The Common −866G>A Variant in the Promoter of UCP2 Is Associated With Decreased Risk of Coronary Artery Disease in Type 2 Diabetic Men

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OBJECTIVE—Uncoupling protein 2 (UCP2) is a physiological downregulator of reactive oxygen species generation and plays an antiatherogenic role in the vascular wall. A common variant in the UCP2 promoter (−866G>A) modulates mRNA expression, with increased expression associated with the A allele. We investigated association of this variant with coronary artery disease (CAD) in two cohorts of type 2 diabetic subjects.

RESEARCH DESIGN AND METHODS—We studied 3,122 subjects from the 6-year prospective Non–Insulin-Dependent Diabetes, Hypertension, Microalbuminuria, Cardiovascular Events, and Ramipril (DIABHYCAR) Study (14.9% of CAD incidence at follow-up). An independent, hospital-based cohort of 335 men, 52% of whom had CAD, was also studied.

RESULTS—We observed an inverse association of the A allele with incident cases of CAD in a dominant model (hazard risk 0.88 [95% CI 0.80–0.96]; $P = 0.006$). Similar results were observed for baseline cases of CAD. Stratification by sex confirmed an allelic association with CAD in men, whereas no association was observed in women. All CAD phenotypes considered—myocardial infarction, angina pectoris, coronary artery bypass graft (CABG), and sudden death—contributed significantly to the association. Results were replicated in a cross-sectional study of an independent cohort (odds ratio 0.47 [95% CI 0.25–0.89]; $P = 0.02$ for a recessive model).

CONCLUSIONS—The A allele of the −866G>A variant of UCP2 was associated with reduced risk of CAD in men with type 2 diabetes in a 6-year prospective study. Decreased risk of myocardial infarction, angina pectoris, CABG, and sudden death contributed individually and significantly to the reduction of CAD risk. This association was independent of other common CAD risk factors. ***Diabetes*** **57:1063–1068, 2008**

Cardiovascular disease accounts for up to 80% of the deaths of type 2 diabetic patients (1). Diabetic patients have a threefold higher risk than nondiabetic individuals of developing atherosclerosis and its clinical complications, such as stroke, myocardial infarction, and peripheral vascular disease (2). Arterial hypertension and dyslipidemia frequently coexist with diabetes and contribute to the increased prevalence of cardiovascular disease in diabetic patients. However, type 2 diabetes is an independent risk factor for cardiovascular disease (3). The molecular mechanisms linking type 2 diabetes and atherosclerosis remain unclear (4). Several metabolic dysfunctions associated with type 2 diabetes have been proposed to play a role in the acceleration of atherosclerosis, including hyperinsulinemia, hyperglycemia, increased formation of advanced glycation end products, platelet hyperaggregability, coagulation abnormalities, endothelial dysfunction, and increased oxidative stress (4). Particularly, increased oxidative stress in vascular cells plays a key role in the formation of atheroma (5) and in the instability of the atherosclerotic plaque, a crucial step in the occurrence of acute coronary events (6).

Uncoupling protein 2 (UCP2) functions as a physiological downregulator of reactive oxygen species (ROS) generation in endothelial and smooth muscle cells of the vascular wall and in macrophages (7–11). Several studies have shown that UCP2 plays an antiatherogenic role in the vascular wall (8,9,11) and may improve tolerance to cardiac ischemia (12). A series of clinical investigations have shown associations of the −866G>A (rs659366) functional single nucleotide polymorphism (SNP) in the promoter region of UCP2 with phenotypes related to obesity (13), glucose homeostasis (14–16), and dyslipidemia (17). In the present study, we investigated the association of this variant with coronary artery disease (CAD) in type 2 diabetic patients.

