

# Insufficient Control of Blood Pressure and Incident Diabetes

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**OBJECTIVE** — Incidence of type 2 diabetes might be associated with preexisting hypertension. There is no information on whether incident diabetes is predicted by blood pressure control. We evaluated the hazard of diabetes in relation to blood pressure control in treated hypertensive patients.

**RESEARCH DESIGN AND METHODS** — Nondiabetic, otherwise healthy, hypertensive patients ( $N = 1,754$ , mean  $\pm$  SD age  $52 \pm 11$  years, 43% women) participated in a network over  $3.4 \pm 1$  years of follow-up. Blood pressure was considered uncontrolled if systolic was  $\geq 140$  mmHg and/or diastolic was  $\geq 90$  mmHg at the last outpatient visit. Diabetes was defined according to American Diabetes Association guidelines.

**RESULTS** — Uncontrolled blood pressure despite antihypertensive treatment was found in 712 patients (41%). At baseline, patients with uncontrolled blood pressure were slightly younger than patients with controlled blood pressure ( $51 \pm 11$  vs.  $53 \pm 12$  years,  $P < 0.001$ ), with no differences in sex distribution, BMI, duration of hypertension, baseline blood pressure, fasting glucose, serum creatinine and potassium, lipid profile, or prevalence of metabolic syndrome. During follow-up, 109 subjects developed diabetes. Incidence of diabetes was significantly higher in patients with uncontrolled (8%) than in those with controlled blood pressure (4%, odds ratio 2.08,  $P < 0.0001$ ). In Cox regression analysis controlling for baseline systolic blood pressure and BMI, family history of diabetes, and physical activity, uncontrolled blood pressure doubled the risk of incident diabetes (hazard ratio [HR] 2.10,  $P < 0.001$ ), independently of significant effects of age (HR 1.02 per year,  $P = 0.03$ ) and baseline fasting glucose (HR 1.10 per mg/dl,  $P < 0.001$ ).

**CONCLUSIONS** — In a large sample of treated nondiabetic hypertensive subjects, uncontrolled blood pressure is associated with twofold increased risk of incident diabetes independently of age, BMI, baseline blood pressure, or fasting glucose.

*Diabetes Care* 32:845–850, 2009

Arterial hypertension is common in patients with type 2 diabetes. A survey of over 1,500 patients with diabetes, conducted between 1988 and 1994, determined that 60–80% had blood pressure higher than 130/85 mmHg or had been prescribed antihypertensive medication (1). Results from MRFIT (Multiple Risk Factor Intervention

Trial) indicated that diabetes confers greater cardiovascular risk for comparable levels of other cardiovascular risk factors, suggesting that blood pressure control should be more rigorous in the presence of diabetes (2). However, there is no clearly defined temporal relationship between diabetes and hypertension. Incidence of type 2 diabetes, in fact,

also increases with increased baseline blood pressure in women without prevalent diabetes, based on modified blood pressure categories from the 2007 European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines (3). There is increasing evidence of a substantial interplay of metabolic factors with arterial hypertension (4,5). We have recently shown that optimal control of blood pressure is blunted by coexisting metabolic risk factors, clustering the phenotype of metabolic syndrome (4). There is no information about whether suboptimal control of blood pressure might also be associated with incident diabetes, independently of confounders. Accordingly, we tested the hypothesis that insufficient control of blood pressure is an independent risk factor for diabetes in a cohort of hypertensive patients with initial normal fasting plasma glucose.

## RESEARCH DESIGN AND METHODS

As previously reported (6), beginning in 1997 we generated a network, the Campania Salute Network, among the Hypertension Center of the Federico II University Hospital (Naples, Italy), 23 community hospital-based hypertension clinics, and 60 general practitioners from our district area, including over 12,000 cardiovascular patients, of whom 10,254 had arterial hypertension. Among hypertensive subjects, 7,422 were initially free of prevalent cardiovascular disease (6). Prevalent cardiovascular disease was defined at each patient's first examination in our outpatient clinic, and criteria included previous myocardial infarction, angina, or procedures of coronary revascularization; stroke or transient ischemic attack; or congestive heart failure. Prevalent cardiovascular disease was excluded by the Committee for Event Adjudication in the Hypertension Center and was based on patient history, contact with the reference general practitioner, and clinical records documenting occurrence of disease.

