

Cholesteryl Ester Transfer Protein TaqIB Variant, High-Density Lipoprotein Cholesterol Levels, Cardiovascular Risk, and Efficacy of Pravastatin Treatment Individual Patient Meta-Analysis of 13 677 Subjects

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Background—Several studies have reported that the cholesteryl ester transfer protein (CETP) *TaqIB* gene polymorphism is associated with HDL cholesterol (HDL-C) levels and the risk of coronary artery disease (CAD), but the results are inconsistent. In addition, an interaction has been implicated between this genetic variant and pravastatin treatment, but this has not been confirmed.

Methods and Results—A meta-analysis was performed on individual patient data from 7 large, population-based studies (each >500 individuals) and 3 randomized, placebo-controlled, pravastatin trials. Linear and logistic regression models were used to assess the relation between *TaqIB* genotype and HDL-C levels and CAD risk. After adjustment for study, age, sex, smoking, body mass index (BMI), diabetes, LDL-C, use of alcohol, and prevalence of CAD, *TaqIB* genotype exhibited a highly significant association with HDL-C levels, such that *B2B2* individuals had 0.11 mmol/L (0.10 to 0.12, $P<0.0001$) higher HDL-C levels than did *B1B1* individuals. Second, after adjustment for study, sex, age, smoking, BMI, diabetes, systolic blood pressure, LDL-C, and use of alcohol, *TaqIB* genotype was significantly associated with the risk of CAD (odds ratio=0.78 [0.66 to 0.93]) in *B2B2* individuals compared with *B1B1* individuals (P for linearity=0.008). Additional adjustment for HDL-C levels rendered a loss of statistical significance ($P=0.4$). Last, no pharmacogenetic interaction between *TaqIB* genotype and pravastatin treatment could be demonstrated.

Conclusions—The CETP *TaqIB* variant is firmly associated with HDL-C plasma levels and as a result, with the risk of CAD. Importantly, this CETP variant does not influence the response to pravastatin therapy. (*Circulation*. 2005;111:278-287.)

Key Words: genetics ■ cholesterol ■ lipoproteins ■ coronary disease

A strong inverse relation exists between HDL cholesterol (HDL-C) plasma levels and the risk of coronary artery disease (CAD).^{1,2} Cholesteryl ester transfer protein (CETP) plays a central role in HDL-C metabolism by shuttling cholesteryl esters from HDL particles to apolipoprotein B-containing particles in exchange for triglycerides.^{3,4} A

common polymorphism in intron 1 of the *CETP* gene, denoted *TaqIB*,⁵ was among the first genetic variations to be associated with HDL-C plasma levels.⁶ The less common *B2* allele occurs at a frequency of $\approx 40\%$ and is associated with lower CETP levels compared with the more common *B1* allele. Since its first description, a relation between the *TaqIB*

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genotype and HDL-C levels and the risk of CAD has been investigated in numerous population-based studies, albeit without consistent results. In addition, a pharmacogenetic interaction has been implicated between *TaqIB* genotype and pravastatin treatment,⁷ but this observation has not been found in other studies.^{8,9} Such inconsistencies are often encountered among genetic association studies and can be due factors such as genetic admixture or lack of statistical power.¹⁰ In this specific case, an alternative explanation may derive from proposed interactions with sex,^{11,12} smoking,^{8,13} body mass index (BMI),^{13,14} and use of alcohol,¹⁵ all modifiers of CETP action, HDL-C levels, and CAD risk. In view of our recent report about an interaction between CETP plasma levels and triglyceride levels,¹⁶ we also explored a potential interaction between *TaqIB* genotype and triglyceride levels.

We hypothesized that a meta-analysis could give better insight into the relations among CETP *TaqIB* genotype, HDL-C levels, and the risk of CAD. However, a conventional meta-analysis does not allow for the assessment of the interactions mentioned earlier. We therefore performed a meta-analysis of individual patient data. To circumvent the risk of publication bias, we included only those studies that were likely to be published irrespective of the results, ie, randomized, controlled trials and large, population-based studies. This approach is likely to yield a less biased result and a more modest effect estimate compared with a meta-analysis that also includes small studies.¹⁷ Using this criterion and taking into account the obligatory presence of CETP *TaqIB* genotyping data, we were able to analyze data from a total of 13 677 individuals.

Methods

Literature Search

We identified all population-based studies published before September 2003 on the CETP *TaqIB* polymorphism and its association with HDL-C plasma levels and/or the risk of CAD. The literature was scanned by a formal search of the MEDLINE electronic database. The search terms were both MeSH terms and (part of) the text words "cholesteryl ester transfer protein" or "CETP," in combination with "polymorphism," "mutation," or "genetics." Reference lists of retrieved articles were scanned for additional potentially relevant publications. Finally, for each retrieved publication, an electronic "cited reference search" was performed (Web of Science version 4.1.1, Institute for Scientific Information 2000, available at <http://www.isinet.com/isi/products/citation/wos/>), identifying all articles citing the index publication.

Selection Criteria

The meta-analysis was limited to population-based studies that included >500 individuals. In addition, we included all randomized, double-blind, placebo-controlled trials of pravastatin treatment from which subanalyses on the role of the *TaqIB* polymorphism were performed. To avoid population admixture due to genetic heterogeneity between races, only white subjects were used in the analyses. All identified publications were independently evaluated by 2 investigators for compliance with these criteria, and the results were compared. Disagreements were very few and were resolved by discussion and rereading of the original manuscripts.