RESEARCH DESIGN AND METHODS

Prospective study. The Non-Insulin-Dependent Diabetes, Hypertension, Microalbuminuria, Cardiovascular Events, and Ramipril (DIABHYCAR) Study was a 6-year double-blind multicenter multinational clinical trial conducted in 4,912 men and women with type 2 diabetes aged ≥50 years or older at baseline and selected on the basis of a persistent micro- or macroalbuminuria (urinary albumin concentration [UAC] ≥20 mg/l) without renal failure (serum creati-

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CABG, coronary artery bypass graft; CAD, coronary artery disease; DIABHYCAR Study, Non-Insulin-Dependent Diabetes, Hypertension, Microalbuminuria, Cardiovascular Events, and Ramipril Study; NCH, Necker and Cochin Hospitals; ROS, reactive oxygen species; SNP, single nucleotide polymorphism; UAC, urinary albumin concentration; UCP2, uncoupling protein 2.

TABLE 1
Characteristics of DIABHYCAR cohorts at baseline according to CAD incidence status

	Incident CAD		
	Yes	No	*P* value
Patients (*n*)	464	2,658	—
Men (%)	80	71	<0.0001
Age (years)	67 ± 8	65 ± 8	<0.0001
Age at diagnosis of diabetes (years)	56 ± 10	55 ± 10	0.11
Known duration of diabetes (years)	11 ± 8	10 ± 8	0.005
Fasting plasma glucose (mmol/l)	9.6 ± 2.9	9.5 ± 3.1	0.53
A1C (%)	8.0 ± 1.8	7.8 ± 1.8	0.02
BMI (kg/m^2)	28.9 ± 4.4	29.5 ± 4.7	0.01
Ponderal status: lean/overweight/obese (%)*	13/49/38	12/43/45	0.03
Triglycerides (mmol/l)	2.38 ± 1.32	2.19 ± 1.44	<0.0003
Total cholesterol (mmol/l)	5.97 ± 1.10	5.76 ± 1.06	0.0002
LDL cholesterol (mmol/l)†	3.68 ± 0.90	3.50 ± 0.88	0.0006
HDL cholesterol (mmol/l)	1.25 ± 0.31	1.33 ± 0.36	<0.0001
Creatinine clearance (ml/min)	80 ± 27	87 ± 30	<0.0001
Urinary albumin excretion (mg/l)	391 ± 1207	202 ± 446	<0.0001
UAE: microalbuminuria/macroalbuminuria (%)‡	68/32	78/22	<0.0001
Arterial hypertension (%)§	62	55	0.01
Tobacco smoking (%)	15	14	0.67
Randomization group: ramipril (%)¶	47	50	0.37
Previous myocardial infarction (%)	13	4	<0.0001
Angina pectoris (%)	23	10	<0.0001

Data are means ± SD. CAD represents the incident cases of myocardial infarction, CABG, or sudden death during the study. Statistics of quantitative parameters are Students *t* test performed with log-transformed data. *Ponderal status: lean, BMI <25 kg/m^2; overweight, 25 kg/m^2 ≤ BMI < 30 kg/m^2; obese, BMI ≥30 kg/m^2. †Data available for 353 subjects with CAD and 2,145 subjects without CAD. ‡UAE: microalbuminuria, 20 mg/l ≤ UAE < 200 mg/l; macroalbuminuria, UAE ≥200 mg/l. §Arterial hypertension: systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg; or systolic blood pressure and diastolic blood pressure below these values in the presence of antihypertensive medication and history of hypertension. ¶Randomization group in the original DIABHYCAR study ramipril versus placebo.

