

THE ROLE OF A COMMON VARIANT OF THE CHOLESTERYL ESTER TRANSFER PROTEIN GENE IN THE PROGRESSION OF CORONARY ATHEROSCLEROSIS

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ABSTRACT

Background The high-density lipoprotein (HDL) cholesterol concentration is inversely related to the risk of coronary artery disease. The cholesteryl ester transfer protein (CETP) has a central role in the metabolism of this lipoprotein and may therefore alter the susceptibility to atherosclerosis.

Methods The DNA of 807 men with angiographically documented coronary atherosclerosis was analyzed for the presence of a polymorphism in the gene coding for CETP. The presence of this DNA variation was referred to as B1, and its absence as B2. All patients participated in a cholesterol-lowering trial designed to induce the regression of coronary atherosclerosis and were randomly assigned to treatment with either pravastatin or placebo for two years.

Results The B1 variant of the *CETP* gene was associated with both higher plasma CETP concentrations (mean [\pm SD], 2.29 ± 0.62 μ g per milliliter for the *B1B1* genotype vs. 1.76 ± 0.51 μ g per milliliter for the *B2B2* genotype) and lower HDL cholesterol concentrations (34 ± 8 vs. 39 ± 10 mg per deciliter). In addition, we observed a significant dose-dependent association between this marker and the progression of coronary atherosclerosis in the placebo group (decrease in mean luminal diameter: 0.14 ± 0.21 mm for the *B1B1* genotype, 0.10 ± 0.20 mm for the *B1B2* genotype, and 0.05 ± 0.22 mm for the *B2B2* genotype). This association was abolished by pravastatin. Pravastatin therapy slowed the progression of coronary atherosclerosis in *B1B1* carriers but not in *B2B2* carriers (representing 16 percent of the patients taking pravastatin).

Conclusions There is a significant relation between variation at the *CETP* gene locus and the progression of coronary atherosclerosis that is independent of plasma HDL cholesterol levels and the activities of lipolytic plasma enzymes. This common DNA variant appears to predict whether men with coronary artery disease will benefit from treatment with pravastatin to delay the progression of coronary atherosclerosis. (N Engl J Med 1998;338:86-93.)

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PATIENTS with clinically apparent coronary artery disease are at high risk for recurrent cardiovascular events. Efforts to prevent such events often involve cholesterol-lowering therapy, which has been demonstrated to reduce total mortality significantly in men with coronary artery disease.¹ Despite the potential of cholesterol-lowering drugs to retard the progression of coronary atherosclerosis^{2,3} and reduce the incidence of cardiovascular events,¹ these drugs did not prevent myocardial infarctions in a substantial percentage of patients. Our understanding of why not all patients benefit from such therapy is limited.⁴ Both environmental and genetic factors are thought to contribute to this lack of response to cholesterol-lowering strategies.

The cholesteryl ester transfer protein (CETP), which has a key role in the metabolism of high-density lipoprotein (HDL), constitutes such a factor. It mediates the exchange of lipids between lipoproteins,^{5,6} resulting in the net transfer of cholesteryl ester from HDL to other lipoproteins and in the subsequent uptake of cholesterol by hepatocytes. This flux of cholesterol toward the liver is known as reverse cholesterol transport. By increasing the cholesteryl ester content of low-density and very-low-density lipoproteins, CETP promotes the atherogenicity of these lipoproteins. In addition, high plasma concentrations of CETP are associated with reduced concentrations of HDL cholesterol,⁷⁻¹¹ a strong and independent risk factor for atherosclerotic vascular disease.^{12,13} These data and the results of other recent studies in both humans^{14,15} and animals^{16,17} support the notion that CETP can contribute to atherogenesis. However, it should be emphasized that the

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relation between plasma concentrations of CETP and HDL cholesterol and atherosclerosis is complex. Several investigators have shown that the role of CETP depends on the metabolic context and may be affected by other plasma enzymes and proteins that are crucial in lipoprotein metabolism.¹⁸⁻²⁰

Polymorphisms of the *CETP* gene have been studied to determine the intricate association between CETP, HDL cholesterol, and coronary artery disease. The majority of these studies have confirmed that variations in the *CETP* gene influence HDL cholesterol concentrations in plasma.^{9,11,21-23}