Data Collection

Principal investigators from all qualifying studies were contacted and asked to provide a database with individual patient data. Variables

from the individual databases were made compatible with each other and entered into a pooled database. Again, this procedure was performed in duplicate by 2 independent investigators, the results were compared, and disagreements were resolved by consensus. An "HDL database" was composed of all studies that assessed the relation between *TaqIB* genotype and HDL-C plasma levels. A "CAD database" was composed of all studies that assessed the risk of prevalent or incident CAD and used (apparently) healthy individuals as a referent group. A "pravastatin database" was composed of all trials that assessed the efficacy of pravastatin therapy.

Data Analysis

A fixed-effects, linear regression model was used to assess the relation between patient characteristics and HDL-C plasma levels, adjusted for study, sex, and age.¹⁸ The variables that had a significant association with HDL-C plasma levels and all 2-way interactions between them were entered into a multivariate linear regression model, and backward stepwise selection was used to identify the variables that had an independent association with HDL-C plasma levels. A fixed-effects logistic regression model was used to assess the relation between patient characteristics and the risk of CAD.¹⁹ Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated for the risk of CAD in *B1B2* individuals and *B2B2* individuals, with *B1B1* individuals as the reference group.

Both for the outcome HDL-C and for the outcome CAD risk, we tested for interactions between *TaqIB* genotype and several environmental factors. To assess whether we had sufficient statistical power to detect interactions of the magnitude that have been reported in the literature, we calculated the magnitude of interactions and corresponding 95% CIs by using the pooled databases. We investigated interactions between *TaqIB* genotype (*B1B1* individuals versus *B2B2* individuals) and risk factors as dichotomous variables (men versus women; smokers versus nonsmokers; use of alcohol, yes versus no; BMI ≥ 27 kg/m² versus < 27 kg/m²; triglycerides ≥ 1.7 mmol/L versus < 1.7 mmol/L; pravastatin use, yes versus no). To adjust for heterogeneity between studies, all regression models were adjusted for study number as a fixed factor in the model. In addition, to adjust for residual heterogeneity, we used hierarchical random-effects models for the outcomes HDL-C and CAD risk, with study number as a random factor. Additional analyses were performed to assess the consistency between prospective and cross-sectional studies and to investigate whether an additive, recessive, or dominant genetic model was the best way to describe the observed data. Only individuals with a complete data set were entered in the linear and logistic regression models. A probability value < 0.05 was considered to indicate statistical significance. Analyses were performed using SPSS version 12.0 (SPSS Inc) and SAS software (SAS Institute).

Results

Our MEDLINE search identified 425 potentially relevant publications. A total of 9 population-based studies qualified for inclusion: 4 prospective studies: the Framingham Offspring Study (FOS),²⁰ the Physicians' Health Study (PHS),²¹ the Northwick Park Heart Study (NPHS),²² and the Reykjavik study;²³ and 5 cross-sectional studies: the European Atherosclerosis Research Study (EARS),²⁴ Etude Cas-Témoins de l'Infarctus du Myocarde (ECTIM),^{15,25,26} the Oulu Project Elucidating Risk of Atherosclerosis (OPERA),^{11,27} a study performed by Arca et al,²⁸ and one performed by Corella et al.²⁹ Databases with individual patient data were obtained from all studies except for the FOS and the study performed by Corella et al.^{20,29}; thus these 2 studies were not included. We identified 3 randomized, double-blind, placebo-controlled trials of pravastatin treatment wherein a subanalysis had been performed on the role of the *TaqIB* polymorphism: the

TABLE 1. Characteristics of Population-Based Studies and Randomized, Controlled Trials Included in the Present Meta-Analysis

Study	Design	Sex	Selection Criteria	CAD Definition
Physicians' Health Study	Prospective, nested case-referent	M	Apparently healthy men developing MI Age- and smoking-matched referents	MI confirmed by medical records
Northwick Park Heart Study	Prospective, nested case-referent	M	Apparently healthy men developing CAD Apparently healthy men not developing CAD	MI by WHO criteria
Reykjavik	Prospective, population based	M	Randomly selected men reporting MI Randomly selected healthy men	MI by WHO criteria
ECTIM	Cross-sectional	M	Patients who survived first MI Age-matched referents	MI by WHO criteria
OPERA	Cross-sectional	M+F	Referent cohort of OPERA study, with CAD Referent cohort of OPERA study, without CAD	By medical history and ECG changes
EARS	Cross-sectional	M	Students with paternal MI Age-matched referents	MI by WHO criteria in fathers
Arca et al	Cross-sectional	M+F	Patients with CAD Individuals without CAD Population referents	Confirmed by angiography Ruled out by angiography
REGRESS	RCT of pravastatin vs placebo	M	Symptomatic CAD, undergoing CABG, developing recurrent MI Symptomatic CAD, undergoing CABG, not developing recurrent MI	Fatal or nonfatal CAD
CARE	RCT of pravastatin vs placebo	M+F	Previous MI, total cholesterol <6.2 mmol/L, developing recurrent MI Previous MI, total cholesterol <6.2 mmol/L, not developing recurrent MI	Fatal or nonfatal CAD
WOSCOPS	RCT of pravastatin vs placebo	M	No CAD, LDL-C >4.0 mmol/L, developing MI during follow-up Controls from WOSCOPS cohort, matched by age and smoking	Fatal or nonfatal CAD

RCT indicates randomized, controlled trial; MI, myocardial infarction; CABG, coronary artery bypass graft; and WHO, World Health Organization. All other abbreviations are as defined in text.