Criteria for selection in the present study included the availability of follow-up data for at least 2 years and absence of diabetes at the time of the first visit. According to these criteria, we excluded 5,668 patients: 4,957 with  $< 2$

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Received 23 October 2008 and accepted 3 February 2009.

Published ahead of print at <http://care.diabetesjournals.org> on 17 February 2009. DOI: 10.2337/dc08-1881.

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years of follow-up (3,258 due to enrollment in the past 2 years and 1,699 lost to follow-up), 386 with prevalent diabetes, and 325 with reported impaired fasting glucose at the time of the first visit. Thus, we analyzed 1,754 Caucasian hypertensive patients (43% women mean  $\pm$  SD age  $52 \pm 11$  years) with normal fasting glucose who had been followed up for  $3.5 \pm 1.8$  years. All eligible participants underwent at least two control visits after the first examination.

The database generation of the Campania Salute Network was approved by the Federico II University Hospital Ethic Committee. Signed informed consent for the possibility of using data for scientific purposes was obtained.

### Laboratory tests and definitions

Fasting plasma glucose and lipid profiles were measured by standard methods. Glomerular filtration rate (GFR) was estimated from serum creatinine by the modified MDRD (Modification of Diet in Renal Disease) equation (7).

According to a questionnaire, patients were asked to classify their lifestyle as sedentary or nonsedentary. This information was used in the analysis as a raw indicator of physical activity.

Systolic and diastolic blood pressure was measured at each visit by a standard sphygmomanometer after patients had been in a sitting position for 5 min, according to ESH/ESC guidelines (8). For each patient, three blood pressure measurements were obtained at 2-min intervals while the patient was in the sitting position. The average of these measurements was used for the analysis (8).

BMI was calculated at each visit; patients with values  $\geq 30$  kg/m<sup>2</sup> were classified as obese and were assumed to have central fat distribution (9). Diagnosis of metabolic syndrome was, therefore, issued according to modified Adult Treatment Panel (ATP)-III criteria (4,5) and required at least two of the following metabolic risk factors: plasma triglycerides  $\geq 150$  mg/dl, fasting plasma glucose  $\geq 110$  mg/dl, HDL cholesterol  $\leq 40$  mg/dl for men or  $\leq 50$  mg/dl for women, and BMI  $\geq 30$  kg/m<sup>2</sup> (as a surrogate of increased waist girth). Non-HDL cholesterol was also determined and was calculated as the difference between total and HDL cholesterol.

The number of antihypertensive medications used at the time of each visit was also evaluated. Blood pressure was considered controlled at  $<140/90$  mmHg

and otherwise considered uncontrolled. Reported medical diagnostic codes for diabetes and prescriptions of oral hypoglycemic drugs or insulin were used to identify prevalent and incident cases of diabetes. Prevalent and incident diabetes was diagnosed when fasting plasma glucose was  $>125$  mg/dl, according to American Diabetes Association guidelines (10).

### Statistical analysis

Data were analyzed using SPSS (version 12.0; SPSS, Chicago, IL) and expressed as means  $\pm$  1 SD. All variables deviating from normal distribution were log transformed before parametric statistics were calculated. Descriptive statistics were performed using ANOVA or  $\chi^2$  distribution, with Monte Carlo simulation to generate exact *P* values.

The last available blood pressure value was used to classify controlled and uncontrolled patients. For patients developing diabetes, we used the last available controlled blood pressure value before diabetes was diagnosed. Incidence of diabetes in relation to controlled or uncontrolled blood pressure was evaluated using Cox regression, by the enter procedure, controlling for baseline values of age, sex, BMI, fasting plasma glucose, family history of diabetes, blood pressure at the time of the first visit, and sedentary or nonsedentary lifestyle. Alternative models were also computed using the last available blood pressure value instead of categories of controlled/uncontrolled blood pressure.

