# The CETP *Taq*IB Polymorphism Is Associated With the Risk of Sudden Death in Type 2 Diabetic Patients

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**OBJECTIVE** — Type 2 diabetic patients have a high risk of coronary heart disease (CHD) and sudden death. This cardiovascular risk can be partly attributed to low levels of HDL cholesterol. The B2 allele of the *CETP Taq*IB polymorphism has been repeatedly reported to be associated with high HDL cholesterol levels in both healthy and type 2 diabetic subjects, but its association with CHD is unclear. We investigated the association of the *CETP Taq*IB polymorphism with CHD, and sudden death in particular, in a prospective cohort of type 2 diabetic patients.

**RESEARCH DESIGN AND METHODS** — The *CETP Taq*IB polymorphism was genotyped in 3,124 type 2 diabetic subjects with high cardiovascular risk: the Noninsulin-Dependent Diabetes, Hypertension, Microalbuminuria, Proteinuria, Cardiovascular Events, and Ramipril (DIABHYCAR) study. We used Cox regression analysis to estimate the impact of the *Taq*IB single nucleotide polymorphism on the CHD events (myocardial infarction or sudden death) during follow-up.

**RESULTS** — The incidence of CHD was higher in B1B1 homozygotes than in B2 carriers ($P = 0.02$). This effect was mainly due to sudden death (hazard ratio [B1B1 vs. $B2^+$] = 1.51 [95% CI = 1.05–2.18]). Although the B1 allele was associated in a dose-dependent fashion with lower HDL cholesterol ($P < 0.001$), the association with sudden death persisted after adjustment for multiple risk factors, including HDL cholesterol levels.

**CONCLUSIONS** — In type 2 diabetic patients, the *CETP Taq*IB polymorphism is a good genetic predictor of cardiac mortality. This association is partly independent of the effect on HDL cholesterol levels.

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Type 2 diabetic patients have a high risk of coronary heart disease (CHD) (1). Sudden death occurs frequently among diabetic patients (2,3). The increased CHD risk is partly due to low HDL cholesterol levels (4,5) that are a common feature of insulin resistance (6). The cholesterol ester transfer protein (CETP) plays a key role in HDL metabolism and reverse cholesterol transport; it exchanges cholesterol ester from HDL for triglycerides from apolipoprotein B–rich particles (7). The *CETP* gene is localized on chromosome 16q31, and several *CETP* gene single nucleotide polymorphisms (SNPs) have been described. The most extensively studied *CETP* SNP is located in the first intron in the gene and disrupts a *Taq*I restriction site (*Taq*IB SNP: rs708272). The B2 allele of this SNP is associated with higher HDL cholesterol concentrations and lower CETP levels in both healthy and type 2 diabetic subjects (8,9), probably because of a nearly complete linkage disequilibrium with the −629G>A functional promoter polymorphism modifying the transcriptional activity of the *CETP* gene (10). Some studies reported that *Taq*IB SNP was associated with CHD (11–14). Nevertheless, other studies showed no correlation, and some studies supported the hypothesis of a CETP effect independent of HDL levels (15). A recent study of a cohort from the general population reported a higher CHD risk with *Taq*IB2 and −629A (16). Only a few longitudinal prospective studies have been reported in type 2 diabetes.

We assessed the association of the *CETP Taq*IB polymorphism with the incidence of CHD and with sudden death in particular in a large cohort of >3,100 French type 2 diabetic patients (the Noninsulin-Dependent Diabetes, Hypertension, Microalbuminuria, Proteinuria, Cardiovascular Events, and Ramipril [DIABHYCAR] study).

## RESEARCH DESIGN AND METHODS

— The design and results of the DIABHYCAR study have been reported (17–19). Briefly, DIABHYCAR was a multicentric, random, double-blind, parallel group trial to compare the cardiovascular and renal outcomes of patients taking ramipril (1.25 mg/day) and those taking placebo, in addition to their usual treatment (both groups). The participants were men or women with type 2 diabetes, aged ≥50 years, with serum creatinine ≤150 μmol/l, and elevated urinary albumin excretion (UAE) (≥20 mg/l, two times consecutively). The investigators examined the participants every 6 months for at least 3 years. The mean duration of follow-up was 4 years. The low dose of ramipril was found to be ineffective (19).