Regression Growth Evaluation Statin Study (REGRESS),⁷ the Cholesterol And Recurrent Events trial (CARE),⁹ and the West of Scotland Coronary Prevention Study (WOSCOPS).⁸ The study databases with individual patient data were obtained from all 3. The characteristics of the selected studies are summarized in Table 1. Four studies matched a referent group to the cases: PHS, WOSCOPS (both age- and smoking-matched), ECTIM, and EARS (both age-matched). The patient characteristics of the individual studies are summarized in Table 2. In all individual studies, the genotype distributions were within the expected range according to Hardy-Weinberg equilibrium. Figure 1 shows the relation between *TaqIB* genotype and HDL-C levels for each of the included studies. Figure 2 shows the relation between *TaqIB* genotype and CAD risk for each of the included studies.

Pooled Databases

The HDL database comprised 13 677 individuals from the following studies: REGRESS, CARE, WOSCOPS, PHS,

ECTIM, OPERA, EARS, NPHS, Reykjavik, and Arca et al. The Reykjavik study (diabetes and use of alcohol) and the study by Arca et al (use of alcohol) did not record all risk factors used in the fully adjusted models. These 2 studies were therefore excluded from the fully adjusted models, which now included a total of 11 751 individuals. The CAD database comprised 8815 individuals from the following studies: PHS, ECTIM, OPERA, NPHS, WOSCOPS, Reykjavik, and Arca et al. Again, the Reykjavik study and the one by Arca et al were excluded from the fully adjusted models, which now included a total of 6889 individuals. The pravastatin database comprised 5691 individuals randomized in the following placebo-controlled pravastatin trials: REGRESS, CARE, and WOSCOPS. The baseline characteristics of the pooled databases used for the analyses are summarized in Table 3.

CETP *TaqIB* Genotype and HDL-C Plasma Levels

After adjusting for study, sex, and age, *TaqIB* genotype was significantly associated with HDL-C plasma levels

TABLE 2. Characteristics of Study Samples Included in the Meta-Analysis

	PHS	NPHS	Reykjavik	ECTIM	OPERA	EARS	Arca et al	REGRESS	CARE	WOSCOPS
Subjects, N	566	1713	1134	2490	524	767	792	706	3389	1596
Age, y	59±8	56±3	74±5	55±8	51±6	23±3	59±11	56±8	59±9	57±5
Male sex	566 (100.0)	1713 (100.0)	1134 (100.0)	1973 (79.2)	259 (49.4)	767 (100.0)	518 (65.4)	706 (100.0)	2936 (86.6)	1596 (100.0)
Smoking	87 (15.4)	454 (26.5)	211 (18.6)	1042 (41.8)	174 (33.2)	196 (25.6)	278 (35.1)	195 (27.6)	528 (15.6)	867 (54.3)
Systolic BP, mm Hg	128±12	138±19	149±23	131±22	141±21	118±11	129±18	135±18	129±18	137±17
Diastolic BP, mm Hg	80±7	84±11	85±11	80±12	85±12	74±10	77±9	81±10	78±10	84±10
BMI, kg/m ²	25.3±3.2	26.4±3.4	26.4±3.9	26.9±4.2	26.4±4.0	23.3±2.9	26.3±3.9	26.0±2.7	27.4±4.3	25.8±3.2
Diabetes	22 (3.9)	19 (1.1)	NA	208 (8.4)	8 (1.5)	0 (0.0)	67 (8.5)	0 (0.0)	431 (12.7)	23 (1.4)
Total cholesterol, mmol/L	5.7±1.0	5.7±1.0	5.9±1.1	5.9±1.1	5.7±1.1	4.4±0.8	5.6±1.2	6.0±0.9	5.4±0.4	7.0±0.6
LDL-C, mmol/L	3.6±0.9	3.1±1.0	4.1±1.0	3.9±1.0	3.5±1.0	2.8±0.8	3.6±1.0	4.3±0.8	3.6±0.4	5.0±0.4
Triglycerides, mmol/L	1.7 (1.1–2.5)	1.7 (1.2–2.5)	1.2 (0.9–1.6)	1.6 (1.2–2.3)	1.2 (0.9–1.6)	0.9 (0.7–1.1)	1.7 (1.2–2.2)	1.7 (1.2–2.3)	1.6 (1.3–2.2)	1.7 (1.3–2.3)
HDL-C, mmol/L	1.2±0.3	0.8±0.3	1.1±0.3	1.2±0.4	1.4±0.4	1.2±0.2	1.2±0.4	0.9±0.2	1.0±0.2	1.1±0.2
Alcohol use	411 (72.6)	1398 (81.6)	NA	1717 (69.0)	432 (82.4)	697 (90.9)	NA	507 (71.8)	1485 (43.8)	1297 (81.3)
CAD*	0 (0.0)*	0 (0.0)*	NA					706 (100.0)*	3389 (100.0)*	0 (0.0)*
Pravastatin allocation†								357 (50.6)	1715 (50.6)	763 (47.8)
<i>TaqIB</i> genotype										
<i>B1B1</i>	182 (32.2)	500 (29.2)	328 (28.9)	845 (33.9)	168 (32.1)	237 (30.9)	284 (35.9)	256 (36.3)	1121 (33.1)	500 (31.3)
<i>B1B2</i>	296 (52.3)	896 (52.3)	596 (52.6)	1236 (49.6)	256 (48.9)	380 (49.5)	369 (46.6)	335 (47.5)	1693 (50.0)	797 (49.9)
<i>B2B2</i>	88 (15.5)	317 (18.5)	210 (18.5)	409 (16.4)	100 (19.1)	150 (19.6)	139 (17.6)	115 (16.3)	575 (15.0)	299 (18.7)
<i>TaqIB</i> allele frequency										
<i>B1</i>	0.583	0.553	0.552	0.588	0.565	0.557	0.592	0.600	0.581	0.563
<i>B2</i>	0.417	0.447	0.448	0.412	0.435	0.443	0.408	0.400	0.419	0.437

Data are presented as mean±SD, n (%), or median (interquartile range). BP indicates blood pressure; NA, not available. All other abbreviations are as defined in text. Because of missing data, means, percentages, and medians may be based on fewer observations than the indicated number of subjects.