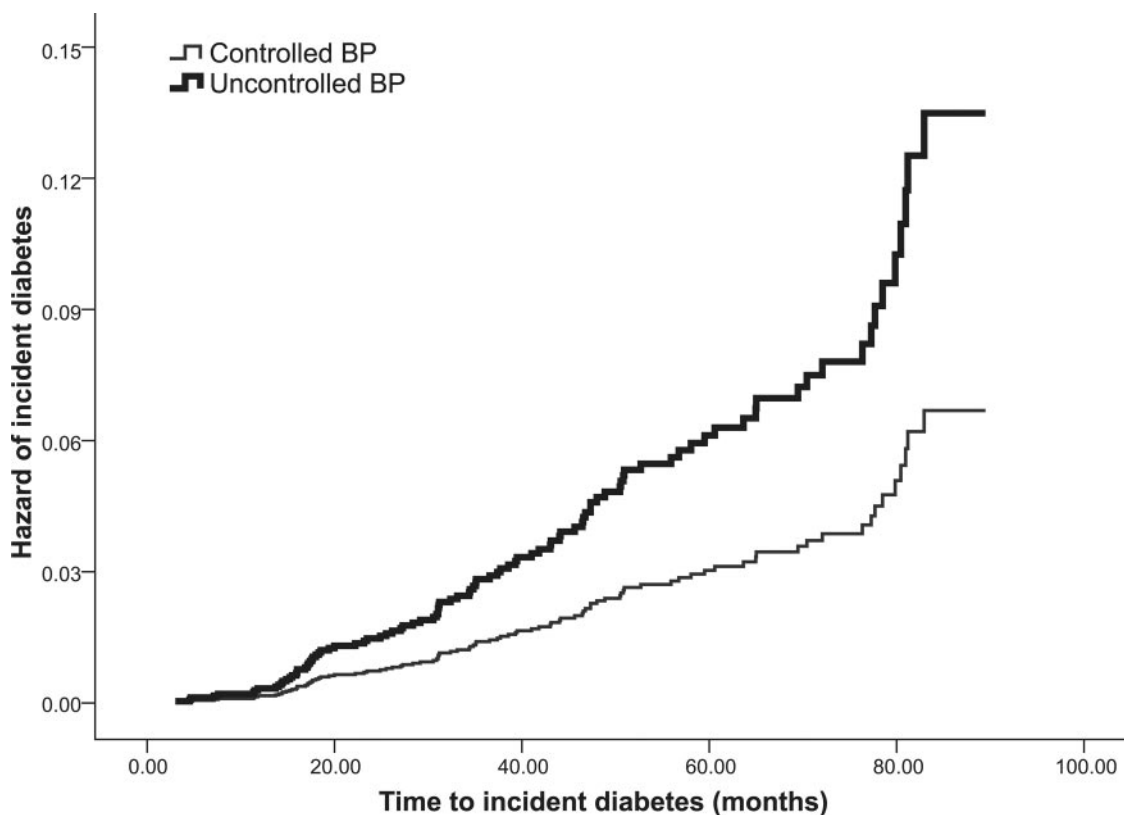
To account for therapy in the Cox model, single classes of medications, including anti-renin-angiotensin system (RAS) drugs (ACE inhibitors and/or AT1 receptor antagonists), calcium-channel blockers (CCBs),  $\beta$ -blockers, and thiazide diuretics, were dichotomized according to their overall use during the individual follow-up, based on the frequency of prescription during the control visits. Thus, all medications used for more than 50% of control visits were considered as covariates in a new proportional hazards analysis. In this Cox model, we used a hierarchical model with a 1st step in which all covariates used in the previous Cox analysis were entered by a backward model-building procedure (*P* to enter  $<0.05$  and *P* to remove  $\geq 0.15$ ) and a 2nd step in which the classes of medications were thereafter forced into the model.

**RESULTS**— Uncontrolled blood pressure despite therapy was found in 712 patients (41% of population). Baseline characteristics in relation to control of blood pressure are shown in Table 1. At baseline, patients with subsequent uncontrolled blood pressure were younger ( $P < 0.001$ ) and had a higher heart rate ( $P < 0.02$ ) than patients with controlled blood pressure, with no differences in sex distribution, BMI, reported duration of hypertension, baseline blood pressure values, metabolic profile (glucose, uric acid, and lipids), serum creatinine and electrolytes, GFR, or prevalence of metabolic syndrome. Uncontrolled blood pressure was also associated with a slightly reduced number of control visits over the follow-up period ( $P = 0.05$ ).

