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HYPERTENSION AND ANTIHYPERTENSIVE THERAPY AS RISK FACTORS FOR TYPE 2 DIABETES MELLITUS

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FOR THE ATHEROSCLEROSIS RISK IN COMMUNITIES STUDY

ABSTRACT

Background Previous research has suggested that thiazide diuretics and beta-blockers may promote the development of type 2 diabetes mellitus. However, the results of these studies have been inconsistent, and many studies have been limited by inadequate data on outcomes and by potential confounding.

Methods We conducted a prospective study of 12,550 adults 45 to 64 years old who did not have diabetes. An extensive health evaluation conducted at base line included assessment of medication use and measurement of blood pressure with a random-zero sphygmomanometer. The incidence of new cases of diabetes was assessed after three years and after six years by measurement of serum glucose concentrations while the subjects were fasting.

Results After simultaneous adjustment for age, sex, race, education, adiposity, family history with respect to diabetes, physical-activity level, other health-related behavior, and coexisting illnesses, subjects with hypertension who were taking thiazide diuretics were not at greater risk for the subsequent development of diabetes than were subjects with hypertension who were not receiving any antihypertensive therapy (relative hazard, 0.91; 95 percent confidence interval, 0.73 to 1.13). Likewise, subjects who were taking angiotensin-converting-enzyme inhibitors and calcium-channel antagonists were not at greater risk than those not taking any medication. In contrast, subjects with hypertension who were taking beta-blockers had a 28 percent higher risk of subsequent diabetes (relative hazard, 1.28; 95 percent confidence interval, 1.04 to 1.57).

Conclusions Concern about the risk of diabetes should not discourage physicians from prescribing thiazide diuretics to nondiabetic adults who have hypertension. The use of beta-blockers appears to increase the risk of diabetes, but this adverse effect must be weighed against the proven benefits of beta-blockers in reducing the risk of cardiovascular events. (N Engl J Med 2000;342:905-12.)

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TYPE 2 diabetes mellitus affects more than 7 million Americans,¹ leading annually to 2.8 million hospitalizations,² more than 300,000 deaths,³ and more than \$100 billion in total costs.⁴ Improved glycemic control is known to slow the onset and progression of microvascular complications, but its effect on atherosclerotic cardiovascular disease has not been demonstrated conclusively.^{5,6} In the absence of completely effective treatment, primary prevention is an attractive, though hypothetical, option. Prevention programs depend on the identification of potentially modifiable risk factors. For example, adiposity, physical inactivity, and insulin resistance, all of which were identified in epidemiologic studies as strong risk factors for type 2 diabetes mellitus, have become targets for intervention in several primary-prevention trials.⁷⁻¹⁰

Use of drugs that impair glucose tolerance constitutes another set of modifiable risk factors for type 2 diabetes. Systemic glucocorticoids, for example, have profound effects on glucose metabolism.¹¹ Antihypertensive medications, though their metabolic effects are weaker than those of glucocorticoids, arouse even greater concern because they are used by more than 20 million adults in the United States alone.¹² Initially, short-term metabolic studies of thiazide diuretics aroused concern about the diabetogenic potential of these drugs.¹³⁻¹⁶ Subsequently, the results of some epidemiologic studies and clinical trials suggested a causal link between the use of beta-blockers

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or thiazide diuretics and the subsequent development of type 2 diabetes.¹⁷⁻²⁵ Given such evidence, investigators in the Diabetes Prevention Program, sponsored by the National Institutes of Health,⁷ excluded persons who used thiazide diuretics or beta-blockers for the treatment of hypertension, despite their proven benefit in reducing the risk of death from cardiovascular causes²⁶ and despite their status as first-line agents in the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.²⁷

Unfortunately, many epidemiologic studies of antihypertensive medications and the development of diabetes have been limited by their small numbers of subjects,^{16,21,24,25,28} lack of adequate comparison groups,^{16,21,25,28,29} short duration of follow-up,¹⁶ suboptimal definitions of diabetes,^{22,23,29,30} or lack of information on important biologic characteristics (such as blood pressure) that may confound this relation.^{19,23} Randomized trials, despite their experimental rigor, have also had limitations, including strict selection criteria that limited the generalizability of the findings^{17,20,22,31-33} and simple designs that precluded simultaneous direct comparisons among different drug classes.^{17,20,22,31,33} With these issues in mind, we conducted a prospective cohort study to determine whether there was an independent relation between the use of antihypertensive medications and the risk of the subsequent development of type 2 diabetes mellitus.