nine ≤150 μmol/l). The trial tested in a parallel design and versus placebo whether a low dose of ramipril (1.25 mg/day) able to reduce UAC would also reduce cardiovascular and/or renal events, such as myocardial infarction, stroke, acute heart failure, end-stage renal failure, and cardiovascular death. Study design, methods, and results of the trial (which were negative regarding the drug effect) were published previously (18,19). For the purpose of the trial, myocardial infarction was diagnosed as the occurrence of at least two of three of the following criteria: constrictive chest pain lasting 20 min or longer, increased serum creatinine phosphokinase and/or troponine levels, or typical electrocardiographic changes. Sudden death was defined as death occurring instantaneously or within 1 h after the onset of new cardiac symptoms (arrhythmia and myocardial infarction) or nonwitnessed death, when the body was found and no cause of death could be discovered. Fatal stroke was not included in this group. All events were adjudicated by an independent event committee (18). DNA banking was undertaken for the 3,137 participants recruited in France. All participants gave written informed consent. The study protocol was approved by the Angers University Hospital Ethics Committee.

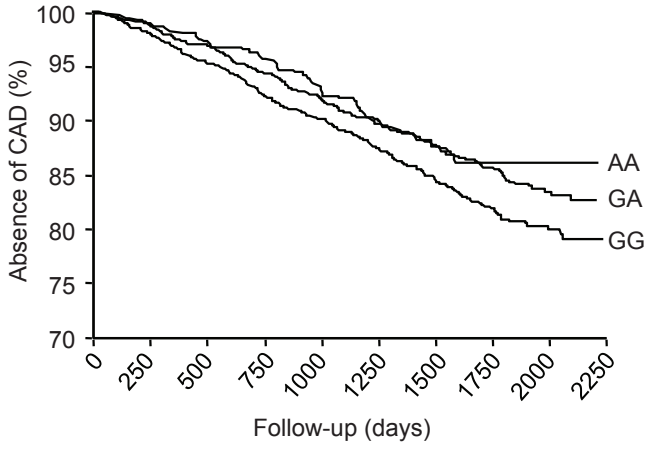

FIG. 1. Kaplan-Meier survival (disease-free) curves for the DIABHYCAR cohort during follow-up according to genotype. Survival (*y*) axis represents absence of CAD defined as myocardial infarction, CABG, or sudden death. The cumulated incidence of CAD can be computed as (100% − survival).

In the present investigation, we studied 3,122 French type 2 diabetic patients from the original DIABHYCAR cohort. Age at baseline was 66 ± 8 years (means ± SD), and 73% of patients were men. Also at baseline, 172 subjects (5.5%) had a previous history of myocardial infarction, and 376 subjects (12%) had a diagnosis of angina pectoris. Myocardial infarction occurred in 95 patients (3%) during the trial, including 10 subjects with history of myocardial infarction at baseline. Coronary artery bypass graft (CABG) was performed in 295 subjects during the trial, including 80 subjects with previous myocardial infarction at baseline or during the study. Sudden death occurred in 137 subjects (4.4%) during the trial, including 25 subjects with previous myocardial infarction at baseline or during the study. For the purpose of this investigation, baseline cases of CAD included the cases of myocardial infarction and/or angina pectoris. Incident cases of CAD included the cases of myocardial infarction or of sudden death or the cases of a history of CABG during the follow-up. Supplemental Table 1, which is detailed in the online appendix (available at http://dx.doi.org/10.2337/db07-1292), shows the stratification of incident cases of CAD according to CAD baseline status.

Cross-sectional study. We have studied a group of 335 French Caucasian men with type 2 diabetes recruited at the Departments of Diabetology of Necker and Cochin Hospitals (NCH) in Paris. The presence or absence of CAD was documented either by a history of myocardial infarction or CABG or by the systematic assessment of myocardial ischemia in asymptomatic patients. In the latter case, patients with cardiovascular risk factors underwent a stress test (stress electrocardiogram, stress thallium-201 single photon emission computed tomography, or dobutamine echocardiography). Patients with a positive stress test underwent coronary angiography. CAD was considered present if significant stenosis (≥50%) was present in at least one major vessel or branch. CAD was considered absent in patients with normal stress test or with no significant coronary stenosis at angiography. Detailed procedures of stress tests and angiography have been previously reported (20). Overall, 174 patients with CAD (35% with a previous history of myocardial infarction or CABG and 65% diagnosed by coronary angiography) and 161 patients without CAD were included in the present study. Subjects were considered to have increased triglycerides, increased LDL cholesterol, and decreased HDL cho-

