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, but this observation has not been found in other studies. Such inconsistencies are often encountered among genetic association studies and can be due factors such as genetic admixture or lack of statistical power. In this specific case, an alternative explanation may derive from proposed interactions with sex, smoking, body mass index (BMI), and use of alcohol, 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, 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. 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 “cholestereryl 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/mc/products/citation/wws/), 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 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. 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. 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.

For both 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), the Physicians’ Health Study (PHS), the Northwick Park Heart Study (NPHS), and the Reykjavik study; and 5 cross-sectional studies: the European Atherosclerosis Research Study (EARS), Etude Cas-Témoins de l’Infarctus du Myocarde (ECTIM), the Oulu Project Elucidating Risk of Atherosclerosis (OPERA), a study performed by Arca et al, and one performed by Corella et al. Databases with individual patient data were obtained from all studies except for the FOS and the study performed by Corella et al; 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...
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 8,815 individuals from the following studies: PHS, ECTIM, OPERA, NPHS, WOSCOPS, Reykjavik, and Arca et al. Again, the Reykjavik study and one by Arca et al were excluded from the fully adjusted models, which now included a total of 6,889 individuals. The pravastatin database comprised 5,691 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.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Sex</th>
<th>Selection Criteria</th>
<th>CAD Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physicians’ Health Study</td>
<td>Prospective, nested case-referent</td>
<td>M</td>
<td>Apparently healthy men developing MI</td>
<td>MI confirmed by medical records</td>
</tr>
<tr>
<td>Northwick Park Heart Study</td>
<td>Prospective, nested case-referent</td>
<td>M</td>
<td>Apparently healthy men developing CAD</td>
<td>MI by WHO criteria</td>
</tr>
<tr>
<td>Reykjavik</td>
<td>Prospective, population based</td>
<td>M</td>
<td>Randomly selected men reporting MI</td>
<td>MI by WHO criteria</td>
</tr>
<tr>
<td>ECTIM</td>
<td>Cross-sectional</td>
<td>M</td>
<td>Patients who survived first MI</td>
<td>MI by WHO criteria</td>
</tr>
<tr>
<td>OPERA</td>
<td>Cross-sectional</td>
<td>M+F</td>
<td>Referent cohort of OPERA study, with CAD</td>
<td>By medical history and ECG changes</td>
</tr>
<tr>
<td>EARS</td>
<td>Cross-sectional</td>
<td>M</td>
<td>Students with paternal MI</td>
<td>MI by WHO criteria in fathers</td>
</tr>
<tr>
<td>Arca et al</td>
<td>Cross-sectional</td>
<td>M+F</td>
<td>Patients with CAD</td>
<td>Confirmed by angiography</td>
</tr>
<tr>
<td>REGRESS</td>
<td>RCT of pravastatin vs placebo</td>
<td>M</td>
<td>Symptomatic CAD, undergoing CABG, developing recurrent MI</td>
<td>Fatal or nonfatal CAD</td>
</tr>
<tr>
<td>CARE</td>
<td>RCT of pravastatin vs placebo</td>
<td>M+F</td>
<td>Previous MI, total cholesterol &lt;6.2 mmol/L, developing recurrent MI</td>
<td>Fatal or nonfatal CAD</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>RCT of pravastatin vs placebo</td>
<td>M</td>
<td>No CAD, LDL-C &gt;4.0 mmol/L, developing MI during follow-up</td>
<td>Fatal or nonfatal CAD</td>
</tr>
</tbody>
</table>

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.
(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 HDLC plasma levels (adjusted for study, sex, and age) were smoking, diabetes, prevalence of CAD, BMI, total cholesterol, LDL-C, use of alcohol, and CAD prevalence. B1B2 individuals had 0.04 mmol/L (0.03 to 0.05, P<0.0001) higher HDLC levels and B2B2 individuals had 0.11 mmol/L (0.10 to 0.12, P<0.0001) higher HDLC levels compared with B1B1 individuals. There was no significant heterogeneity between the studies for the relation between TaqIB genotype and HDLC levels (P=0.9). There was, however, significant heterogeneity between the studies for absolute HDLC levels, but when we adjusted for this in a random-effects model, the results were similar to those in the fixed-effects model: HDLC 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 HDLC levels deviated significantly from linearity (P=0.002). Given this observation and the absolute HDLC 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-
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 0.91, 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.
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 significant 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. 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.
located 629 bp upstream from the transcription start site. This −629C→A variant has been shown to directly affect CETP promoter activity. However, not all studies are consistent with this. Because almost complete linkage disequilibrium exists between the TaqIB and the −629C→A gene variants 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. 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. The inconsistency with our results may derive from the fact that those studies assessed different CETP variants or studied individuals with prevalent CAD.

