-controlled trial with atorvastatin 10 mg (A10) and 80 mg (A80) in 217 unrelated patients with diabetes.

RESULTS — CETP TaqIB and A-629C polymorphisms were tightly concordant (P < 0.001). At baseline, B1B1 carriers had lower plasma HDL cholesterol (0.99 ± 0.2 vs. 1.11 ± 0.2 mmol/l, P < 0.05), higher CETP mass (2.62 ± 0.8 vs. 2.05 ± 0.4 mg/l, P < 0.001), and slightly increased, though not significant, plasma TGs (2.7 ± 1.05 vs. 2.47 ± 0.86, P = 0.34) compared with B2B2 carriers. Atorvastatin treatment significantly reduced CETP mass dose-dependently by 18% (A10) and 29% (A80); both vs. placebo (P < 0.001). CETP mass and activity were strongly correlated (r = 0.89, P < 0.0001). CETP TaqIB polymorphism appeared to modify the effect of atorvastatin on HDL cholesterol elevation (B1B1 7.2%, B1B2 6.1%, B2B2 21.9%; P < 0.05), TG reduction (B1B1 39.7%, B1B2 38.4%, B2B2 18.4%; P < 0.05), and CETP mass reduction (B1B1 32.1%, B1B2 29.6%, B2B2 21.9%; P = 0.27, NS). Similar results were obtained for the A-629C polymorphism.

CONCLUSIONS — In conclusion, the B1B1/CC carriers of the CETP polymorphisms have a more atherogenic lipid profile, including low HDL, and they respond better to statin therapy. These results favor the hypothesis that CETP polymorphisms modify the effect of statin treatment and may help to identify patients who will benefit most from statin therapy.

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Cholesteryl ester transfer protein (CETP) plays a key role in lipoprotein metabolism, promoting the exchange of triglycerides (TGs) and cholesteryl esters (CEs) between lipoprotein particles, resulting in both a net transfer of CEs from HDL cholesterol to apolipoprotein B (apoB)-containing lipoproteins and a subsequent uptake of cholesterol by hepatocytes (1). This reverse cholesterol transport is considered an antiatherogenic phenomenon. However, in the presence of elevated TG concentrations, an increased CE/TG transfer may induce the formation of smaller-sized TG-rich particles and decreased HDL cholesterol levels (2,3), providing a proatherogenic property of the action of CETP (4,5). The lipoprotein profile in type 2 diabetes is characterized by the presence of increased TG-rich lipoprotein remnants, small dense LDL particles, and decreased levels of HDL cholesterol. These conditions favor an increased transfer of CE from HDL (6–8). However, reports on CETP mass and activity in type 2 diabetes appear to be conflicting (9–11). These differences may be explained by differences in baseline plasma TG concentrations in the study populations (6,12).

Genetic heterogeneity at the CETP gene locus is associated with plasma CETP activity and HDL cholesterol levels. The most frequently studied polymorphism is a silent base change affecting the 277th nucleotide in the first intron of the gene, resulting in the disruption of a restriction site for the enzyme TaqI. The B2 allele (absence of the TaqI restriction site) has been associated with normolipidemic subjects with increased HDL cholesterol levels and decreased CETP activity and mass. An association between the TaqIB genotype and progression of coronary heart disease (CHD) after pravastatin therapy was found in men with angiographically documented coronary atherosclerosis (13). This CETP polymorphism may thus affect the response to cholesterol-lowering treatment. In the Framingham cohort, men with the B2 allele had a lower CHD risk (14). In line with these results, it has been observed that male patients with type 2 diabetes and the CETP B2B2 genotype may have a decreased risk for coronary artery disease (CAD) pro-