*Presence of CAD at baseline (in prospective studies).

†Allocation to pravastatin treatment in randomized, controlled trials.

($P<0.0001$). Mean HDL-C levels were 1.05 (± 0.32), 1.08 (± 0.33), and 1.1 (± 0.33) mmol/L in *B1B1*, *B1B2*, and *B2B2* individuals, respectively. Among men, the respective values were 1.02 (± 0.29), 1.05 (± 0.30), and 1.12 (± 0.3) mmol/L, and among women they were 1.26 (± 0.39), 1.32 (± 0.39), and 1.41 (± 0.40) mmol/L. Other variables that had a significant association with HDL-C plasma levels (adjusted for study, sex, and age) were smoking, diabetes, prevalence of CAD, BMI, total cholesterol, LDL-C, (logarithmically transformed) triglycerides, and use of alcohol ($P<0.0001$ for each). *TaqIB* genotype (adjusted for study, sex, and age) was also significantly associated with total cholesterol ($P=0.01$) and triglyceride levels (logarithmically transformed, $P=0.02$), so we did not adjust for these variables in subsequent analyses in this section. Mean total cholesterol levels for *B1B1*, *B1B2*, and *B2B2* individuals were 5.75 (± 1.05), 5.77 (± 1.07), and 5.82 (± 1.06) mmol/L and mean triglyceride levels were 1.83 (± 1.01), 1.80 (± 1.02), 1.79 (± 1.17) mmol/L, respectively.

After adjustment for study, sex, age, BMI, diabetes, smoking, LDL-C, and use of alcohol, *TaqIB* genotype still exhibited a highly significant association with HDL-C among cases and among people without CAD. No significant interaction was observed between CAD prevalence and *TaqIB* genotype for HDL-C levels, so people with and without CAD were combined. In the combined dataset,

after adjusting for study, sex, age, BMI, diabetes, smoking, LDL-C, use of alcohol, and CAD prevalence, *B1B2* individuals had 0.04 mmol/L (0.03 to 0.05, $P<0.0001$) higher HDL-C levels and *B2B2* individuals had 0.11 mmol/L (0.10 to 0.12, $P<0.0001$) higher HDL-C levels compared with *B1B1* individuals. There was no significant heterogeneity between the studies for the relation between *TaqIB* genotype and HDL-C levels ($P=0.9$). There was, however, significant heterogeneity between the studies for absolute HDL-C levels, but when we adjusted for this in a random-effects model, the results were similar to those in the fixed-effects model: HDL-C levels were 0.04 mmol/L (0.03 to 0.05, $P<0.0001$) higher among *B1B2* individuals and 0.11 mmol/L (0.10 to 0.12, $P<0.0001$) higher among *B2B2* individuals than in *B1B1* individuals. The relation between the number of *B2* alleles and HDL-C levels deviated significantly from linearity ($P=0.002$). Given this observation and the absolute HDL-C differences observed in *B1B2* and *B2B2* individuals compared with *B1B1* individuals, we conclude that *B2* homozygosity has a higher penetrance than heterozygosity.

Subsequently, we tested for gene-environment interactions between *TaqIB* genotype and several risk factors that have been previously reported to show an interaction with *TaqIB* genotype: sex, BMI, smoking, and use of alcohol. In addition, we tested for an interaction with triglyceride levels. Signifi-