One specific polymorphism in the *CETP* gene, referred to as TaqIB, is associated with an effect on lipid-transfer activity⁹ and HDL cholesterol concentrations.^{9,21} We recently reported that this polymorphism is also associated with plasma CETP concentrations in healthy men.¹¹ To extend our knowledge of this *CETP* gene variant, we studied a large cohort of men with angiographically documented coronary atherosclerosis who were randomly assigned to treatment with a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor or placebo.² The primary objective of this study was to examine the relation between this frequent variant of the *CETP* gene and the progression of coronary atherosclerosis, as well as the influence of this variant on cholesterol-lowering therapy.

METHODS

Subjects with Coronary Artery Disease

We prospectively studied 807 men who were participating in the Regression Growth Evaluation Statin Study (REGRESS), which has previously been described in detail.² In short, study participants were required to have at least one coronary artery with stenosis of more than 50 percent as assessed by coronary angiography, a plasma total cholesterol concentration of 155 to 310 mg per deciliter (4 to 8 mmol per liter), and a plasma triglyceride concentration of less than 350 mg per deciliter (4 mmol per liter). Patients were subsequently randomly assigned to treatment with pravastatin sodium (Pravachol, Bristol-Myers Squibb, Princeton, N.J.) at a dose of 40 mg per day or placebo for a period of two years. Computer-assisted quantitative coronary angiography was carried out at the start and the end of the study.² The following two primary measures of outcome were used: the change in the average mean luminal diameter per patient (which we have previously referred to as the mean segment diameter²), reflecting diffuse changes of atherosclerosis, and the change in the average minimal luminal diameter per patient (which we have previously referred to as the minimum obstruction diameter²), which reflects focal changes of atherosclerosis. A greater decrease in the mean luminal diameter or the minimal luminal diameter reflects more progression of coronary atherosclerosis.

Both the REGRESS trial and the DNA substudy were approved by all seven institutional review boards of the participating centers and by the medical ethics committees of all centers.

DNA Analysis

Blood was collected at base line, and DNA was extracted according to standard procedures. The polymerase-chain-reaction-based method of screening for the TaqIB polymorphism in intron 1 of the *CETP* gene was carried out as described previously.¹¹

Biochemical Analyses

Plasma lipids and lipoproteins were measured with standard techniques.²⁴ Due to a lack of sufficient aliquots of plasma, CETP concentrations were determined in 237 patients at base line and in only 68 pravastatin-treated subjects at the end of the trial. These measurements were performed by solid-phase radioimmunoassay with recombinant human protein (provided by Dr. A. Tall, Columbia University, New York) as a standard and a CETP monoclonal antibody, TP2 (produced by Dr. R. Milne, University of Ottawa Heart Institute, Ottawa).¹⁰ In addition, the hepatic lipase and lipoprotein lipase activities were measured as reported previously.²⁴

Statistical Analysis

Differences in base-line clinical characteristics and concentrations of lipids, lipoproteins, lipolytic enzymes, and plasma CETP among the TaqIB subgroups were measured. Since triglyceride concentrations had a skewed distribution, the statistical analyses were based on log-transformed data. However, the triglyceride concentrations in the tables are given as means (\pm SD). The differences between the carriers of the three *CETP* genotypes (*B1B1*, *B1B2*, and *B2B2*) were tested by one-way analysis of variance or Pearson's chi-square test. Changes in lipid concentrations, lipoprotein concentrations, and angiographic measurements during the trial were expressed as means (\pm SD), and the differences within the two treatment groups were tested with one-way analysis of covariance, with base-line values as covariates.

The interaction between the three genotypes and treatment (placebo or pravastatin) was tested with the interaction test of two-way covariance analysis. We tested whether the interaction between genotype and medication was independent of the base-line HDL cholesterol concentration, changes in the HDL concentration during the trial, base-line mean luminal diameter, base-line minimal luminal diameter, hepatic lipase activity, and lipoprotein lipase activity by using these as covariates in a two-way analysis of covariance. This analysis was also carried out to test whether the significant differences in the decreases in either mean luminal diameter or minimal luminal diameter, as identified among the TaqIB subgroups in the placebo group, were dependent on the above variables.