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Abbreviations: A10, atorvastatin 10 mg; A80, atorvastatin 80 mg; apo, apolipoprotein; CAD, coronary artery disease; CE, cholesteryl ester; CETP, CE transfer protein; CHD, coronary heart disease; FFA, free fatty acid; Lp(a), lipoprotein A-I; SREBP-1, sterol regulatory element binding protein-1; TC, total cholesterol; TG, triglyceride.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
gression (11). Recently, a new polymorphism was described, located at −629 (A-629C) in the promoter region of the CETP gene. The A allele was associated with 25% lower transcription activity in vitro (15), whereas in vivo, individuals with the A-allele had lower plasma CETP mass and increased HDL cholesterol levels. This polymorphism appeared in linkage disequilibrium with the CETP TaqIB polymorphism in nondiabetic European Caucasian men with cardiovascular disease (15,16). Additional less-frequently occurring CETP gene polymorphisms have been extensively studied as well (16). The latter study nicely illustrates the complexity of gene-phenotype interactions, and it illustrates the importance of strong additional influences of environmental factors on plasma lipid traits.

The aim of the present study was to investigate the role of the frequently occurring CETP TaqIB and A-629C gene polymorphisms on the efficacy of atorvasstatin treatment in patients with type 2 diabetes taking part in the Diabetes Atorvastatin Lipid Intervention (DALI) study. We hypothesize that the highly concordant genetic variation in the CETP gene promoter region at −629 could explain the observed associations of the TaqIB variant with respect to the lipid-lowering effect of statin treatment in type 2 diabetes.

**Research Design and Methods** — This study comprised all patients enrolled in the DALI study. DALI is a double-blind, randomized, placebo controlled, multicenter study evaluating the effect of atorvastatin 10 mg (A10) vs. 80 mg (A80) on lipid metabolism, endothelial function, coagulation, and inflammatory factors in unrelated men and women with type 2 diabetes. The protocol and eligibility criteria have been described in detail elsewhere (17). Briefly, men and women aged 45–75 years with a duration of diabetes of at least 1 year and HbA1c ≤10% were eligible. The diagnosis type 2 diabetes was defined according to the American Diabetes Association classification (18). Lipid inclusion criteria were total cholesterol (TC) between 4.0 and 8.0 mmol/L and fasting TGs between 1.5 and 6.0 mmol/L. Patients were recruited in Leiden, Rotterdam, and Utrecht, the Netherlands. Of the study population, 84% was of Caucasian origin. The study protocol was approved by the ethical committees of the participating centers, and written informed consent was obtained from all subjects.

**Laboratory Measurements** — After an overnight fast for a minimum of 12 h, blood was drawn for analysis of lipid profiles. Plasma was prepared by immediate centrifugation. Lipids and apos were quantified as extensively described elsewhere (17). Plasma CETP mass was analyzed as described (19). We used a two-antibody sandwich immunoassay with a combination of the monoclonal antibodies TP1 and TP2 as coating and TP20 as secondary antibody, labeled with digoxigenine. The intra- and interassay coefficients of variance were 7.8 and 6.0%, respectively. The CETP control samples were validated using a radioactive immunoassay (kindly performed by Dr. R.M. McPherson, Montreal, Canada). Plasma CETP activity was measured as described elsewhere (20). CETP activity is expressed relative to the activity in a reference pool plasma (%).