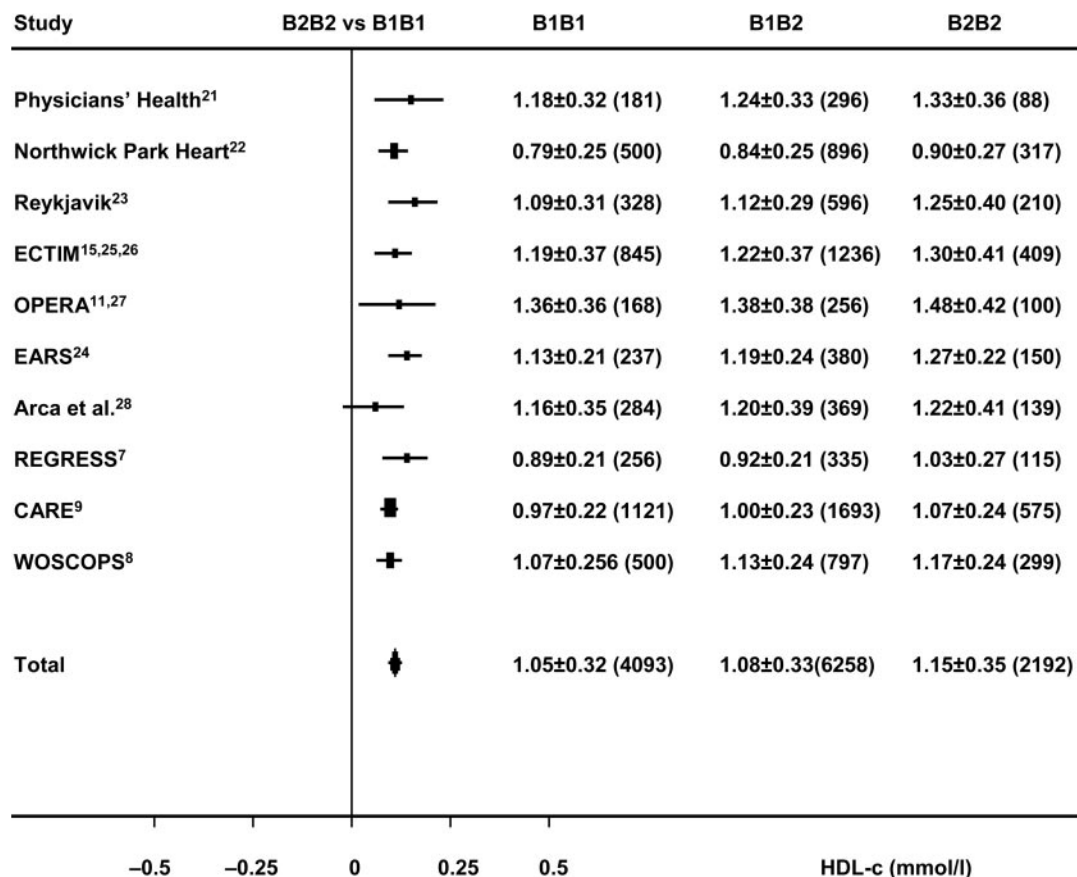


Figure 1. HDL-C levels according to *TaqIB* genotype in individual studies. Graphical representation of absolute HDL-C difference between *B2B2* vs *B1B1* individuals. Mean±SD levels of HDL-C and number of observations in parentheses are shown for *B1B1*, *B1B2*, and *B2B2* individuals. Data shown here were defined by inclusion criteria of present meta-analysis and were used in meta-analysis. Thus, data may differ from those in original publication, for instance, because present meta-analysis was restricted to whites only. Abbreviations are as defined in text.

cant interactions with *TaqIB* genotype (*B2B2* versus *B1B1* individuals) were identified for both sex and smoking ($P=0.02$ for each), such that the relation was attenuated among men and among smokers (Table 4). The adjusted HDL-C difference in *B2B2* individuals relative to *B1B1* individuals was 0.16 mmol/L (0.10 to 0.22) among women and 0.10 mmol/L (0.09 to 0.12) among men. The corresponding values were 0.11 mmol/L (0.09 to 0.13) and 0.09 mmol/L (0.06 to 0.12) among nonsmokers and smokers, respectively. These interactions were no longer statistically significant when we adjusted for the testing of multiple hypotheses. We did not observe a significant interaction between *TaqIB* genotype and any other variable.

CETP *TaqIB* Genotype and Risk of CAD

When we adjusted for study number, sex, and age, the *TaqIB* genotype was significantly associated with the risk of CAD (P for linearity=0.001). The OR for CAD was 0.93 (0.84 to 1.04, $P=0.2$) in *B1B2* individuals and 0.77 (0.66 to 0.89, $P=0.001$) in *B2B2* individuals compared with *B1B1* individuals. Other significant predictors of the risk of CAD were smoking, diabetes, BMI, systolic and diastolic blood pressure, total cholesterol, LDL-C, HDL-C, triglyceride levels (logarithmically transformed), and the use of alcohol. Because *TaqIB* genotype was

associated with HDL-C and triglyceride levels (logarithmically transformed), we did not adjust for these variables in the subsequent analysis in this section.

After adjustment for study, sex, age, smoking, diabetes, BMI, systolic blood pressure, LDL-C, and use of alcohol, *TaqIB* genotype was still significantly associated with a lower risk of CAD: OR=0.95 (0.83 to 1.07) in *B1B2* individuals and OR=0.78 (0.66 to 0.93) in *B2B2* individuals compared with *B1B1* individuals (P for linearity=0.008). On additional adjustment for HDL-C, this association was considerably attenuated and became statistically nonsignificant: OR=1.04 (0.90 to 1.19) in *B1B2* individuals and OR=0.92 (0.77 to 1.11) in *B2B2* individuals compared with *B1B1* individuals (P for linearity=0.4). There was no significant heterogeneity between the studies for the relation between *TaqIB* genotype and CAD risk ($P=0.8$). There was significant heterogeneity between the studies for absolute CAD risk, but when we adjusted for this in the random-effects model, the point estimates were similar to those in the fixed-effects model. However, the 95% CIs were importantly narrower, causing the risk estimate for *B1B2* individuals to become significant: OR=0.96 (0.92 to 0.99, $P=0.03$) in *B1B2* individuals and OR=0.82 (0.75 to 0.91, $P<0.0001$) in *B2B2* individuals compared with *B1B1* individuals.