Differences in the rate of events between genotypes were analyzed with Pearson chi-square tests within the treatment groups, and the interaction between genotype and treatment was assessed with logistic regression. Within each of the treatment groups, the assumption of Hardy-Weinberg equilibrium was tested by means of gene counting and chi-square analysis. Throughout, a two-tailed P value of 0.05 was interpreted as indicating a statistically significant difference. All statistical analyses were carried out with SAS software (version 6.1, SAS Institute, Cary, N.C.) and adapted from the Egret manual.²⁵

RESULTS

Frequency of the *CETP* TaqIB Polymorphism

B1 and B2 were used to denote the presence and absence, respectively, of a restriction site for the enzyme *TaqI* in intron 1. In the total cohort, the B1 and B2 alleles were found at frequencies of 0.594 and 0.406, respectively. These frequencies did not differ significantly between the two treatment groups (data not shown). For the placebo group, the pravastatin group, and the total cohort, the observed frequencies were in Hardy-Weinberg equilibrium.

Base-Line Characteristics of the Patients

When the patients were classified according to their TaqIB genotype, there were no statistically sig-

nificant differences between groups at base line with respect to risk factors for coronary artery disease or the severity or treatment of coronary atherosclerosis (Table 1). In each of the three groups, approximately 50 percent of the patients had been randomly assigned to cholesterol-lowering therapy with pravastatin.

There was a clear association of the B1 allele with lower HDL cholesterol concentrations (Table 2). The observed differences in plasma HDL cholesterol concentrations among the genotypes were significant ($P<0.001$). There were no significant differences among the three genotypes in lipoprotein lipase or hepatic lipase activity (Table 2) or in other risk factors for coronary artery disease, including concentrations of lipoprotein(a), fibrinogen, and serum glucose (data not shown).

Association between *CETP* Genotypes and *CETP* Concentrations in Plasma

At base line, the B1 allele was strongly associated with higher *CETP* concentrations in all patients ($P<0.001$) (Table 2). At the end of the trial, the patients assigned to pravastatin had a 16 percent reduction in plasma *CETP* concentrations (from

2.03 ± 0.53 μg per milliliter at base line to 1.71 ± 0.46 μg per milliliter; $P<0.001$). There were too few patients in the analysis to allow meaningful conclusions about differences in reductions in the *CETP* concentration as a result of the use of pravastatin.

Changes in Lipid and Lipoprotein Concentrations during the Study

The *TaqIB* polymorphism had no effect on the changes in total cholesterol, low-density lipoprotein cholesterol, triglyceride, and HDL cholesterol concentrations in the two study groups. Pravastatin reduced total cholesterol, low-density lipoprotein cholesterol, and triglyceride and increased HDL cholesterol to a similar extent in all three subgroups of patients.

Angiographic Measurements

The angiographic measurements and clinical events (myocardial infarction or death from cardiovascular causes) are shown according to the *CETP* genotype in the placebo and pravastatin groups in Table 3. A larger decrease in the mean luminal diameter or minimal luminal diameter indicates greater progression of atherosclerosis.

TABLE 1. BASE-LINE DEMOGRAPHIC AND CORONARY ARTERY DISEASE CHARACTERISTICS, ACCORDING TO THE *CETP* *TaqIB* GENOTYPE.*

CHARACTERISTIC	B1B1 (N=281)	B1B2 (N=397)	B2B2 (N=129)
Demographic			
Age — yr	55±8	57±8	56±7
Body-mass index†	26±3	26±3	26±3
Systolic blood pressure — mm Hg	135±19	135±18	135±17
Diastolic blood pressure — mm Hg	82±10	82±10	81±9
Current or former smoker — no. (%)	246 (88)	346 (87)	118 (91)
Current smoker — no. (%)	76 (27)	113 (28)	30 (23)
Coronary artery disease			
History of myocardial infarction — no. (%)	129 (46)	183 (46)	68 (53)
Left ventricular ejection fraction — %	70±13	71±12	70±12
Mean luminal diameter — mm	2.80±0.45	2.81±0.49	2.81±0.45
Minimal luminal diameter — mm	1.90±0.53	1.92±0.55	1.86±0.56
Stenosis — %	35±13	35±12	37±15
Coronary artery disease — no. (%)‡			
1 vessel	115 (41)	165 (42)	54 (42)
2 vessels	103 (37)	128 (32)	45 (35)
3 vessels	62 (22)	101 (25)	30 (23)
Medications — no. (%)			
Pravastatin	136 (48)	212 (53)	63 (49)
Long-acting nitrates	149 (53)	229 (58)	70 (54)
β -Blocking agents	208 (74)	295 (74)	93 (72)
Calcium-blocking agents	163 (58)	252 (63)	73 (57)