METHODS

Subjects

The Atherosclerosis Risk in Communities (ARIC) study is an ongoing, prospective study of clinical and subclinical atherosclerotic vascular disease in a cohort of 15,792 adults, 45 to 64 years old, who were selected by probability sampling from four geographically separate communities in the United States: Forsyth County, North Carolina; Jackson, Mississippi; the northwest suburbs of Minneapolis; and Washington County, Maryland. Enrollment and base-line examinations were performed between 1987 and 1989. The sampling procedure and methods used in the ARIC study have been described in detail elsewhere.³⁴ For this analysis, participants were excluded for the following reasons: race other than white or black (48 participants); preexisting diabetes mellitus (1867); missing data at base line (379); and missing data at the three-year and six-year follow-up examinations (948). After these exclusions, 12,550 nondiabetic subjects remained and were enrolled in this study. The ARIC study was approved by the institutional review boards of the participating institutions, and written informed consent was obtained from all subjects.

Base-Line Assessments

The base-line examinations included interviews conducted at the subjects' homes and examinations and completion of questionnaires at the clinic. Subjects were asked to fast for at least 12 hours before blood collection. Blood chemical analyses were performed at the Central Chemistry Laboratory of the University of Minnesota, and blood lipid analyses were performed at the University of Texas, Houston.³⁵

Blood pressure was measured with a random-zero sphygmomanometer with subjects in the sitting position, and the average of the last two measurements was recorded. Hypertension was considered present if any of the following conditions were met: systolic blood

pressure of 140 mm Hg or more, diastolic blood pressure of 90 mm Hg or more, or reported use of a medication for hypertension. Use of medications was directly assessed by inspection of pill bottles, and subjects were asked whether the medication had been prescribed to treat high blood pressure. The categories of medication assessed in this study were angiotensin-converting-enzyme (ACE) inhibitors, beta-blockers, calcium-channel antagonists, and thiazide diuretics.

Data on demographic variables (age, sex, and race), smoking status, use of alcohol, physical-activity level (measured with a modified version of the questionnaire on leisure-time sports developed by Baecke et al.,³⁶ scored on a scale from 1 to 4, with a score of 4 indicating the greatest activity), education level, and family history of diabetes (considered present if one or more first-degree relatives had diabetes) were obtained by interview. Body-mass index (the weight in kilograms divided by the square of the height in meters) and waist-to-hip ratio were calculated from anthropometric measurements taken at the base-line clinic visit. Serum glucose was measured according to the national glucose reference method of the Centers for Disease Control³⁷; serum insulin was measured by radioimmunoassay (¹²⁵I Insulin kit, Cambridge Medical Diagnostics, Billerica, Mass.); serum cholesterol by a technique developed by Siedel et al.³⁸; and serum creatinine by a modification of the kinetic Jaffe reaction.³⁹

Coexisting conditions were assessed by a variety of methods. Renal insufficiency was defined as a serum creatinine concentration of 2.0 mg per deciliter (177 μ mol per liter) or more, and hypercholesterolemia was defined as a serum cholesterol concentration of 220 mg per deciliter (5.7 mmol per liter) or more. The presence of peripheral vascular disease was determined according to the subject's response on the questionnaire developed by Rose and Blackburn⁴⁰ or according to the patient's report of a diagnosis given by a physician. Subjects were considered to have coronary artery disease if they had any of the following: electrocardiographic evidence of myocardial infarction, a physician's diagnosis of angina or myocardial infarction (according to the patient's report), or a history of coronary-artery bypass surgery or angioplasty. The presence or a history of stroke, chronic obstructive pulmonary disease, or asthma was assessed by asking subjects whether a physician had given them a diagnosis of any of those conditions.

Follow-up and Assessment of Outcomes

The main outcome we studied was the development of type 2 diabetes mellitus, which was assessed after three years and after six years of follow-up. Diabetes was defined by the presence of any of the following: a blood glucose concentration of 126 mg per deciliter (7.0 mmol per liter) or more while fasting, a nonfasting blood glucose concentration of 200 mg per deciliter (11.1 mmol per liter) or more, use of insulin or an oral hypoglycemic drug, or a physician's diagnosis of diabetes mellitus. The same definition was used to exclude subjects with preexisting diabetes from enrollment.