TABLE 2
Genotype frequency and incidence of CAD in the DIABHYCAR cohort

		−866G>A:N (genotype frequency)			A allele in a dominant model			
					Unadjusted model		Adjusted model*	
Subjects	CAD	GG	GA	AA	HR (95% CI)	*P* value	HR (95% CI)	*P* value
All	Yes	217 (0.468)	197 (0.424)	50 (0.108)				
	No	1,058 (0.398)	1,230 (0.463)	370 (0.139)	0.88 (0.80–0.96)	0.006	0.87 (0.80–0.96)	0.005
Men	Yes	179 (0.480)	154 (0.413)	40 (0.107)				
	No	744 (0.390)	903 (0.473)	261 (0.137)	0.85 (0.77–0.94)	0.002	0.84 (0.76–0.93)	0.001
Women	Yes	38 (0.418)	43 (0.472)	10 (0.110)				
	No	314 (0.419)	327 (0.436)	109 (0.145)	1.00 (0.82–1.24)	0.98	1.04 (0.84–1.29)	0.72

CAD: incident cases of myocardial infarction, CABG or sudden death. HRs for the A-allele in a dominant model (XA vs. GG) determined by Cox proportional hazards survival regression analyses. Time to event was defined either as the number of days of follow-up until the occurrence of a CAD event for subjects with CAD or as the duration of follow-up for right-censored subjects without CAD at the end of follow-up. Computations performed without adjustment for covariables or *adjusted for allocation group in the original DIABHYCAR trial (drug or placebo), age, BMI, total cholesterol, HDL cholesterol, triglycerides, urinary albumin excretion, creatinine clearance, A1C, duration of diabetes, and arterial hypertension.

lesterol levels if current or pretreatment plasma levels were ≥1.70, >3.35, or <1.02 mmol/l, respectively (21). Arterial hypertension was defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg (22) or by the presence of antihypertensive therapy. Creatinine clearance was computed with the Cockcroft formula (23). All participants gave written informed consent. The study was approved by the ethics committee of Hôpital Necker (CCPPRB Paris Necker).

DNA studies. The SNP at position −866 in the promoter region of the UCP2 gene (rs659366) was genotyped using the Assay by Design kit from Applied Biosystems. The conditions for TaqMan reaction were as follows: 50°C for 2 min, 95°C for 10 min, and 45 cycles of 95°C for 15 s and 66°C for 1 min.

Statistical analyses. Results are expressed as means ± SD. Differences between groups were assessed by Student's *t* test, contingency table χ^2 test, and Fisher's exact test. Before genotype-related statistical analyses were performed, it was verified that genotypes were in Hardy-Weinberg equilibrium in all groups of subjects. Genotype associations with CAD were assessed by regression models. Cox proportional hazards survival regression analyses were used to examine the effect of explanatory variables on time-related survival (disease-free) rates in prospective analyses. Kaplan-Meier curves were used to plot survival (disease-free) rates over time according to genotype. Logistic regression analyses were used for cross-sectional analyses. Hazard ratios (HRs) or odds ratios (ORs), respectively, with their 95% CIs were computed in these analyses for the minor A allele. For dominant (XA vs. GG genotypes) and recessive (AA vs. XG genotypes) models, HRs and/or ORs were considered to be 1 for GG or XG genotypes, respectively. For the codominant model, genotype data were coded as the number of A-allele copies (0, 1, or 2), and HR was computed for the number of A alleles as a quantitative variable (1 vs. 0 and 2 vs. 1 copies, with the lower number of copies of each pair considered to present an OR of 1). Interaction between sex and genotype was assessed by including in the regression model a "crossed" compound covariable (sex/genotype). Stratification by sex of genotype-related effects was then performed by nesting the genotype variable within the sex variable in the regression analysis. This results in the computation of statistical effects for men and women separately and adjusted for multiple comparisons due to the stratification by sex. Adjustments for other clinical and biological parameters were carried out by including these parameters as covariables in the regressive model. Data were log transformed for the analyses when the normality of the distribution was rejected by the Shapiro-Wilk *W* test. $P < 0.05$ was considered significant. Statistics were performed with the JMP software (SAS Institute, Cary, NC).