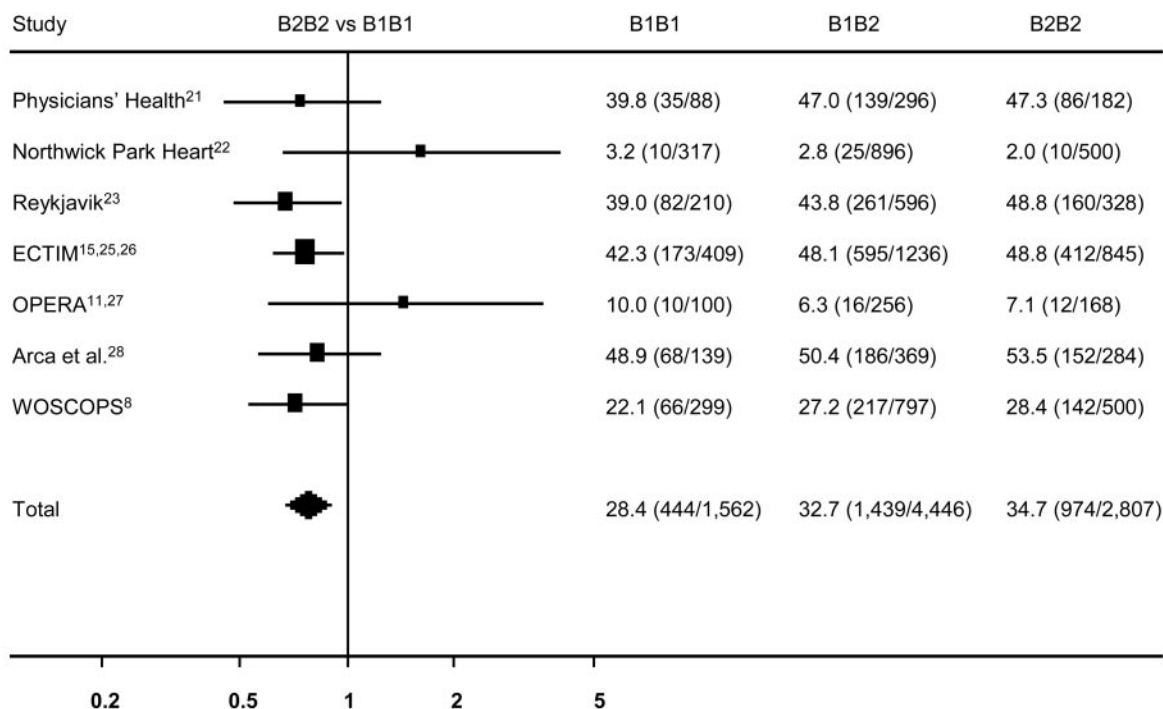


Figure 2. ORs for CAD according to *TaqIB* genotype in individual studies. Graphical representation of OR for CAD among *B2B2* compared with *B1B1* individuals. For each study, percentages of individuals with CAD and numbers of cases and controls in parentheses are shown for *B1B1*, *B1B2*, and *B2B2* individuals. Data shown here were defined by inclusion criteria of present meta-analysis and were used in meta-analysis. Thus, data may differ from those in original publication, for instance, because present meta-analysis was restricted to whites only. Abbreviations are as defined in text.

The relation between the number of *B2* alleles and CAD risk did not deviate significantly from linearity ($P=0.3$). This implies that an additive model and not a dominant or recessive one is the best genetic model to describe the data. To assess the consistency between cross-sectional and prospective studies, we excluded the cross-sectional studies and retained only the prospective studies. The point estimates did not change substantially (OR=0.97, 0.79 to 1.21 in *B1B2* individuals and OR=0.79, 0.59 to 1.05 in *B2B2* individuals), but due to the loss of statistical power, the CIs widened and now included unity ($P=0.1$).

As described earlier for the outcome HDL-C, we tested whether gene-environment interactions existed between *TaqIB* genotype and traditional risk factors for the outcome CAD risk. No significant interaction terms were observed. As for HDL-C levels, smoking again appeared to attenuate the relation between *TaqIB* genotype and CAD risk, but this interaction was not statistically significant ($P=0.2$).

Relation Between CETP *TaqIB* Genotype and Efficacy of Pravastatin Therapy

In the pravastatin database, pravastatin significantly reduced the risk of incident CAD: OR=0.68 (0.58 to 0.78), $P<0.0001$. In this database, *TaqIB* genotype was not significantly associated with CAD risk: OR=1.06 (0.90 to 1.25) in *B1B2* individuals and OR=0.93 (0.74 to 1.16) in *B2B2* individuals relative to *B1B1* individuals ($P=0.5$). No signif-

icant interaction was observed between *TaqIB* genotype and pravastatin therapy ($P=0.7$).

Discussion

In this meta-analysis, we observed that after adjustment for study, age, sex, smoking, BMI, diabetes, LDL-C, use of alcohol, and prevalence of CAD, the *TaqIB* variant in the CETP gene still exhibited a highly significant association with HDL-C levels ($P<0.0001$). In quantitative terms, *B2B2* individuals had 0.11 mmol/L (0.10 to 0.12, $P<0.0001$) higher HDL-C values than did *B1B1* individuals. Second and more important, we observed that after adjustment for study, sex, age, smoking, BMI, diabetes, systolic blood pressure, LDL-C, and use of alcohol, the CETP genotype was significantly associated with the risk of CAD: OR=0.78 (0.66 to 0.93) in *B2B2* individuals compared with *B1B1* individuals (P for linearity=0.008). Finally, we could eliminate the notion of a significant interaction between *TaqIB* genotype and pravastatin in reducing the risk of cardiovascular events.

Since the discovery of CETP as a modulator of HDL-C levels, there has been much speculation about its role in human atherogenesis.^{4,30} Because of its high frequency among whites and based on some reports of a strong association with HDL-C, the *TaqIB* variant in the CETP gene has played a prominent role in genetic association studies investigating the relation between CETP activity, lipids, and CAD risk. This variant, located in intron 1, has been suggested to act as a marker for a functional C→A polymorphism in the promoter region of the CETP gene,

TABLE 3. Characteristics of Pooled Study Databases Used for the Present Meta-Analysis

	HDL Database	CAD Database	Pravastatin Database
Subjects, n	13 677	8815	5691
Age, y	56±12	59±9	58±8
Male sex	12 168 (89.0)	7759 (88.0)	5238 (92.0)
Smoking	4032 (29.5)	3113 (35.3)	1590 (27.9)
Systolic blood pressure, mm Hg	133±20	136±21	132±18
Diastolic blood pressure, mm Hg	81±11	82±11	80±10
BMI, kg/m ²	26.4±3.9	26.3±3.8	26.8±3.9
Diabetes	778 (6.2)	347 (4.5)	454 (8.0)
Total cholesterol, mmol/L	5.8±1.1	6.0±1.1	5.9±0.9
LDL-C, mmol/L	3.8±1.0	3.9±1.1	4.1±0.8
HDL-C, mmol/L	1.1±0.3	1.1±0.4	1.0±0.2
Triglycerides, mmol/L	1.5 (1.1–2.2)	1.6 (1.1–2.2)	1.7 (1.3–2.2)
Alcohol use	7944 (67.7)	5255 (76.5)	3289 (57.9)
CAD*			4095 (72.0)
Genotype frequency			
<i>B1B1</i>	4421 (32.3)	2807 (31.8)	1877 (33.0)
<i>B1B2</i>	6854 (50.1)	4446 (50.4)	2825 (49.6)
<i>B2B2</i>	2402 (17.6)	1562 (17.7)	989 (17.4)
Allele frequency			
<i>B1</i>	0.574	0.571	0.578
<i>B2</i>	0.426	0.429	0.422

Data are presented as mean±SD, n (%), or median (interquartile range). Because some variables were not available in all studies, means or percentages may be based on fewer observations than the indicated number of subjects.