Statistical Analysis

Two types of analysis were conducted. In the first analysis, we stratified subjects according to the presence or absence of hypertension in order to minimize the influence of this strong confounder and calculated the incidence of diabetes in terms of new cases per 1000 person-years. Chiang's method⁴¹ was used to determine 95 percent confidence intervals for incidence rates. For this analysis, antihypertensive medications used by the 3804 subjects with hypertension were classified in one of five categories of monotherapy — ACE inhibitors (162 subjects), beta-blockers (543), calcium-channel antagonists (96), thiazide diuretics (458), or other single agents (137) — or one category of multidrug therapy (two or more medications) (934). Other single agents, grouped together because of the small numbers of subjects using them, were central and peripheral adrenergic antagonists (104 subjects), reserpine (10), loop and potassium-sparing diuretics (17), and vasodilator medications (6). The remaining 1474 subjects with hypertension were not taking any antihypertensive medication.

In the second analysis, we performed a series of multivariate analyses, with adjustment for potential confounders by proportional-hazards regression, to assess the independent relation between the use of antihypertensive medications and the incidence of subsequent diabetes among subjects with hypertension. In this analysis, use of medications was sorted into non-mutually exclusive categories by assigning subjects classified as receiving multidrug therapy in the first analysis to categories according to the component drugs (for example, a subject taking a thiazide, a beta-blocker, and an ACE inhibitor, who was considered to be receiving multidrug therapy in the first analysis, was now included in each of those separate drug categories). Models were created by the successive addition of sets of related covariates, such as social and demographic characteristics, health-related behavior, and coexisting conditions. In each model we adjusted simultaneously for age, sex, and race, as well as for use of antihypertensive medications other than the medication of interest. To account for the severity of hypertension, a dichotomous variable was created for subjects taking multiple antihypertensive medications and was included in each model. All possible two-way interactions among the four main categories of single drugs (ACE inhibitors, beta-blockers, calcium-channel antagonists, and thiazides) were analyzed; none of these interactions were statistically significant. The assumption of proportionality was confirmed by an analysis of Schoenfeld residuals.⁴²

Finally, we performed a series of subsidiary analyses to confirm the robustness of our main results. First, we repeated the multivariate analyses by using logistic regression. Second, we accounted for changes in subjects' medications after three years by repeating the person-year analyses according to medication use determined at the three-year follow-up. Third, we used multiple linear regression to estimate the association between the use of antihypertensive medications and changes in the fasting serum glucose concentration. Analyses were performed with Stata statistical software,⁴³ and all statistical tests of significance were two-tailed.

RESULTS

Base-Line Characteristics

The 3804 subjects with hypertension had greater adiposity and higher fasting serum glucose concentrations than the 8746 subjects with normal blood pressure; were older; and were more likely to be black, to have a lower level of education, and to have coexisting conditions (such as cardiovascular disease) (Table 1). However, subjects with hypertension were less likely to be current smokers or users of alcohol than those without hypertension (Table 1).

Among subjects with hypertension, those receiving antihypertensive-drug therapy differed in important ways from those not receiving any therapy (Table 2). Subjects taking a single agent were more likely to have hypercholesterolemia than those taking no medication (P<0.01). Subjects taking a thiazide diuretic were more likely to be female and not to be users of alcohol than those taking no medication (P<0.01 for both comparisons). Those taking an ACE inhibitor or a beta-blocker were more likely to be white (P<0.01 for both comparisons). As expected, subjects taking a beta-blocker or a calcium-channel antagonist were more likely to have a history of coronary artery disease than those taking no medication (P<0.01 for both comparisons). Finally, subjects receiving multidrug antihypertensive therapy had a higher body-mass index and more often had coexisting diseases than those taking no medication.