**DNA Analysis** — Blood for DNA analysis was collected at baseline, and DNA was isolated according to standard procedures (21). For the CETP TaqIB polymorphism, the following primers were used: 5′-ACATAATTA AGCAATTATCCAGAT-3′ (sense), 5′CA CTGTGCAACCCATACCTGACT-3′ (antisense). The PCR was performed in 100 μl containing 500 ng genomic DNA, 0.1 mmol/L of each dNTP, 2.0 units of Expand high fidelity Taq polymerase (Boehringer Mannheim, Mannheim, Germany), 10% reaction buffer, and 100 pmol of each primer. The PCR conditions were as follows: denaturation for 5 min at 94°C, 30 cycles of denaturation for 1 min at 94°C, annealing for 1 min at 50°C, extension for 1 min at 72°C, and a final extension of 10 min at 72°C. The final product was 1,420 bp. After digestion with TaqI (10 units) for 2 h at 65°C, the final product was resolved on 1% agarose gel. After restriction, two fragments (670 and 750 bp) were found. This genotype was referred to as B1B1. For the A-629C polymorphism, the following primers were used: 5′-TCTCTTGCC CCCCCGTGTAAG-3′ (sense) and 5′- GAAAAGCTCCCTATGTAGACTT TCCCTGATATGCATAACCACT GG-3′ (antisense). The PCR was performed in 25 μl containing 100 ng DNA, 2.5 μmol/L of each primer, 0.4 mmol/L of each dNTP, 0.5 units Supertaq (Amersham), and 10% reaction buffer. The PCR conditions were as follows: denaturation for 5 min at 94°C followed by 30 cycles of denaturation for 1 min at 94°C, annealing for 1 min at 62°C, and extension for 30 s at 72°C. The final product was 232 bp. After restriction with Van91I and analysis on 4% Metaphor agarose (Biozyme), two fragments were resolved from 47 and 175 bp. This genotype was referred to as AA.

**Statistical Analysis** — All data were analyzed by intention-to-treat. Mean differences between the study groups (either treatment or genotype groups) were analyzed using ANCOVA, adjusted for baseline levels and study location. Additional adjustments for potential confounders (e.g., smoking, alcohol use, and sex) were performed by including these as covariates. When logarithmic transformation was applied to parameters with skewed distributions, similar results were obtained. Additional explanatory analyses were performed by including interaction terms into the model. Within each of the treatment groups, the assumption of Hardy-Weinberg equilibrium was tested by means of gene counting and χ² analyses. Linkage disequilibrium was calculated using the programs EH and Arlequin. Pearson correlation coefficients were calculated to study associations between plasma CETP mass and lipid variables at baseline. Spearman’s correlation coefficients were calculated to study associations between plasma CETP mass and CETP polymorphisms. All analyses were performed using SPSS software version 9.0 for Windows.

**Results**

**Frequencies of the CETP TaqIB and A-629C Polymorphism** — From 212 patients, DNA was analyzed for CETP TaqIB polymorphism, and 215 samples were available for analysis of A-629C polymorphism. The allele frequencies for the TaqIB and A-629C polymorphism in the total cohort was 0.571 for the B1 allele and 0.429 for the A allele. These frequencies were similar among the three treatment groups. The observed genotype frequencies were in Hardy-Weinberg equilibrium. Both polymorphisms were in tight but not complete
linkage disequilibrium ($D = 0.21287; D' = 0.9661$). The majority of the carriers of the B1B1 genotype were carriers of the CC genotype (Table 1). Because 16% of the patients were of non-Caucasian origin, we performed additional analyses for Caucasian patients only and revealed similar results. The other groups were not analyzed separately because of the small numbers.

**Baseline characteristics according to genotype**

When the patients were classified according to their TaqIB or A-629C genotype, no statistically significant differences between groups at baseline were found with respect to patient characteristics and diabetes-related variables (Table 2). However, patients with the B1B1 genotype had a more severe atherogenic lipoprotein profile (Table 2). B1B1 carriers had significantly decreased HDL cholesterol levels $(0.99 ± 0.2$ vs. $1.11 ± 0.2$ mmol/l, $P < 0.01$ vs. B2B2). This was apparent in both men and women. B1B1 carriers had significantly increased plasma CETP mass $(2.62 ± 0.81$ vs. $2.05 ± 0.40$ mg/l, $P < 0.001$ vs. B2B2). Plasma TG levels were higher in B1B1 carriers, although this difference did not reach the level of statistical significance. Similarly, carriers with the B2B2 genotype had significantly lower plasma CETP mass than B2B2 carriers $(2.51 ± 0.20$ mg/l, $P < 0.001$). No differences were found in TC, LDL cholesterol, free fatty acid (FFA), apoB, and lipoprotein A-I (LpA-I) concentrations. Similar observations were found with stratification for the A-629C polymorphism (Table 2).