*Plus-minus values are means \pm SD. B1 denotes the presence of a restriction site for *TaqI* in intron 1 of the *CETP* gene, and B2 its absence. There were no significant differences between the subgroups.

†The body-mass index was calculated as the weight in kilograms divided by the square of the height in meters.

‡Data on one patient with the *B1B1* and three patients with the *B1B2* genotype were missing. Because of rounding, not all percentages total 100.

Placebo Group

In the placebo group there were statistically significant differences among the TaqIB subgroups in the decreases in both the mean luminal diameter ($P < 0.03$) and the minimal luminal diameter ($P < 0.05$). There was an association between the B1 allele and the degree of coronary atherosclerosis, with the most pronounced progression of atherosclerosis in the *B1B1* carriers, an intermediate degree of progression in the *B1B2* carriers, and the least progression in *B2B2* carriers.

Pravastatin Group

In the pravastatin group, the differences in the decreases in the mean luminal diameter ($P = 0.36$) and the minimal luminal diameter ($P = 0.38$) among the genotype subgroups did not reach statistical significance. However, the same dose-dependent effect noted in the placebo group was evident, with *B1B1*, *B1B2*, and *B2B2* carriers having the lowest, intermediate, and highest degrees of progression in diffuse atherosclerosis, respectively. In addition, we observed less focal atherosclerosis — as reflected by the smallest reduction in minimal luminal diameter — in the *B1B1* carriers than in the carriers of the other two genotypes.

Comparison of Placebo and Pravastatin Groups

There was a significant interaction between pravastatin treatment and decreases in the mean luminal diameter ($P = 0.01$) (Fig. 1) and the minimal luminal diameter ($P = 0.05$). As shown in Figure 1, the association of the B1 allele with greater progression of

diffuse atherosclerosis (i.e., greater decreases in the mean luminal diameter), as observed in the placebo group, was influenced by the use of pravastatin. In fact, the B1 allele appeared to be associated with less progression in the patients who were receiving pravastatin.

There was a dose-dependent relation between the B1 allele and the efficacy of pravastatin in retarding the progression of coronary atherosclerosis. Carriers of two B1 alleles benefited most from treatment with pravastatin: they had significantly less progression of coronary atherosclerosis, as evidenced by smaller decreases in both the mean luminal diameter ($P = 0.001$) and the minimal luminal diameter ($P = 0.002$), than their *B1B1* counterparts in the placebo group. Furthermore, carriers of only one B1 allele (*B1B2*) who were receiving pravastatin had significantly less focal atherosclerosis ($P = 0.01$) than their counterparts in the placebo group. Finally, *B2B2* homozygotes had a nonsignificantly greater progression at the end of the study than their counterparts in the placebo group.

Both the association of the *CETP* TaqIB genotype with the decrease in either the mean luminal diameter or the minimal luminal diameter in the placebo group and the interaction between the genotype and pravastatin treatment remained significant after adjustments were made for the mean luminal diameter (or minimal luminal diameter) at base line, the base-line HDL cholesterol concentration, changes in HDL cholesterol concentrations, and activities of both hepatic lipase and lipoprotein lipase (data not shown).