RESULTS

Prospective study: DIABHYCAR cohort. The incidence of CAD during the follow-up of the French subset of the DIABHYCAR cohort was 14.9%. CAD events comprised 95 cases of myocardial infarction, 295 cases of CABG, and 137 cases of sudden death reported in 464 subjects. Main baseline characteristics of subjects with or without CAD during the follow-up (incident cases) are shown in Table 1. Known cardiovascular risk factors, such as the male sex, dyslipidemia, arterial hypertension, decreased renal function, and albuminuria, were more frequent or more severe in subjects with CAD compared with subjects without CAD.

Incidence of CAD according to genotype was 17.0% for GG, 13.8% for GA, and 11.9% for AA (Fig. 1). Cox proportional hazards survival regression analyses showed an inverse association of the A allele with the incidence of CAD in a dominant model (HR 0.88 [95% CI 0.80–0.96]; $P = 0.006$) (Table 2). A significant interaction between genotype and sex ($P = 0.008$) was observed in this association with CAD. Stratification by sex confirmed the allelic association with CAD in men, whereas no association was observed in women (Table 2). The association persisted after adjustment for allocation group in the original DIABHYCAR trial (drug or placebo), age, BMI, total cholesterol, HDL cholesterol, triglycerides, urinary albumin excretion, creatinine clearance, A1C, duration of diabetes, and arterial hypertension (Table 2). There was no interaction between the treatment group in the original DIABHYCAR study and the effect of genotype on CAD. To assess which CAD phenotypes contributed to this association, we computed individual HRs for cases of myocardial infarction or CABG or sudden death by excluding from the calculations for each phenotype the other incident cases of CAD. HRs for the A allele in men were 0.71 (0.56–0.90) ($P = 0.004$) for myocardial infarction, 0.88 (0.78–0.99) ($P = 0.05$) for CABG, and 0.82 (0.67–0.99) ($P = 0.04$) for sudden death. Analyses in a codominant model were also significant ($P = 0.02$ for the whole population; $P = 0.007$ for men) but only confirmed a dominant effect. The HR for the presence of one A allele (AG vs. GG) in men was 0.73 (0.59–0.90), with no significant additional effect for the second A allele (AA vs. AG, 0.95 [0.66–0.1.33]). Similar association in a dominant model was observed when we considered the prevalent cases of CAD at baseline, defined as a previous history of myocardial infarction or angina pectoris (Table 3).

To investigate the role of possible intermediate phenotypes in these allelic associations with CAD, we compared clinical and biological profiles at baseline according to genotype (Supplemental Table 2). Age of diagnosis of diabetes, severity of hyperglycemia, BMI and ponderal status, renal function, prevalence of arterial hypertension, plasma levels of triglycerides, total cholesterol, and HDL cholesterol were similar in carriers of different genotypes. LDL cholesterol levels were slightly but significantly lower

TABLE 3
Genotype frequency and prevalence of CAD at baseline in the DIABHYCAR cohort