For logistical reasons, only French participants (3,124 of the 4,912 participants) were included in this study. Inci-

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**Abbreviations:** CHD, coronary heart disease; CETP, cholesteryl ester transfer protein; CRP, C-reactive protein; DIABHYCAR, Noninsulin-Dependent Diabetes, Hypertension, Microalbuminuria, Proteinuria, Cardiovascular Events, and Ramipril; SNP, single nucleotide polymorphism; UAE, urinary albumin excretion.

The design, funding, and interpretation of this genetic association analysis were independent of the sponsor of the DIABHYCAR trial (sanofi-aventis, France).

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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**Table 1—*Baseline characteristics of subjects in the DIABHYCAR study***

| | Incident CHD | | | |
|---|---|---|---|---|
| | Overall | No | Yes | *P** |
| *n* | 3,124 | 2,901 | 223 | |
| Age (years) | 65.5 ± 8.4 | 65.3 ± 8.2 | 69.1 ± 9.2 | <0.001 |
| BMI (kg/m²) | 29.4 ± 4.6 | 29.4 ± 4.6 | 28.9 ± 4.6 | NS |
| Male (%) | 73.1 | 73.1 | 74.0 | NS |
| Smoking (%) | 14.3 | 14.5 | 12.6 | NS |
| Prior myocardial infarction (%) | 6.1 | 4.9 | 11.9 | <0.001 |
| Diabetes duration (years) | 7.7 (7.6–7.8) | 7.6 (7.5–7.7) | 8.8 (8.5–9.1) | 0.003 |
| Glucose (mmol/l) | 9.51 ± 3.04 | 9.51 ± 3.05 | 9.48 ± 3.01 | NS |
| A1C (%) | 7.86 ± 1.76 | 7.84 ± 1.75 | 8.09 ± 1.87 | 0.03 |
| Systolic blood pressure (mmHg) | 145.0 ± 14.1 | 144.8 ± 14.1 | 147.4 ± 13.6 | 0.010 |
| Diastolic blood pressure (mmHg) | 82.1 ± 8.5 | 82.1 ± 8.5 | 82.6 ± 8.0 | NS |
| Total cholesterol (mmol/l) | 5.79 ± 1.07 | 5.77 ± 1.06 | 5.97 ± 1.16 | 0.004 |
| HDL cholesterol (mmol/l) | 1.31 ± 0.35 | 1.32 ± 0.36 | 1.25 ± 0.30 | 0.004 |
| LDL cholesterol (mmol/l) | 3.52 ± 0.88 | 3.51 ± 0.88 | 3.65 ± 0.93 | 0.03 |
| Triglycerides (mmol/l) | 1.90 (1.85–1.97) | 1.89 (1.84–1.96) | 2.04 (1.84–2.24) | 0.03 |
| CRP (mg/l) | 3.15 (3.04–3.26) | 3.09 (2.99–3.21) | 3.81 (3.45–4.19) | 0.004 |
| UAE (mg/l) | 98.2 (98.1–98.3) | 95.2 (95.1–95.3) | 139.5 (139,0–139.9) | <0.001 |
| Serum creatinine (μmol/l) | 87.0 (87.0–87.1) | 86.6 (86.5–86.6) | 92.4 (92.3–92.6) | <0.001 |
| Ramipril group (%) | 49.5 | 49.5 | 49.6 | NS |

Data are mean ± SD, %, or geometric mean (95% CI). *Comparison between CHD = "yes" and CHD = "no" by ANOVA or $\chi^2$ as appropriate.

dent myocardial infarction was defined as the first occurrence of a fatal or nonfatal myocardial infarction after the baseline examination. Sudden death was defined as death occurring instantaneously or within 1 h after the onset of new cardiac symptoms (arrhythmia or other cardiovascular causes) or nonwitnessed death, where the body of the deceased was found, and no cause could be discovered. Fatal stroke and myocardial infarction were not included in this group. CHD was defined as the combination of myocardial infarction and sudden death. However, as some people with myocardial infarction died from sudden death, the number of CHD patients is not the sum of myocardial infarction and sudden death groups. An independent adjudication committee without access to the genotyping data evaluated the events (18). The study design was approved by the Angers University Ethics Committee. All participants provided written informed consent.