TABLE 2. BASE-LINE LIPASE ACTIVITY AND PLASMA LIPID, LIPOPROTEIN, AND CETP CONCENTRATIONS, ACCORDING TO THE *CETP* TaqIB GENOTYPE.*

VARIABLE	<i>B1B1</i> (N=281)	<i>B1B2</i> (N=397)	<i>B2B2</i> (N=129)	P VALUE†
Lipid concentrations (mg/dl)‡				
Total cholesterol	234±33	232±34	237±32	0.35
HDL cholesterol	34±8	36±8	39±10	<0.001
LDL cholesterol	167±31	166±31	169±29	0.66
Triglycerides	151±38	143±38	117±40	0.04
Lipase activity (U/liter)				
Lipoprotein lipase activity	108±45	112±47	109±41	0.63
Hepatic lipase activity	388±114	381±119	393±135	0.65
CETP concentration (µg/ml)§	2.29±0.62	2.01±0.51	1.76±0.51	<0.001

*B1 denotes the presence of a restriction site for *TaqI* in intron 1 of the *CETP* gene, and B2 its absence. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.

†The P values were calculated by one-way analysis of variance.

‡To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. The statistical analysis of triglyceride levels was performed on log-transformed values, but untransformed mean values are given in the table.

§Data on CETP concentrations were available for 85 men with the *B1B1* genotype, 89 men with the *B1B2* genotype, and 63 men with the *B2B2* genotype.

DISCUSSION

We investigated the relation between a common TaqIB polymorphism of the *CETP* gene and the progression of coronary atherosclerosis in a large cohort of men.² The results indicate that this genetic marker not only is associated with the progression of coronary atherosclerosis in a dose-dependent manner but also can predict the angiographic response to cholesterol-lowering therapy. This study complements previous reports in which we attempted to define the genetic factors that affect the clinical presentation of the patients and their response to the study protocol.^{24,26,27} Such studies are warranted since the majority of trials assessing the progression of coronary atherosclerosis have focused primarily on base-line concentrations of lipids and lipoproteins and environmental factors to predict outcome.^{1,3,28,29}

Frequency of the TaqIB Polymorphism and Its Influence on Plasma CETP and HDL Cholesterol Concentrations

Screening of all study participants for the TaqIB polymorphism revealed frequencies that were similar to those reported for other white populations,^{9,21,30} suggesting that our study population is not genetically different from other cohorts. The respective frequencies of the *B1B1*, *B1B2*, and *B2B2* genotypes were 35 percent, 49 percent, and 16 percent, confirming that this marker is a common genetic variation among white subjects. Moreover, we identified a significant relation between the *CETP* genotype and plasma concentrations of CETP at base line. Specifically, our results showed that the B1 allele was associated in a dose-dependent fashion with higher CETP concentrations, which is in agreement with our previous findings in healthy men.¹¹

Pravastatin reduced CETP concentrations by 16

TABLE 3. CHANGES IN LIPID AND LIPOPROTEIN CONCENTRATIONS AND ANGIOGRAPHIC OUTCOMES DURING THE TRIAL IN THE PLACEBO AND PRAVASTATIN GROUPS.*

VARIABLE	PLACEBO				PRAVASTATIN				
	<i>B1B1</i> (N=145)	<i>B1B2</i> (N=185)	<i>B2B2</i> (N=66)	P VALUE†	<i>B1B1</i> (N=136)	<i>B1B2</i> (N=212)	<i>B2B2</i> (N=63)	P VALUE†	P VALUE‡
Lipids and lipoproteins — mg/dl§									
Mean (±SD) decrease in total cholesterol	-3.9±28.6	-5.8±28.6	-8.5±30.5	0.51	53.8±32.1	48.3±32.5	54.1±35.2	0.71	0.77
Mean (±SD) decrease in LDL cholesterol	-0.8±25.9	-0.4±25.1	-0.4±25.5	0.99	56.8±26.7	49.5±29	56.5±33.6	0.20	0.35
Geometric mean (±CV) decrease in triglycerides	-6.2±29.2	-10.6±36.3	-15.1±39	0.45	7.1±32.8	7.1±37.2	5.3±38.1	0.62	0.35
Mean (±SD) increase in HDL cholesterol	-1.2±5.4	1.2±5.8	1.2±6.6	0.35	4.3±6.2	3.9±7.0	3.5±6.6	0.72	0.86
Angiographic outcome									
Mean (±SD) decrease in mean luminal diameter — mm	0.14±0.21¶	0.10±0.20	0.05±0.22	0.03	0.05±0.16	0.07±0.20	0.09±0.16	0.36	0.01
Median decrease in minimal luminal diameter — mm (interquartile range)	0.13 (0.22)	0.09 (0.22)**	0.01 (0.19)	0.05	0.01 (0.19)	0.04 (0.21)	0.04 (0.22)	0.38	0.05
Myocardial infarction or death from cardiovascular causes — no. of patients (%)	3 (2.1)	9 (4.9)	2 (3)	0.38	4 (2.9)	4 (1.9)	0	0.38	0.49