TABLE 1. BASE-LINE CHARACTERISTICS OF 12,550 NONDIABETIC SUBJECTS ACCORDING TO THE PRESENCE OR ABSENCE OF HYPERTENSION.*

CHARACTERISTIC	NO HYPERTENSION (N=8746)	HYPERTENSION (N=3804)	P VALUE†
Age (yr)	53.3±5.6	55.3±5.6	<0.001
Female sex (%)	55.5	55.6	0.91
Black race (%)	15.9	37.5	<0.001
Body-mass index	26.4±4.5	28.9±5.6	<0.001
Waist-to-hip ratio	0.91±0.08	0.94±0.07	<0.001
Education ≤11 yr (%)	17.0	27.6	<0.001
Current alcohol use (%)	62.2	52.5	<0.001
Current smoking (%)	26.0	23.0	<0.001
Physical-activity score‡	2.5±0.8	2.4±0.8	<0.001
Serum glucose (mg/dl)	97.6±8.8	101.0±9.7	<0.001
Serum insulin (pmol/liter)	68.4±50.0	97.8±68.9	<0.001
Blood pressure (mm Hg)			
Systolic	113.2±12.3	134.4±19.7	<0.001
Diastolic	69.9±8.6	80.9±11.8	<0.001
Coronary artery disease (%)	3.1	6.2	<0.001
Peripheral vascular disease (%)	0.5	1.2	<0.001
History of stroke (%)	0.7	2.6	<0.001
Hypercholesterolemia (%)	18.9	24.6	<0.001
Renal insufficiency (%)	2.4	5.7	<0.001
COPD or asthma (%)	8.3	8.6	0.62
Family history of diabetes (%)	22.8	21.6	0.17

*Plus-minus values are means ±SD. COPD denotes chronic obstructive pulmonary disease.

†Body-mass index is the weight in kilograms divided by the square of the height in meters. To convert values for glucose to millimoles per liter, multiply by 0.05551. To convert values for insulin to microunits per milliliter, divide by 6.0.

‡P values were calculated by Pearson's chi-square test for categorical variables and by one-way analysis of variance for continuous variables.

§The physical-activity level was measured on a scale from 1 to 4, with a score of 4 indicating the greatest activity.

New Cases of Type 2 Diabetes Mellitus

During six years of follow-up, there were 1146 new cases of diabetes, corresponding to an overall incidence of 16.6 cases per 1000 person-years. Of these, 569 occurred in subjects with hypertension and 577 in those without hypertension, corresponding to incidence rates of 29.1 and 12.0 per 1000 person-years, respectively, and a relative risk of 2.43 (95 percent confidence interval, 2.16 to 2.73) in the subjects with hypertension.

The incidence of diabetes mellitus stratified according to the presence or absence of hypertension and the category of antihypertensive medication is shown in Figure 1. The most striking finding is that much of the risk of diabetes associated with antihypertensive-drug therapy appears to be explained by the presence of hypertension. Among the subjects who were not taking any antihypertensive medication, the risk of diabetes was much higher among those who had hypertension than among those who

TABLE 2. BASE-LINE CHARACTERISTICS OF 3804 NONDIABETIC SUBJECTS WITH HYPERTENSION, ACCORDING TO CATEGORY OF ANTIHYPERTENSIVE MEDICATION.*