The *CETP Taq*IB SNP was genotyped using a PCR molecular beacon technique (20). The PCR was performed in a 96-well microtitration plate. A total of 200 ng of DNA was amplified in a total volume of 25 μl containing 20 pmol of 5′ and 3′ primers, 0.2 mmol/l dNTPs, 4 mmol/l $MgCl_2$, 10 mmol/l Tris-HCl (pH 8.3), 5 pmol of each allele-specific molecular beacon, and 1 unit of *Taq* polymerase (gold *Taq*; Perkin-Elmer, Paris, France). DNA denaturation and *Taq* activation were performed at 95°C for 10 min in a thermocycler (PTC-200; MJ Research, Watertown, MA) followed by 40 cycles of 20 s at 55°C, 10 s at 72°C, and 10 s at 95°C. After a final denaturation at 95°C for 2 min, hybridization with the probes was performed at 60°C for 1 min. Fluorescence emission was recorded with a plate fluorometer (FLUOstar; BMG Labtech, Offenburg, Germany) using two wavelength systems: 480–520 nm for fluorescein and 520–590 nm for tetramethylrhodamine. The amplifiers and allele-specific probes were synthesized by Eurogentec (Seraing, Belgium). All of the sequences of primers and probes are available from the authors on request.

Quantitative variables are described by means ± SD or geometric means (95% CI) if the distribution was skewed. The association of *CETP Taq*IB genotypes with baseline characteristics, not including lipids, was tested by ANOVA (continuous variables) or a $\chi^2$ test (categorical variables) in univariate analysis. The association of *CETP Taq*IB genotypes with baseline lipid levels was tested by ANCOVA, adjusting for potential confounding variables (age, sex, BMI, A1C, smoking, and alcohol). We defined survival time as the period from the date of entry into the study to the date of the first event (myocardial infarction or sudden death) or the end of the study. Cox regression was used to estimate the hazard ratio; we adjusted for age, sex, prior myocardial infarction, systolic blood pressure, A1C, C-reactive protein (CRP), UAE, serum creatinine, total and HDL cholesterol, smoking, diabetes duration, BMI, and triglyceride levels and for the use of drugs at baseline: different antidiabetes and lipid-lowering treatments, treatments for hypertension, and platelet antiaggregants. We also adjusted for insulin and ACE inhibitor treatments, which could only be introduced during the follow-up (treatments by insulin and/or an ACE inhibitor at entry were exclusion criteria). The distribution of the use of the different drugs did not differ among genotypes. There was no interaction effect between genotype and the use of drugs. No interaction effect was found between sex and genotype, either on lipid levels or on CHD events. Therefore, data are not presented separately according to sex. All calculations were performed using SYSTAT 11 for Windows.

**RESULTS** — Table 1 provides a summary of features and clinical and lipid profiles at baseline of the DIABHYCAR population as well as the stratified data according to combined CHD incidence (myocardial infarction or cardiovascular death). Subjects with incident CHD during follow-up differed in age; total, LDL, and HDL cholesterol and triglyceride lev-

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**Table 2—*Association of* Taq*1B SNP with plasma lipid levels***

| | Total cholesterol (mmol/l) | LDL cholesterol (mmol/l) | HDL cholesterol (mmol/l) | Triglycerides (mmol/l) |
|---|---|---|---|---|
| B1B1 ($n$ = 1,107) | 5.73 ± 1.01 | 3.50 ± 0.89 | 1.25 ± 0.35 | 1.93 (1.83–2.03) |
| B1B2 ($n$ = 1,526) | 5.82 ± 1.05 | 3.55 ± 0.87 | 1.33 ± 0.35 | 1.89 (1.80–1.98) |
| B2B2 ($n$ = 491) | 5.84 ± 1.12 | 3.49 ± 0.89 | 1.39 ± 0.37 | 1.91 (1.76–2.06) |
| $P$* | 0.009 | 0.30 | <0.001 | 0.71 |

Data are means ± SD or geometric mean (95% CI) in millimoles per liter. *By ANCOVA, adjusting for age, sex, BMI, A1C, smoking, and alcohol.

els; blood pressure; known duration of diabetes; prevalence of prior coronary antecedents (myocardial infarction and angina pectoris); serum CRP; serum creatinine; and UAE. The sex ratio was similar in the two groups. Genotype and allele distributions of the *Taq*IB SNP are shown in Table 2. The genotype frequencies were in Hardy-Weinberg equilibrium. None of the variables (distribution or levels), including prior coronary events, differed according to CETP *Taq*1B genotypes (data not shown) except lipid levels (Table 2). The *CETP Taq*I B1 allele was associated with low levels of HDL cholesterol ($P < 0.001$), with a gene dose effect (Table 2).