Plasma CETP mass was associated with both the A-629C (allele C present: $r = 0.355, P < 0.001$) and CETP TaqIB polymorphisms (allele B1 present: $r = 0.326, P < 0.001$, TC ($r = 0.209, P < 0.01$), apoB ($r = 0.216, P < 0.01$), LDL cholesterol ($r = 0.174, P < 0.05$), HDL cholesterol ($r = -0.184, P < 0.01$), and

### Table 1—Genotype sharing of CETP TaqIB and A-629C polymorphisms in type 2 diabetes

<table>
<thead>
<tr>
<th>CETP TaqIB</th>
<th>A-629A</th>
<th>A-629C</th>
<th>C-629C</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1B1</td>
<td>1</td>
<td>19</td>
<td>52</td>
</tr>
<tr>
<td>B1B2</td>
<td>10</td>
<td>85</td>
<td>2</td>
</tr>
<tr>
<td>B2B2</td>
<td>39</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are n.
TG (r = 0.163, P < 0.05) but not with FFA and LpA-I, thereby illustrating the fact that genetic polymorphisms are not the only determinant for plasma CETP mass levels.

Effect of atorvastatin treatment

The baseline characteristics of the DALI study population and the effects of A10 and A80 on the main lipid parameters have been described extensively elsewhere (17). In short, administration of A10 or A80 resulted in a 25 and 35% decrease, respectively, in plasma TG, whereas plasma LDL cholesterol decreased with 40 and 52%, respectively (Table 3). After 10 weeks, A10 and A80 significantly lowered plasma CETP mass when compared with placebo (P < 0.001) (Fig. 1). This effect on CETP mass was dose-dependent (18% after A10 vs. 29% after A80 treatment, P < 0.001; A10 vs. A80, P < 0.001). CETP activity was analyzed in a subgroup. In this randomly selected subset, plasma CETP activity was analyzed before and after treatment with atorvastatin. Both at baseline and after treatment, plasma CETP mass was highly significantly correlated with CETP activity (baseline r = 0.685 P < 0.001, after treatment r = 0.854; P < 0.0001) (Fig. 2).

Effect of atorvastatin according to genotype

CETP TaqIB polymorphism appeared to modulate the effect of atorvastatin on plasma HDL cholesterol (Fig. 3). In carriers with the B1B1 genotype, HDL cholesterol levels increased 8.4% after A10 and 7.2% after A80, whereas in B2B2 carriers, atorvastatin had no effect on HDL cholesterol (allele B1 present versus allele B1 absent, P < 0.05). These results were similar in the CETP A-629C polymorphism only after adjustment for alcohol and smoking. Interaction between the CETP TaqIB polymorphism and the TG-lowering effect of atorvastatin was borderline significant (β = −0.812, P = 0.08) (Fig. 3). The decrease in TGs after atorvastatin was more pronounced in the B1B1 carriers than in the B2B2 carriers (−40% [A80] and −28% [A10] for B1B1 versus −18% [A80] and −22% [A10] for B2B2). Adjustment for smoking and alcohol use did not change the effects on TGs. Stratification of the data according to A-629C polymorphism produced similar results in A80 only. The lowering effect of atorvastatin on plasma CETP mass was only partly explained by CETP gene variation, and it was most pronounced in the A80 treatment group (Fig. 3). Patients with the B1B1 or CC genotype had the largest dose-dependent plasma CETP mass reduction. Adjustment for potential confounders such as smoking and alcohol consumption did not affect the results. The effect of atorvastatin on TC and LDL cholesterol was independent of the presence of the CETP TaqIB and A-629C polymorphisms (all P > 0.5).