During follow-up, 109 patients (6% of the population, 41% women) developed diabetes. At baseline, patients with subsequent diabetes were older ( $56.2 \pm 9.7$  vs.  $51.6 \pm 11.6$  years) and had greater BMI ( $29.2 \pm 4$  vs.  $27.3 \pm 4$  kg/m<sup>2</sup>), fasting glucose ( $107.9 \pm 10$  vs.  $92.5 \pm 11.6$  mg/dl), uric acid ( $5.7 \pm 1.8$  vs.  $5.0 \pm 1.5$  mg/dl), plasma triglycerides ( $169.4 \pm 112.7$  vs.  $126.5 \pm 68.4$  mg/dl), and prevalence of metabolic syndrome (60.7 vs. 21.4%) than patients without incident diabetes (all  $P < 0.001$ ). In univariate cross-tabulation, incident diabetes was 35% less in nonsedentary than in sedentary participants (odds ratio [OR] 0.65 [95% CI 0.44–0.97],  $P = 0.041$ ). Reported duration of hypertension was also longer ( $8.7 \pm 7.5$  vs.  $6.8 \pm 6.7$  years,  $P = 0.013$ ), and family history of diabetes was more frequent (8.2 vs. 5.1%,  $P = 0.017$ ). In univariate cross-tabulation, incident diabetes was 2.45-fold higher in participants with BMI  $\geq 30$  kg/m<sup>2</sup> (2.45 [1.62–3.71],  $P < 0.0001$ ). No differences were found in sex distribution, number of visits per year, baseline blood pressure and heart rate, serum creatinine and electrolytes, GFR, total cholesterol, HDL cholesterol, and uric acid. There was no significant variation of BMI over time in either group.

### Prediction of incident diabetes and blood pressure control

Risk of incident diabetes was significantly higher in patients with uncontrolled (8%) than in those with controlled blood pressure (4%, OR 2.08,  $P < 0.0001$ ). In Cox analysis controlling for age at the time of the first visit, sex, baseline values of systolic blood pressure, family history of diabetes, fasting glucose, BMI, and reported



**Figure 1**—Cumulative hazard of incident diabetes in nondiabetic hypertensive patients under antihypertensive therapy in relation to blood pressure control, after adjusting for age, sex, systolic blood pressure, family history of diabetes, BMI, and plasma glucose at baseline (see text for explanation).

physical activity, incident diabetes remained more than twofold higher in patients with uncontrolled than in those with controlled blood pressure (hazard ratio [HR] 2.1 [95% CI 1.41–3.12],  $P < 0.0003$ ), with additional significant effects for higher baseline fasting glucose (1.1 [1.08–1.13],  $P < 0.0001$ ) and older age (1.02 [1.00–1.04],  $P < 0.03$ ) and no detectable effect for the other covariates (Fig. 1). Wald statistics suggest that fasting plasma glucose was the strongest predictor of incident diabetes and that suboptimal control of blood pressure was the second strongest predictor.

Alternative Cox models were generated using blood pressure as a continuous variable rather than dichotomizing it into controlled and uncontrolled. In these alternative models, both systolic (not diastolic) blood pressure (HR 1.02 per mmHg [95% CI 1.01–1.03],  $P < 0.01$ ) and mean blood pressure (1.03 per mmHg [1.01–1.06],  $P < 0.01$ ) were significant, independent predictors of incident diabetes.

In another Cox model, using the modified ATP-III definition of metabolic syndrome instead of fasting plasma glucose and BMI, together with the risk

of incident diabetes associated with metabolic syndrome (HR 4.4 [95% CI 2.9–6.7]), uncontrolled blood pressure maintained or even increased its predictive value (2.7 [1.7–4.1], both  $P < 0.0001$ ).

#### Antihypertensive therapy

During follow-up, slightly more antihypertensive medications were prescribed in patients with controlled than in those with uncontrolled blood pressure ( $1.57 \pm 0.94$  vs.  $1.47 \pm 0.90$  drugs,  $P < 0.03$ ). Single classes of antihypertensive medications were, therefore, examined in relation to incident diabetes, and the frequency of use over the entire follow-up time in censored and uncensored observations was considered. We arbitrarily evaluated medications prescribed in more than 50% of available visits. Because of potential pharmacological interaction favoring development of diabetes, the association between thiazides and  $\beta$ -blockers was also specifically examined. Thus, the classes of antihypertensive medications analyzed were thiazides,  $\beta$ -blockers, anti-RAS drugs, CCBs, and combinations of thiazides and  $\beta$ -blockers.

The frequency of prescription of  $\beta$ -blockers was twofold higher in patients with incident diabetes than in those without incident diabetes (HR 2.04 [95% CI 1.36–3.07],  $P < 0.0008$ ). Similarly, combinations of thiazides and  $\beta$ -blockers were threefold more frequent in patients with than in those without incident diabetes (3.00 [1.72–5.26],  $P < 0.0002$ ). There was no difference in prescriptions for thiazides without  $\beta$ -blockers, anti-RAS drugs, or CCBs. Another Cox model was, therefore, generated including classes of antihypertensive medications in addition to the covariates used in the previous Cox model. Table 2 shows that uncontrolled blood pressure retained a nearly twofold higher probability of association with incident diabetes, independently of all covariates, including treatment. In this model, additional significant predictors were older age, higher baseline fasting glucose, higher BMI, and therapy with  $\beta$ -blockers (Table 2).