The CHD incidence (myocardial infarction and/or sudden death) according to the *CETP* genotype is shown in Table 3. There was a higher percentage of B1B1 subjects in the CHD group than in the group without CHD. Cox survival analysis indicated that B1B1 homozygotes had more risk than carriers of the B2 allele, independent of other risk factors, including many variables listed in Table 1 (age, A1C, systolic blood pressure, diabetes duration, prior myocardial infarction, total plasma cholesterol, triglycerides, serum CRP, serum creatinine, and UAE). There was no interaction between genotype and the presence of prior coronary events on the incidence of CHD. Nevertheless, the association was still significant when we excluded subjects with prior myocardial infarction.

After further adjustment for HDL cholesterol levels, the association remained significant and only slightly lower than that without the adjustment. Sudden death was a major factor in this association (Table 3). The 4-year overall and sudden death–free survival rates were 91 and 95% for B1B1 and B2 carriers, respectively. The B1B1 genotype was also more frequent in the "incident myocardial infarction" group (Table 3), but the association was not significant. This could be due to a lack of power of the study because there were so few cases of incident myocardial infarction.

**CONCLUSIONS** — We report a prospective study based on a large cohort of French type 2 diabetic patients with micro- or macroalbuminuria and found, for the first time, a strong negative association between the B2 allele and CHD incidence and particularly sudden death. Although the *CETP Taq*IB polymorphism was associated with HDL cholesterol in these patients, the association with the occurrence of sudden death remained highly significant after adjustment for most potential confounders, including age and HDL cholesterol.

The association of the *CETP Taq*IB polymorphism and HDL cholesterol levels is widely recognized in many different populations, including type 2 diabetic patients. The B1 allele has also been associated with a higher prevalence of CHD (11–13). Nevertheless, there is a lack of consistent correlation between the *CETP* genotype and the clinical outcome. This association may depend on gene-gene or gene-environment interactions (21). A recent meta-analysis of large studies (11) showed that *CETP Taq*IB was associated with cardiovascular risk and that this relationship was mediated by lower HDL cholesterol levels. In contrast, we show that HDL cholesterol modified the risk associated with the *Taq*IB genotype only slightly. One reason could be the interaction with the diabetic phenotype. Studies of type 2 diabetic populations mostly show an association between CETP and cardiovascular disease (9,12,22,23). HDL cholesterol levels do not greatly modify the relationship between the *CETP* genotype and the clinical outcome. This finding could be specific to type 2 diabetic subjects in whom HDL cholesterol levels are already lower than those in nondiabetic subjects.

The most striking result from our study is the association with sudden death. There have been only a few prospective studies of *CETP Taq*IB polymorphisms. Blankenberg et al. (24) investigated

**Table 3—*Frequencies of* CETP *genotypes according to the incidence of coronary events***

| | Combined CHD | | Sudden death | | Incident myocardial infarction | |
|---|---|---|---|---|---|---|
| | No | Yes | No | Yes | No | Yes |
| *Taq*IB *CETP* | | | | | | |
| B1B1 | 1,012 (34.9) | 95 (42.6) | 1,046 (35.0) | 61 (44.5) | 1,068 (35.2) | 39 (41.2) |
| B1B2 | 1,431 (49.3) | 95 (42.6) | 1,469 (49.2) | 57 (41.6) | 1,484 (49.1) | 42 (44.2) |
| B2B2 | 458 (15.8) | 33 (14.8) | 472 (15.8) | 19 (13.9) | 477 (15.8) | 14 (14.7) |
| B1B1 vs. B2$^+$ | | | | | | |
| Unadjusted | 1.37 (1.05–1.79), 0.020 | | 1.47 (1.05–2.08), 0.023 | | 1.30 (0.85–1.96), 0.22 | |
| Model 1* | 1.41 (1.06–1.87), 0.018 | | 1.51 (1.05–2.18), 0.027 | | 1.42 (0.93–2.17), 0.10 | |
| Model 1† | 1.35 (1.01–1.79), 0.043 | | 1.46 (1.01–2.12), 0.043 | | 1.33 (0.87–2.05), 0.19 | |

Data are given as $n$ (%) or hazard ratio (95% CI), $P$. *Model 1: adjusted for age, systolic blood pressure, sex, prior myocardial infarction, UAE, serum CRP, serum creatinine, total cholesterol, A1C, smoking, diabetes duration, BMI, triglycerides, and drug treatments. †Model 2: model 1 + adjustment for HDL cholesterol.