*B1 denotes the presence of a restriction site for *TaqI* in intron 1 of the *CETP* gene, and B2 its absence. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, and CV coefficient of variation. A larger decrease in the mean luminal diameter or minimal luminal diameter indicates more progression of atherosclerosis.

†The P value is for analysis of covariance of the changes, with base-line values as the covariate, or the chi-square test (where appropriate), among the three genotype subgroups.

‡The P value is for the interaction between treatment (placebo or pravastatin) and the genotype (*B1B1*, *B1B2*, or *B2B2*) by analysis of covariance, with base-line values as the covariate, or by logistic regression, where appropriate.

§To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. The statistical analysis of triglyceride levels was performed on log-transformed values, but untransformed geometric mean values are given in the table.

¶P=0.001 for the comparison with the respective genotype in the pravastatin group.

||P=0.002 for the comparison with the respective genotype in the pravastatin group.

**P=0.01 for the comparison with the respective genotype in the pravastatin group.

percent in our cohort, a finding that supports previous reports that the plasma CETP concentration is influenced by 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors.³¹⁻³⁴ By contrast, others did not find such an effect, a fact that may be related to differences in assay procedures or to the small number of subjects studied.³⁵

In addition to the association of the TaqIB genotype with plasma CETP concentrations, we also identified a significant relation between the B1 allele and low HDL cholesterol concentrations, which confirms earlier reports.^{9,21} Since plasma CETP concentrations are closely related to CETP activity,¹⁰ and plasma CETP activity is inversely related to HDL cholesterol concentrations, it is tempting to suggest that the TaqIB polymorphism is associated with HDL cholesterol concentrations through its relation with plasma CETP concentrations. However, it is more likely that this polymorphism constitutes a nonfunctional marker and that these relations can be explained by linkage disequilibrium between TaqIB and functional variants of the *CETP* gene or other closely linked genes, such as that for lecithin-cholesterol acyltransferase.

TaqIB, Coronary Atherosclerosis, and the Response to Treatment with Pravastatin

Our study revealed a dose-dependent relation between the TaqIB genotype and the progression of coronary atherosclerosis. This relation was independent of HDL cholesterol concentrations, and it was not influenced by plasma lipase activities. The latter results disagree with recent findings.³⁶

In patients randomly assigned to placebo, angiographic measurements demonstrated that the B1 allele was associated with increased progression of coronary atherosclerosis. Subsequently, we identified a dose-dependent interaction between the B1 allele and the ability of pravastatin to inhibit the progression of coronary atherosclerosis. The association between the B1 allele and the progression of coronary atherosclerosis observed in the placebo group was not observed in the pravastatin-treated patients. In contrast to those in the placebo group, carriers of the *B1B1*, *B1B2*, and *B2B2* genotypes in the pravastatin group had the lowest, intermediate, and highest degrees of progression of coronary atherosclerosis, respectively. In other words, the response to pravastatin with regard to coronary atherosclerosis was greatest for *B1B1* carriers, whereas *B2B2* carriers did not appear to benefit from this treatment.

Thus, our study has revealed a genetic predisposition to the response to cholesterol-lowering drugs. It should be noted that although the *CETP* genotype was predictive of the outcome, HDL cholesterol concentrations were not.² However, a direct comparison between the *CETP* genotype and the CETP plasma concentration remains to be carried out. The

predictive value of this polymorphism in terms of the clinical outcome may, however, be limited, since the data not only were based on a post hoc analysis, but also are valid only with respect to the progression of coronary atherosclerosis. But, since anatomical changes are likely to predict future clinical events, as was shown by the collective results of several angiographic trials,³⁷⁻³⁹ the implications of our results are most likely clinically significant. Specifically, our data suggest that it may soon be possible to predict the magnitude of the clinical benefit of cholesterol-lowering strategies.