**CONCLUSIONS** — In this study, for the first time we demonstrate that suboptimal control of blood pressure is a strong predictor of incident type 2 diabetes in initially normoglycemic, hypertensive in-

Table 1—Demographic, clinical, and laboratory characteristics of the study population

	Controlled blood pressure	Uncontrolled blood pressure	P ≤
n	1,042	712	
Age (years)	52.7 ± 11.6	50.6 ± 11.3	0.0001
Sex (%M/F)	58/42	56/44	NS
BMI (kg/m <sup>2</sup> )	27.3 ± 3.9	27.6 ± 4.1	NS
Reported duration of hypertension (years)	7.2 ± 7.1	6.5 ± 6.3	NS
Visits per year (n)	2.34 ± 1.03	2.25 ± 1.02	0.047
Systolic blood pressure (mmHg)	159.8 ± 21.8	158.0 ± 19.2	NS
Diastolic blood pressure (mmHg)	99.6 ± 10.8	99.6 ± 10.2	NS
Heart rate (bpm)	71.87 ± 11.29	73.16 ± 12.58	0.028
Fasting glucose (mg/dl)	93.5 ± 12.2	93.2 ± 12.0	NS
Uric acid (mg/dl)	5.1 ± 1.4	5.1 ± 1.7	NS
Blood urea nitrogen (mg/dl)	37.6 ± 10.1	36.3 ± 11.8	NS
Serum creatinine (mg/dl)	0.94 ± 0.2	0.93 ± 0.2	NS
GFR (ml/min)	82.7 ± 19.9	83.7 ± 19.1	NS
K <sup>+</sup> (mEq/l)	4.4 ± 0.4	4.4 ± 0.4	NS
Na <sup>+</sup> (mEq/l)	141.2 ± 3.3	141.3 ± 3.1	NS
Cholesterol (mg/dl)	206.5 ± 38.6	207.2 ± 37.4	NS
HDL cholesterol (mg/dl)	50.2 ± 12.3	50.7 ± 12.7	NS
Non-HDL cholesterolemia (mg/dl)	156.5 ± 37.9	156.7 ± 37.7	NS
Triglycerides (mg/dl)	129.2 ± 67.7	128.8 ± 79.0	NS
Metabolic syndrome (%)	24.2	23.6	NS

Data are means ± SD or percentage of the relevant group of patients. NS, not significant.

dividuals after a follow-up of at least 2 years on antihypertensive treatment. This effect is independent of age, baseline fasting glucose, presence of metabolic syndrome, and type of antihypertensive therapy. Prescription of β-blockers, but not of thiazides, is also strongly and independently associated with new onset of diabetes.

Our findings extend previous observations indicating that incident type 2 diabetes is more frequent in hypertensive than in normotensive subjects (3,11). In particular, Conen et al. (3) recently reported a clear correlation between higher incidence of type 2 diabetes and blood pressure levels in a large population of

women, based on modified categories from the 2007 ESH/ESC guidelines.

The relation between suboptimal control of blood pressure and incident diabetes also paralleled evidence of different follow-up profiles in censored and uncensored individuals. Patients with incident diabetes underwent fewer visits each year, were prescribed fewer medications, and presented with a larger BMI. It is possible that a less attentive adherence to the suggestions of the specialist both in terms of compliance to the treatment and changes in lifestyle could be at least in part associated with the increased risk of developing diabetes. However, this possibility was partly contradicted by our pre-

Table 2—Hazard of incident diabetes in nondiabetic, treated hypertensive patients, including classes of antihypertensive medications

	B	Wald	P ≤	HR	95.0% CI	
					Lower	Upper
Fasting glucose (mg/dl)					1.07	1.12
BMI (kg/m <sup>2</sup> )	0.03	7.09	0.01	1.08	1.02	1.14
Age (years)	0.03	6.33	0.014	1.03	1.01	1.05
Sex (M/F)	0.03	0.02	0.9	1.03	0.67	1.60
Thiazide diuretics	−0.28	1.73	0.21	0.75	0.48	1.18
β-Blockers	0.77	13.05	0.0001	2.17	1.41	3.34
Anti-RAS drugs	0.12	0.19	0.65	1.12	0.68	1.86
Suboptimal blood pressure control	0.63	7.58	0.004	1.88	1.23	2.88

vious demonstration that the phenotype of metabolic syndrome, a potent risk factor for diabetes in our analysis also, is associated with a high likelihood of uncontrolled blood pressure, despite the greater number of prescribed medications.