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the association between the risk of fatal cardiovascular events in 1,211 patients with coronary artery disease and −629C>A, an SNP in near complete positive linkage disequilibrium with the *Taq*IB polymorphism (10). Mortality was lower for carriers of the minor A allele (4–4.6%) (the one linked to *Taq*IB2 allele) than for CC homozygotes (10.8%); this was not the case for other cardiovascular outcomes. This allele was also associated with higher HDL cholesterol levels and lower CETP activity, but, similarly to our results, the strong protective effect on future cardiovascular mortality was independent of its effect on HDL cholesterol levels. The *Taq*IB polymorphism in cases of micro- and macroalbuminuria has been associated with atrial fibrillation (25). This association is very relevant to our findings for type 2 diabetic patients with micro- or macroalbuminuria as atrial fibrillation is associated with an increase in cardiovascular mortality (26,27).

The B2 allele has been associated with lower levels and activity of CETP, which leads to higher HDL cholesterol levels. However, there is evidence that CETP inhibition goes beyond raising HDL cholesterol levels alone for the purpose of prevention of cardiovascular risk (28,29), and our study supports this hypothesis. Nevertheless, the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE) trial with a CETP inhibitor, torcetrapib, was interrupted because of a higher mortality rate in the torcetrapib and atorvastatin group than in the atorvastatin group (30). In another trial (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation [ILLUSTRATE]), there was no significant difference in the atherosclerotic plaque burden in the two study groups (atorvastatin with or without torcetrapib) (31). In both of these trials, the use of torcetrapib was associated with increased blood pressure. In our study, the *Taq*IB polymorphism was not associated with blood pressure (data not shown). Therefore, our results indirectly suggest that the problem may have been due to an adverse effect of the drug, unrelated to the CETP inhibition, as already suggested (32).

We did not observe associations between the *CETP Taq*IB SNP and prior myocardial infarction. We think that the prospective design of the DIABHYCAR study allowed us to avoid the biases of cross-sectional/case-control studies, which can lower the power to detect associations, but such biases could explain why we observed only an effect on the CHD incidence but not on the prevalence at entry.

In summary, we have demonstrated that the *Taq*IB polymorphism of the *CETP* gene is a good genetic predictor of CHD complications of type 2 diabetes and especially cardiac mortality. This association is not fully explained by the effect of *Taq*IB SNP on HDL cholesterol levels.

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**APPENDIX**— The DIABHYCAR study group included the following: Principal Investigator: Prof. M. Marre (Bichat Hospital, Paris, France); Steering Committee: F. Alhenc-Gelas, J.P. Boissel, F. Cambien, S. Etienne, A. Girault-Louvel, P. Gueret, M. Lièvre, J. Mann (Vice-Chairman), M. Marre, J. Ménard, P. Passa (Chairman), P.F. Plouin, D. Vasmant, L. Vaur (Secretary), G.C. Viberti, and C. Weisselberg; Central Co-ordinating Center: J.P. Boissel and M. Lièvre; Executive Committee: J.P. Boissel, V. Bost, M. Cambien, Y. Gallois, N. Genes, J. Gillet, M. Hervé, M. Lièvre, M. Marre, L. Martin, A. Perret-Hantzperg, P.F. Plouin, and L. Vaur; Biological Committee: F. Alhenc-Gelas (Chairman), F. Cambien, A. Girault-Louvel (Vice-Chairman), M. Lièvre, M. Marre, and J. Ménard; Central End Point Committee: E. Bonnefoy, G. Chatellier (Chairman), T. Moreau, and L. Pinède; and Independent Data and Safety Committee: E. Eschwege, C.E. Mogensen, N. Victor, and S. Weber.

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