*Presence of CAD at baseline (in prospective studies).

located 629 bp upstream from the transcription start site.³¹ This –629C→A variant has been shown to directly affect CETP promoter activity.³² However, not all studies are consistent with this.²³ Because almost complete linkage disequilibrium exists between the *TaqIB* and the –629C→A gene variants³¹ and because of the extent of data available on *TaqIB* and not on –629C→A, the first is at present the best candidate for a meta-analysis.

***TaqIB* Genotype, HDL-C Levels, and Risk of CAD**

The results of the present meta-analysis support a strong relation among the *TaqIB* variant, HDL-C levels, and CAD risk. Of note, 2 studies that qualified for inclusion in our meta-analysis but from which the data could not be obtained both reported a significant relation with CAD that is consistent with the present results.^{20,29} In other words, it is unlikely that additional inclusion of these 2 studies would have affected the evident relation between *TaqIB* genotype and CAD risk.

We observed that the significant association between *TaqIB* genotype and CAD risk was substantially attenuated on adjustment for HDL-C levels, suggesting that the association between *TaqIB* genotype and CAD risk is largely mediated through HDL-C levels. However, the risk estimate did not completely return to unity (OR=0.92, 0.77 to 1.11), so this observation does not confirm an association between CETP genotype and CAD risk independent of HDL-C levels,

nor does it rule out a small residual association. Such a relation between CETP genotype and CAD risk independent of HDL-C levels would be consistent with several previous studies.^{7,27,33} The inconsistency with our results may derive from the fact that those studies assessed different CETP variants,^{27,33} used surrogate markers of CAD,^{7,27} or studied individuals with prevalent CAD.^{7,33}

Effect Modification by Environmental Factors

We investigated whether our pooled dataset provided any evidence for the published interactions between *TaqIB* genotype and sex,^{11,12} smoking,^{8,13} BMI,^{13,14} and use of alcohol.¹⁵ The present meta-analysis provides some evidence that interactions exist for both sex and smoking ($P=0.02$ for each), such that the effect of *TaqIB* genotype on HDL-C levels was attenuated among men and among smokers. However, these observations must be interpreted with caution because of the multitude of interaction terms tested in this analysis. In addition, assessment of the *TaqIB*×smoking interaction may have been influenced by the fact that 2 large studies included controls that were matched to CAD cases based on smoking habit.^{8,21} Effects of smoking on HDL-C plasma levels are well established,³⁴ but studies that investigated whether these effects are related to CETP activity have not yielded consistent results; smoking has been reported to reduce CETP activ-

TABLE 4. Interaction Between *TaqIB* Genotype and Several Risk Factors for the Outcomes HDL-C and CAD Risk

	Regression Coefficients (SE)		<i>P</i>	Interaction
	Men	Women		
Gender				
HDL-C	0.101 (0.009)	0.170 (0.034)	0.02	-0.069 (-0.140-0.000)
CAD	-1.153 (0.071)	-1.078 (0.205)	0.1	0.075 (-0.350-0.200)
Alcohol use	Yes	No		
HDL-C	0.112 (0.011)	0.083 (0.014)	0.1	0.029 (-0.006-0.064)
CAD	0.389 (0.097)	0.053 (0.156)	0.07	0.336 (-0.024-0.696)
BMI	≥27 kg/m ²	<27 kg/m ²		
HDL-C	0.108 (0.012)	0.101 (0.012)	0.7	0.007 (-0.026-0.040)
CAD	0.412 (0.130)	0.236 (0.106)	0.3	0.176 (-0.153-0.505)
Smoking	Yes	No		
HDL-C	0.087 (0.009)	0.112 (0.009)	0.02	-0.025 (-0.050-0.000)
CAD	0.223 (0.122)	0.353 (0.112)	0.4	-0.132 (-0.457-0.192)
Triglycerides	≥1.7 mmol/L	<1.7 mmol/L		
HDL-C	0.100 (0.011)	0.087 (0.012)	0.4	0.013 (-0.019-0.045)
CAD	0.236 (0.116)	0.318 (0.119)	0.6	-0.082 (-0.408-0.244)
Pravastatin	Yes	No		
HDL-C	0.097 (0.013)	0.111 (0.013)	0.5	-0.014 (-0.050-0.022)
CAD	0.143 (0.174)	-0.053 (0.146)	0.4	0.090 (-0.355-0.535)

The table presents regression coefficients (SE) for the differences in HDL-C and CAD risk between *B2B2* individuals and *B1B1* individuals. *P* indicates the probability value for interaction between *TaqIB* genotype (*B2B2* vs *B1B1*) and several risk factors for the outcome HDL-C and CAD risk. The last column contains the interaction term and corresponding 95% CI calculated in the appropriate pooled database. All other abbreviations are as defined in text.