Table 3—Plasma lipid variables in type 2 diabetes after 30 weeks’ statin treatment

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>10 mg Atorva</th>
<th>80 mg Atorva</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>6.0 ± 0.1</td>
<td>5.9 ± 0.1</td>
<td>6.0 ± 0.1</td>
</tr>
<tr>
<td>Week 30</td>
<td>6.0 ± 0.1</td>
<td>4.1 ± 0.1*</td>
<td>3.6 ± 0.1*</td>
</tr>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>3.8 ± 0.1</td>
<td>3.7 ± 0.1</td>
<td>3.7 ± 0.1</td>
</tr>
<tr>
<td>Week 30</td>
<td>3.6 ± 0.1</td>
<td>2.2 ± 0.1*</td>
<td>1.7 ± 0.1*</td>
</tr>
<tr>
<td>HDL-C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>1.05 ± 0.02</td>
<td>1.05 ± 0.03</td>
<td>1.03 ± 0.03</td>
</tr>
<tr>
<td>Week 30</td>
<td>1.04 ± 0.03</td>
<td>1.10 ± 0.04</td>
<td>1.09 ± 0.04</td>
</tr>
<tr>
<td>Triglycerides</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>2.62 ± 0.11</td>
<td>2.51 ± 0.10</td>
<td>2.85 ± 0.13</td>
</tr>
<tr>
<td>Week 30</td>
<td>2.88 ± 0.22</td>
<td>1.84 ± 0.10*</td>
<td>1.78 ± 0.16*</td>
</tr>
</tbody>
</table>

Data are means ± SE. All lipid parameters are expressed as mmol/l. *P < 0.001, test for differences among the three groups, adjusted for baseline value and study location. †For extended details see reference (17).
candidates to explain the observed associations.

Carriers with the B1B1 and the CC genotype have atherogenic diabetic dyslipidemia, whereas the B2B2 variant carriers exhibit a milder form of dyslipidemia. B1B1 carriers have increased plasma CETP mass and activity as well as decreased plasma HDL cholesterol and apoA-I concentrations compared with heterozygous (B1B2 or AC) and homozygous (B2B2 or AA) carriers of the mutant allele. In our study, the effect of CETP polymorphisms on CETP mass and HDL cholesterol levels was independent of sex, which is in agreement with results in the Framingham study. However, two other reports were published showing only an effect of TaqIB in a Finnish population cohort in women (23) or in men with type 2 diabetes (11). In the Framingham cohort, the association between CETP gene polymorphism and HDL cholesterol was found in both men and women, but men with the B2 allele only show a protective effect on CHD (14). Additional statistical analysis revealed that the concentration of plasma CETP mass is dependent not only on the presence of genetic variation in the CETP gene but also on the concentrations of plasma TC, apoB, LDL cholesterol, HDL cholesterol, and TGs. Genetic variation in the CETP gene will thus explain only part of the variation observed in plasma CETP levels (13). The mechanism behind the observed associations is still not understood. Because the TaqIB variant is located in intron 1 of the CETP gene, it is unlikely that this polymorphism constitutes a functional mutation. Instead, the observed associations are likely to be explained by a newly described functional genetic variation in the promoter region of the CETP gene (15), A-629C, which is in strong linkage disequilibrium with the TaqIB polymorphism. In in vitro transfection studies, it was demonstrated that the presence of the A allele resulted in a decreased (25%) transcriptional activity of the CETP promoter by disrupting a possible consensus

Figure 2—Correlation between CETP mass and CETP activity at baseline (A) and after treatment (B). Correlations were calculated as described.
sequence site for Sp1 and Sp3 transcription factors. Furthermore, it has been shown that plasma CETP mass is independently determined by both the TaqIB/A-629C polymorphisms and the C405/G524T polymorphisms in the CETP gene (16). The latter polymorphisms could not be analyzed in our cohort because of the lower genotype frequency. Furthermore, transcriptional regulation of CETP synthesis occurs and may influence the homeostasis of plasma CETP (24,25). It is therefore not surprising that genetic variation in the CETP gene does not completely explain the variability in plasma CETP mass.