		−866G>A:N (genotype frequency)			A allele in a dominant model			
					Unadjusted model		Adjusted model*	
Subjects	CAD	GG	GA	AA	OR (95% CI)	*P* value	OR (95% CI)	*P* value
All	Yes	216 (0.451)	197 (0.411)	66 (0.138)				
	No	1059 (0.401)	1230 (0.465)	354 (0.134)	0.81 (0.67–0.98)	0.04	0.81 (0.66–0.99)	0.04
Men	Yes	179 (0.469)	149 (0.390)	54 (0.141)				
	No	744 (0.392)	908 (0.478)	247 (0.130)	0.73 (0.59–0.91)	0.005	0.74 (0.59–0.92)	0.008
Women	Yes	37 (0.381)	48 (0.495)	12 (0.124)				
	No	315 (0.423)	322 (0.433)	107 (0.144)	1.19 (0.77–1.85)	0.43	1.13 (0.71–1.80)	0.61

CAD: history of myocardial infarction or angina pectoris at baseline. OR for the A allele in a dominant model (XA vs. GG) determined in logistic regression analyses. Computations performed without adjustment for covariables or *adjusted for age, BMI, total cholesterol, HDL cholesterol, triglycerides, urinary albumin excretion, creatinine clearance, A1C, duration of diabetes, and arterial hypertension.

in carriers of the A allele: 3.50 ± 0.89 vs. 3.57 ± 0.87 mmol/l ($P = 0.02$), respectively, for XA and GG subjects.

Cross-sectional study: NCH cohort. Main clinical characteristics of subjects with or without CAD are shown in Supplemental Table 3. Cardiovascular risk factors, such as dyslipidemia, arterial hypertension, decreased renal function, albuminuria, and a history of cigarette smoking, were more frequent or more severe in subjects with CAD. A logistic regression analysis was performed to assess association of genotype with CAD (Table 4). We observed an inverse association of the A allele with CAD in a recessive model (OR 0.47 [0.25–0.89]; $P = 0.02$). This genotype effect remained significant when adjusted for other individual risk factors (LDL cholesterol, HDL cholesterol, arterial hypertension, creatinine clearance, and albuminuria). These associations are in keeping with genotype-related prevalences of CAD: 56 vs. 53 vs. 36% in G allele homozygous, heterozygous, and A allele homozygous subjects, respectively.

DISCUSSION

We have observed in two independent cohorts of French Caucasian subjects that the common −866G>A SNP in the UCP2 promoter region strongly modulates the risk of CAD in type 2 diabetic men. The first cohort was recruited for a multicenter prospective clinical trial. Inverse associations of the A allele with both baseline and incident cases of CAD were observed in a dominant model with a 12–25% decrease in CAD risk for A allele carriers. The four types of CAD events that we have considered, namely, myocardial infarction, angina pectoris, CABG, and sudden death, contributed significantly to these results. Interestingly, these associations showed interaction with sex and were observed in men but not in women. We have no established explanation for this lack of association in women, but it is not possible to exclude true sex-related biological differences in UCP2 protection against CAD.

These results were confirmed in a smaller, hospital-based cohort recruited from a single Diabetes department and consisting of type 2 diabetic men with a history of myocardial event (infarction or CABG) or who underwent a systematic assessment of myocardial ischemia. A allele homozygosis was associated with a 50% decrease in the risk of CAD in the NCH cohort. Apparently, this effect is larger than the 25% decrease observed, for instance, for the baseline cases of CAD in men of the DIABHYCAR cohort, also computed by OR. However, the wide CIs associated with both ORs preclude the drawing of such a conclusion. It is also noteworthy that A allele association with decreased risk of CAD in men was observed for different genetic models in the two cohorts of our study: in dominant models for the DIABHYCAR cohort and in a recessive model for the NCH cohort. We do not have an established explanation for this observation, but it could be related to phenotype differences due to different study design and CAD ascertainment methods in the two cohorts.

Previous studies have shown that the −866G>A SNP is a functional polymorphism (13,14). The A allele has been associated with enhanced adipose tissue mRNA expression in vivo and has been shown to result in increased transcription of a reporter gene in a human adipocyte cell line (13). Studies in pancreatic β-cell line INS1-E have shown that the pancreatic transcription factor PAX6 preferentially binds to and more effectively transactivates the A allele (14). To our knowledge, allele-related expression studies in cell types directly implicated in the atherosclerosis process or plaque stability are not available.