The other interesting aspect emerging from our analysis is the evidence of the independent relation of β-blocker therapy to the incidence of diabetes, which was consistent with recent literature (12). In contrast, diuretic therapy did not independently predict diabetes, a finding that was inconsistent with some (13) but not all studies (11,14). Gress et al. (11) have shown no significant, independent effect of thiazides in their population-based study once demographic, environmental, and metabolic cofactors were taken into account. In the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) study, other than adjustment for chlorthalidone and increased risk of diabetes after 2 and 4 years (14), no multivariate adjustment comparable with that used in the model of the present study was attempted to verify whether this effect was independent of confounders. In addition, whereas in the ALLHAT study design diuretic therapy was not associated with any anti-RAS medication (and in fact K<sup>+</sup> levels were significantly lower in the group on diuretics), in all analyzed patients in the present study thiazides were associated with other medications and K<sup>+</sup> levels were indistinguishable between the groups. Another characteristic to consider in our population is that thiazides were used at very low doses. There is some evidence that thiazides may also produce or increase hepatic insulin resistance, but this effect is dose dependent and associated with hypokalemia (15).

The two main findings in our study (i.e., regarding the relation of uncontrolled blood pressure and use of β-blockers to incident diabetes) are biologically plausible and in accord with most recent findings suggesting that microvascular alterations might precede development of diabetes (16). Because the goal of our study was to assess the risk of incident diabetes in poorly controlled hypertensive patients, independent of therapeutic aggressiveness (and therefore including patients with possible suboptimal therapy at the time of censoring), these findings suggest that the timing of achieving target blood pressure values might also be substantially relevant to preventing diabetes,



a possibility that should be tested in ad hoc clinical trials.

The temporal sequence observed in our study suggests some possibilities to be explored in future research. First, both hypertension and diabetes might share a common abnormality of microvascular function that might be corrected by anti-hypertensive therapy. When generalized, dysfunction is more easily detectable with increased blood pressure than with metabolic alterations preceding diabetes, which provides an explanation for hypertension appearing before diabetes. This hypothesis is supported by increasing evidence that microvascular dysfunction might be the background abnormality in experimental diabetes (17). However, although vascular rarefaction has been generally suggested to contribute to insulin resistance (17), a cause-and-effect relationship has not been demonstrated. Another possibility is that the lack of effective control of blood pressure parallels persistent neurohormonal abnormalities, including potential defects in the sympathetic system (18) and/or RAS activity (19), which in the long run participate in the precipitation of diabetes.

The unfavorable metabolic consequence of  $\beta$ -blockade is likely due to decreased insulin sensitivity, which is also demonstrated in hypertensive patients (20), associated with insulin-related metabolic features (21) and deleterious effects on insulin secretion (22). As widely reported, insulin resistance evolves into diabetes once  $\beta$ -cell failure occurs (23). In addition to this mechanism,  $\beta$ -receptor blockade might favor enhancement of hepatic glucose output, which has been demonstrated in rats but not humans (24).

A potential limitation of this study is the absence of direct information on body fat distribution. Because of this limitation, in addition to our use of BMI as a continuous variable, we used a cut point of BMI to categorize obesity. The cut point of BMI for obesity has been previously used as a surrogate of waist girth in studies on metabolic syndrome, and the International Diabetes Federation indicates that when BMI is in the range of obesity, a central fat distribution can be assumed. In addition, at least in terms of prediction of diabetes, BMI has been shown to be as informative as waist circumference, waist-to-hip ratio, or direct visceral fat measured by computed tomography (25). Finally, the prevalence of obesity in this population is likely affected by our initial selection, which excluded subjects with type 2 dia-

betes or impaired fasting glucose at baseline examination.

Another potential limitation of this study is the unavailability of information regarding albuminuria because the data collection was initiated at a time when albuminuria was not yet required as a primary workup test in all outpatients. According to selection criteria in the present study, we included relatively healthy patients who did not require assessment of albuminuria.

**Acknowledgments**—No potential conflicts of interest relevant to this article were reported.

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