Putative Mechanism

The molecular mechanism that underlies the relation between the *CETP* gene variant and the angiographic response to pravastatin treatment cannot be deduced from this study. However, it may be related to plasma concentrations of CETP. Although pravastatin significantly reduced CETP concentrations, base-line CETP concentrations differed among the genotype subgroups, and this may account for the

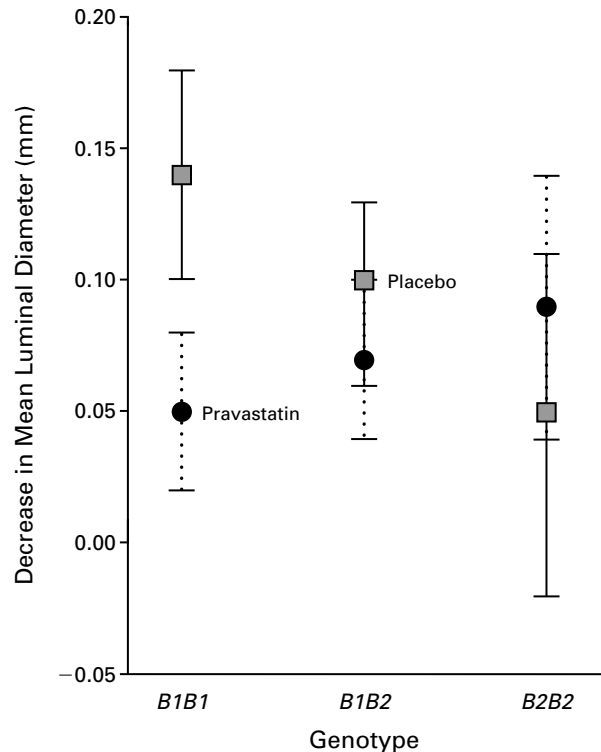


Figure 1. Changes in Mean Luminal Diameter (and 95 Percent Confidence Intervals) According to the *CETP* TaqIB Genotype in Patients with Established Coronary Atherosclerosis Treated with Either Placebo or Pravastatin.

Higher values reflect increased diffuse progression of coronary atherosclerosis.

effects observed. One could argue that high CETP concentrations, and therefore high levels of CETP activity,¹⁰ result in an enhanced transfer of cholesteryl esters to atherogenic lipoproteins and have negative effects on the structure and function of the HDL pool, which increases the risk of coronary artery disease. This possibility is in agreement with the observation that the pravastatin-induced reduction in CETP concentrations was associated with beneficial angiographic effects in patients who had high CETP concentrations — that is, those who were homozygous for the B1 allele. In contrast, the reduction in CETP concentrations induced by pravastatin in patients with genetically determined low plasma concentrations of CETP — that is, those who were homozygous for the B2 allele — was associated with a lack of retardation of the progression of coronary atherosclerosis. On the basis of these results and the finding of an increased risk of coronary artery disease in subjects who are heterozygous for CETP deficiency,²⁷ we hypothesize that a critical concentration of CETP is required for normal reverse cholesterol transport. In contrast, high plasma concentrations of CETP, as seen in placebo-treated *BIBI* patients, may promote atherosclerosis by increasing the cholesterol component of atherogenic lipoproteins.

Conclusions

We found that, at least among Dutch men with established coronary artery disease, the TaqIB polymorphism of the *CETP* gene is associated with the progression of coronary atherosclerosis. This relation was dose-dependent and independent of HDL cholesterol concentrations and plasma lipase activity. This marker also predicts the angiographic response to pravastatin and therefore appears to enable one to identify those who will and those who will not benefit from cholesterol-lowering therapy. The relevance of this finding is emphasized by the high frequency of this polymorphism: 16 percent of our population had the *B2B2* genotype. Therefore, we believe that this genetic variant of the *CETP* gene could become an important factor in designing better treatment regimens and in improving the cost-effectiveness of treatment for coronary artery disease.

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