ity,³⁵ to increase CETP activity in diabetics,³⁶ and to have no effect on CETP activity.³⁷ These inconsistencies may derive from differences between study samples or from differences between the complex CETP activity assays that were used. The significant *TaqIB*×sex interaction observed in this meta-analysis is consistent with a publication from the OPERA study (which was included in this meta-analysis) suggesting that the relation between *TaqIB* genotype and HDL-C levels is stronger in women.¹¹ The regression coefficient of the significant *TaqIB*×sex interaction in OPERA was 0.148, which is substantially larger than the one calculated in our pooled database, but the 95% CIs overlap, so the results are compatible with each other. It is also consistent with the observation that the relation between 2 other CETP variants in almost complete linkage disequilibrium with *TaqIB* (A373P and R451Q) and CAD risk is stronger among women not receiving hormone replacement therapy than in men.³⁸ However, in that study, the interaction term was not statistically significant. Our observation is not consistent with a study that suggested that the *TaqIB*-HDL-C relation is stronger in men,¹² but that study was performed among Japanese, whereas the present meta-analysis was restricted to whites.

In addition to smoking and male sex, obesity, visceral fat accumulation, and hyperinsulinemia have also been reported to blunt the effect of *TaqIB* genotype on HDL-C levels.^{13,14} In the present analysis, we were only able to study an interaction with BMI, which we did not detect. Given the fact that the

interactions described in the literature were of greater magnitude than the detectable effect size shown in Table 4, we conclude that an interaction between *TaqIB* genotype and BMI is unlikely. In the ECTIM study, an interaction was observed between the use of alcohol and *TaqIB* genotype for both HDL-C levels and CAD risk.¹⁵ We observed a strong trend toward an interaction between *TaqIB* genotype and use of alcohol for HDL-C levels (*P*=0.07). However, it must be kept in mind that the interaction observed in the ECTIM study was dose dependent and strongest in heavy drinkers. Because most studies included in this meta-analysis did not record alcohol consumption in a detailed manner, we were unable to differentiate between moderate and heavy drinkers and were therefore forced to study alcohol consumption as a dichotomous variable, which may have attenuated our power to detect such an interaction.

In addition to the environmental factors mentioned earlier that have been reported to interact with *TaqIB* genotype, we also studied a potential interaction with triglyceride levels. Triglycerides, which are substrates for CETP, are known to affect CETP metabolism.³⁹ In fact, we have recently reported an interaction between CETP plasma levels and triglycerides, such that the risk of future CAD increased with increasing CETP levels but only among individuals with high triglyceride levels.¹⁶ However, an interaction between *TaqIB* genotype and triglyceride levels has never been reported, and we did not observe one in the present analysis either.

Pharmacogenetic Interaction Between *TaqIB* Genotype and Efficacy of Pravastatin Therapy

The original description of a pharmacogenetic interaction between *TaqIB* genotype and pravastatin efficacy was based on angiographic progression of coronary atherosclerosis as outcome⁷ and is therefore not comparable to our analyses, which used HDL-C levels and CAD events as outcome. The only study ever to observe a pharmacogenetic interaction for clinical CAD events was published recently (and after the closure of our database), but the effect of *TaqIB* genotype on statin efficacy was opposite from that expected based on the angiographic trial.⁴⁰ The interaction term between *TaqIB* genotype (*B2B2* versus *B1B1*) and statin use described in that study was 0.285 (−0.160 to 0.730), which is substantially larger than the one observed in our meta-analysis, although CIs overlap (0.090 [−0.355 to 0.535]). We conclude that a clinically relevant interaction for cardiovascular events does not exist between pravastatin and *TaqIB* genotype. It warrants mentioning that 2 of the 3 studies were secondary prevention trials,^{7,9} which may have had limited statistical power to detect an effect on cardiovascular events, because both the CAD group and the control group consisted of CAD patients; the difference was defined by the incidence of a recurrent cardiovascular event during follow-up. However, an effect of *TaqIB* genotype on pravastatin efficacy was also not observed in WOSCOPS, which only enrolled patients who were free of clinical CAD.

Considerations

Any meta-analysis carries the risk of publication bias caused by the fact that small studies with positive results are more likely to be published than those with negative results. Therefore, a meta-analysis of large studies will generally yield more conservative results than a meta-analysis of all published studies.¹⁷ In the present meta-analysis, we therefore only included studies that were likely to be published irrespective of the results, ie, subanalyses of randomized, controlled trials and large, population-based studies.

Another drawback of any meta-analysis is the heterogeneity between the included studies in terms of the genetic structure of the studied samples, distribution of other cardiovascular risk factors, and CAD outcome definitions. First, to reduce the potential for population admixture, we restricted our analysis to whites. Indeed, the allele frequencies of the studied samples were very similar (Table 2). Second, to reduce the possibility that differential risk factor distributions would affect our results, we performed our analysis on individual patient data, which gave us the possibility to adjust for potential interacting or confounding variables. Finally, we adopted the outcome definitions used in each study, which included myocardial infarction by various definitions and CAD by various definitions, including both fatal and nonfatal events. This heterogeneity of outcome definitions is likely to have introduced random error, which may only lead to an underestimation of the real effect.

Conclusions

In summary, the CETP *TaqIB* genotype was strongly associated with HDL-C levels and with the risk of CAD. *B2B2* individuals had 0.11 mmol/L higher HDL-C plasma levels

and consistently a 20% lower risk of CAD than did *B1B1* individuals. The relation between *TaqIB* genotype and CAD risk was substantially attenuated on adjustment for HDL-C levels, suggesting that the association between *TaqIB* genotype and CAD risk is largely mediated through HDL-C plasma levels. Our observation that individuals with genetically determined lower CETP levels have a substantially lower risk of CAD supports further exploration of the potential benefits of pharmacological inhibition of CETP activity.

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