The TaqIB and the A-629C CETP polymorphisms appeared to modulate the effect of atorvastatin on plasma lipid variables (Fig. 2). B1B1 and/or the CC carriers, with higher baseline CETP mass and a more atherogenic lipoprotein profile (lower HDL cholesterol and increased plasma TGs), appear to benefit most from lipid-lowering therapy. Others observed higher baseline CAD risk in B1B1 carriers and diminished progression of coronary atherosclerosis in B1B1 carriers compared with B2B2 carriers after 2 years of pravastatin therapy in nondiabetic men with CAD (13). Although no difference in efficacy of statin treatment on HDL cholesterol and TG levels between the TaqIB genotypes was found, B1B1 carriers appeared to benefit most from statin therapy with respect to morphologic changes in coronary arteries (13). This may apply to subjects with type 2 diabetes as well (11).

We further analyzed whether the modifying effect of CETP polymorphisms on the efficacy of atorvastatin treatment is a direct consequence of the fact that these two CETP polymorphisms have a major contribution to the level of plasma CETP mass. However, additional analysis showed that baseline CETP mass did not influence the efficacy of atorvastatin treatment.

In a subset of the present study cohort, we were able to analyze both CETP mass and CETP activity to test the hypothesis that both activity and mass are affected to a similar extent by the treatment. After treatment with atorvastatin, an even stronger correlation between CETP mass and activity was observed. In the present study, we show that plasma CETP mass is significantly and dose-dependently reduced after statin therapy in patients with type 2 diabetes and dyslipidemia. The basic effect of statin treatment is the large reduction in plasma TC and LDL cholesterol, with an accompanied decrease in plasma TG levels, by inhibition of the enzyme hydroxymethylglutaryl-CoA reductase. The result of this action is a change in cellular cholesterol homeostasis. To pro-

Figure 3—The effect of atorvastatin on CETP mass, TGs, and HDL cholesterol in patients with type 2 diabetes according to CETP genotypes (DALI study). Test for difference between genotypes, adjusted for study location and baseline value, is shown. *P < 0.05, **P = 0.08. A: CETP TaqIB polymorphism after A10 treatment. B: CETP TaqIB polymorphism after A80 treatment. C: CETP A-629C polymorphism after A10 treatment. D: CETP A-629C polymorphism after A80 treatment.
vide the cell with enough cholesterol, the LDL receptor expression will be upregulated, facilitating enhanced lipoprotein clearance and uptake of cholesterol in the hepatocyte. Sterol regulatory element binding protein-1 (SREBP-1), a membrane-bound transcription factor, plays an important role in this process (26). In addition, the secretion of newly synthesized VLDL particles may be decreased by statins, resulting in lower plasma VLDL and TG levels. This lowering of the plasma levels of circulating TG donor particles for CETP-mediated TG/CE exchange results in a decreased input of CEs into circulating VLDL and LDL. Statin treatment may also result in a down-regulation of CETP gene expression by interference with the SREBP pathway. SREBP-1a is known to bind with the sterol regulatory element present in the promoter region of the CETP gene (27,28).

CETP may also be regulated by direct activation of transcription via SREBP-1–independent pathways, as has been indicated in CETP transgenic mice (27).

In conclusion, we demonstrated in type 2 diabetic patients that B1B1 and CC carriers (of the TaqIB and A-629C polymorphisms, respectively) are associated with elevated CETP mass and low HDL cholesterol concentrations. Atorvastatin dose-dependently reduced CETP mass in these patients. The efficacy of lipid-lowering therapy with atorvastatin may be modified by these polymorphisms with respect to HDL cholesterol and fasting TG levels, which together are the key characteristics of the atherogenic lipid profile in diabetic dyslipidemia. The relevance of this finding is emphasized by the high frequency of these polymorphisms in Caucasian populations: 34% of our population had the B1B1 genotype and 25% the CC genotype. These genetic variants of the CETP gene may help to identify those diabetic patients with increased cardiovascular risk, who may benefit most from statin therapy.

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