**Effect Modification by Environmental Factors**

We investigated whether our pooled dataset provided any evidence for the published interactions between TaqIB genotype and sex, smoking, BMI, and use of alcohol. 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. Effects of smoking on HDL-C plasma levels are well established, 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-

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HDL Database</th>
<th>CAD Database</th>
<th>Pravastatin Database</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, n</td>
<td>13 677</td>
<td>8815</td>
<td>5691</td>
</tr>
<tr>
<td>Age, y</td>
<td>56±12</td>
<td>59±9</td>
<td>58±8</td>
</tr>
<tr>
<td>Male sex</td>
<td>12 168 (89.0)</td>
<td>7759 (88.0)</td>
<td>5238 (92.0)</td>
</tr>
<tr>
<td>Smoking</td>
<td>4032 (29.5)</td>
<td>3113 (35.3)</td>
<td>1590 (27.9)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>133±20</td>
<td>136±21</td>
<td>132±18</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>81±11</td>
<td>82±11</td>
<td>80±10</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.4±3.9</td>
<td>26.3±3.8</td>
<td>26.8±3.9</td>
</tr>
<tr>
<td>Diabetes</td>
<td>778 (6.2)</td>
<td>347 (4.5)</td>
<td>454 (8.0)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.8±1.1</td>
<td>6.0±1.1</td>
<td>5.9±0.9</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>3.8±1.0</td>
<td>3.9±1.1</td>
<td>4.1±0.8</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.1±0.3</td>
<td>1.1±0.4</td>
<td>1.0±0.2</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.5 (1.1–2.2)</td>
<td>1.6 (1.1–2.2)</td>
<td>1.7 (1.3–2.2)</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>7944 (67.7)</td>
<td>5255 (76.5)</td>
<td>3289 (57.9)</td>
</tr>
<tr>
<td>CAD*</td>
<td></td>
<td></td>
<td>4095 (72.0)</td>
</tr>
</tbody>
</table>

Genotype frequency
- B1B1 4421 (32.3) 2807 (31.8) 1877 (33.0)
- B1B2 6854 (50.1) 4446 (50.4) 2825 (49.6)
- B2B2 2402 (17.6) 1562 (17.7) 989 (17.4)

Allele frequency
- B1 0.574 0.571 0.578
- B2 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).
The meta-analysis and other studies suggest that the relation between CETP and HDL-C levels is stronger in women.\(^{11}\) The relation between CETP and CAD risk is stronger among women not receiving hormone replacement therapy than in men.\(^{38}\) However, in that study, action 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.

The significant \(\text{TaqIB} \times \text{sex}\) interaction observed in this meta-analysis is consistent with a publication served in this meta-analysis is consistent with a publication derived from differences between study samples or from differences between the complex CETP activity assays that were used. The significant \(\text{TaqIB} \times \text{sex}\) interaction observed in this meta-analysis was restricted to whites.\(^{28}\) To increase CETP activity in diabetics,\(^{35}\) 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 \(\text{TaqIB} \times \text{sex}\) interaction observed in this meta-analysis was restricted to whites.\(^{28}\)

In addition to smoking and male sex, obesity, visceral fat accumulation, and hyperinsulinemia have also been reported to blunt the effect of \(\text{TaqIB}\) 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 \(\text{TaqIB}\) genotype and BMI is unlikely. In the ECTIM study, an interaction was observed between the use of alcohol and \(\text{TaqIB}\) genotype for both HDL-C levels and CAD risk.\(^{15}\) We observed a strong trend toward an interaction between \(\text{TaqIB}\) 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 \(\text{TaqIB}\) 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 \(\text{TaqIB}\) 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 outcome 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. 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, 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. 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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