Several investigations have established a link between UCP2 and atherosclerosis. UCP2 is a physiological down-regulator of ROS generation in endothelial and smooth muscle cells of the vascular wall, in macrophages (7–11), and in cardiomyocytes (24). It has antiatherogenic effects in the arterial wall (8,9,11) and could protect cardiomyocytes from oxidative stress–induced cell death by reducing ROS production in mitochondria (24). Blanc et al. (8)

TABLE 4
Genotype frequency and prevalence of CAD in the NCH cohort

	−866G>A:N (genotype frequency)			A allele in a recessive model	
	GG	GA	AA	OR (95% CI)	*P* value
With CAD	76 (0.437)	81 (0.465)	17 (0.098)	0.47 (0.25–0.89)	0.02
Without CAD	60 (0.373)	71 (0.441)	30 (0.186)		

OR for the A allele (AA vs. GX) determined in logistic regression analyses.

studied LDL receptor–deficient mice fed an atherogenic diet, an animal model of accelerated atherosclerosis. Animals were irradiated and then transplanted with bone marrow from either UCP2-deficient mice ($Ucp2^{-/-}$) or wild-type mice ($Ucp2^{+/+}$). Larger atherosclerotic lesions with a more severe plaque phenotype (increased macrophage accumulation, apoptosis, and histological markers of enhanced oxidative stress along with decreased collagen content) were observed in the thoracic aorta of $Ucp2^{-/-}$ transplanted mice compared with $Ucp2^{+/+}$ transplanted mice. Park et al. (11) showed that overexpression of UCP2 in human vascular smooth muscle cells reversed the increase in ROS production and cellular proliferation and migration elicited by high glucose and angiotensin II concentrations in the culture medium. Moreover, it was recently shown in mouse models that UCP2 positively modulates adiponectin gene expression and influences circulating adiponectin levels (25). Adiponectin has many protective actions in the initiation and progression of atherosclerosis by means of direct anti-inflammatory and anti-atherogenic effects (26,27). All of these results suggest a protective role for UCP2 against atherosclerosis and could explain the protective effect of the A allele observed in our study.

A series of clinical studies showed associations of this polymorphism with several phenotypes related to obesity, diabetes, insulin sensitivity, insulin secretion, and dyslipidemia (13–17,28). We have observed in the DIABHYCAR cohort slightly decreased LDL cholesterol levels in A allele carriers compared with GG carriers. However, it is interesting to note that the protection against CAD afforded by the A allele in our study was independent from effects on other known cardiovascular risk factors, including obesity, arterial hypertension, and dyslipidemia. Our results contrast with those in the study by Dhamrait et al. (29) in a cohort of healthy men prospectively studied for 10 years. In that study, A allele homozygosis doubled CAD risk after adjustment for other risk factors. Moreover, in that study, the A allele was also associated with obesity, which also contrasts with results from two independent cohorts of nondiabetic subjects, in whom a reduction in the prevalence of obesity was observed for A allele carriers (13). The reasons for all of these discrepancies remain unclear. Regarding obesity, a protective effect of A allele would be in keeping with the observation of inverse correlations between UCP2 mRNA expression in human adipose tissue of nondiabetic subjects and BMI, percentage of body fat, and blood levels of leptin, insulin, and triglyceride (30).

In summary, we found that the A allele of the −866G>A SNP in the UCP2 promoter region was associated with a significantly lower risk of CAD in type 2 diabetic men. This effect was independent of effects of other risk factors, such as age, duration of diabetes, dyslipidemia, arterial hypertension, proteinuria, and smoking. The mechanisms underlying this allelic association need to be investigated in further studies. They could be related to a modulation of antiatherogenic effects of UCP2 in the vascular wall.

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