CHARACTERISTIC†	NO ANTI-HYPERTENSIVE MEDICATION (N=1474)	ACE INHIBITOR (N=162)	BETA-BLOCKER (N=543)	CALCIUM-CHANNEL ANTAGONIST (N=96)	THIAZIDE DIURETIC (N=458)	OTHER SINGLE AGENT (N=137)	MULTIPLE AGENTS (N=934)	P VALUE‡
Age (yr)	55.0±5.7	55.0±5.7	55.4±5.4	55.2±6.1	55.5±5.4	54.7±5.7	55.6±5.6	0.18
Female sex (%)	54.7	46.9	50.6	46.9	68.3§	64.2	54.9	<0.001
Black race (%)	40.6	22.2§	23.8§	28.1	44.3	51.8	38.8	<0.001
Body-mass index	28.4±5.6	28.7±5.4	28.7±4.9	28.1±4.8	29.0±6.2	29.1±5.8	29.8±5.8§	<0.001
Waist-to-hip ratio	0.93±0.07	0.95±0.06	0.94±0.07	0.95±0.08	0.93±0.08	0.93±0.07	0.95±0.07§	<0.001
Education ≤11 yr (%)	26.7	20.4	21.9	25.0	31.4	31.4	31.5	<0.001
Current alcohol use (%)	54.7	63.0	57.6	58.3	43.4§	47.4	48.9§	<0.001
Current smoking (%)	23.0	21.0	22.5	26.0	26.2	24.1	21.6	0.58
Physical-activity score¶	2.4±0.8	2.4±0.8	2.4±0.7	2.4±0.8	2.3±0.8	2.2±0.8	2.3±0.8	0.93
Serum glucose (mg/dl)	100.5±9.7	101.6±10.1	101.9±9.8	98.0±8.2	100.5±9.4	100.0±9.4	101.8±9.8§	<0.001
Serum insulin (pmol/liter)	90.2±61.7	100.2±61.3	96.2±68.3	96.1±83.0	101.4±76.9	99.0±82.8	108.4±72.1§	<0.001
Blood pressure (mm Hg)								
Systolic	142.0±18	132.1±19§	129.7±19§	131.4±18§	125.2±16§	133.0±24§	130.4±20§	<0.001
Diastolic	84.7±12	80.0±11§	78.2±11§	78.8±11§	77.0±10§	82.1±12	78.7±12§	<0.001
Coronary artery disease (%)	2.2	5.0	12.9§	17.0	1.8	4.4	10.1§	<0.001
Peripheral vascular disease (%)	1.0	1.8	1.3	3.1	0.7	4.4	10.1	0.50
History of stroke (%)	1.7	1.8	3.0	3.1	1.1	0.7	4.7§	<0.001
Hypercholesterolemia (%)	18.0	31.0§	28.7§	32.3§	25.8§	35.0§	28.8§	<0.001
Renal insufficiency (%)	4.3	5.6	5.9	6.2	3.1	8.0	8.7§	<0.001
COPD or asthma (%)	8.0	10.5	5.7	15.6§	9.4	14.6§	8.8	0.003
Family history of diabetes (%)	21.8	19.8	17.9	19.8	23.8	27.7	22.1	0.15

*Plus-minus values are means ±SD. ACE denotes angiotensin-converting enzyme, and COPD chronic obstructive pulmonary disease.

†Body-mass index is the weight in kilograms divided by the square of the height in meters. To convert values for glucose to millimoles per liter, multiply by 0.05551. To convert values for insulin to microunits per milliliter, divide by 6.0.

‡P values are for the test for homogeneity across all seven categories of antihypertensive-medication use, calculated by Pearson's chi-square test for categorical variables and by one-way analysis of variance for continuous variables.

§P<0.05 (after the Bonferroni correction) for the comparison with subjects taking no antihypertensive medication. These pairwise comparisons were performed only for variables for which heterogeneity was detected across all seven categories of medication.

¶The physical-activity level was measured on a scale from 1 to 4, with a score of 4 indicating the greatest activity.

did not; however, among the subjects who had hypertension, the risk among those not taking medication was similar to that among those taking one or more agents. The small numbers of subjects taking specific categories of medication for reasons other than hypertension limit the extent to which conclusions can be drawn about the risk of diabetes in relation to specific drugs.

Results of Multivariate Analysis

To determine whether there was an independent relation between the use of antihypertensive medication and the risk of subsequent diabetes mellitus, we constructed a series of proportional-hazards models confined to the 3804 adults who had hypertension at base line (Table 3). According to models that adjusted for age, sex, race, and use of antihypertensive medications other than the medication of interest, subjects who were taking a thiazide diuretic, ACE inhibitor, or calcium-channel antagonist were not at

greater risk for the subsequent development of diabetes mellitus than were their untreated counterparts. In contrast, diabetes mellitus was 28 percent more likely to develop in subjects taking a beta-blocker than in those taking no medication (relative hazard, 1.28; 95 percent confidence interval, 1.04 to 1.57). These findings were not influenced by additional adjustment for adiposity, health-related behavior, or level of education or for those factors as well as a variety of diabetes-related clinical traits and coexisting conditions.

Results of Subsidiary Analyses

Results similar to those obtained in the multivariate analyses were observed when the onset of diabetes was treated as a dichotomous dependent variable in a logistic-regression analysis restricted to subjects with hypertension. In the fully adjusted model, the relative odds of diabetes in subjects taking a beta-blocker was 1.34 (95 percent confidence interval, 1.06 to 1.69), whereas in those taking a thiazide it was 0.88

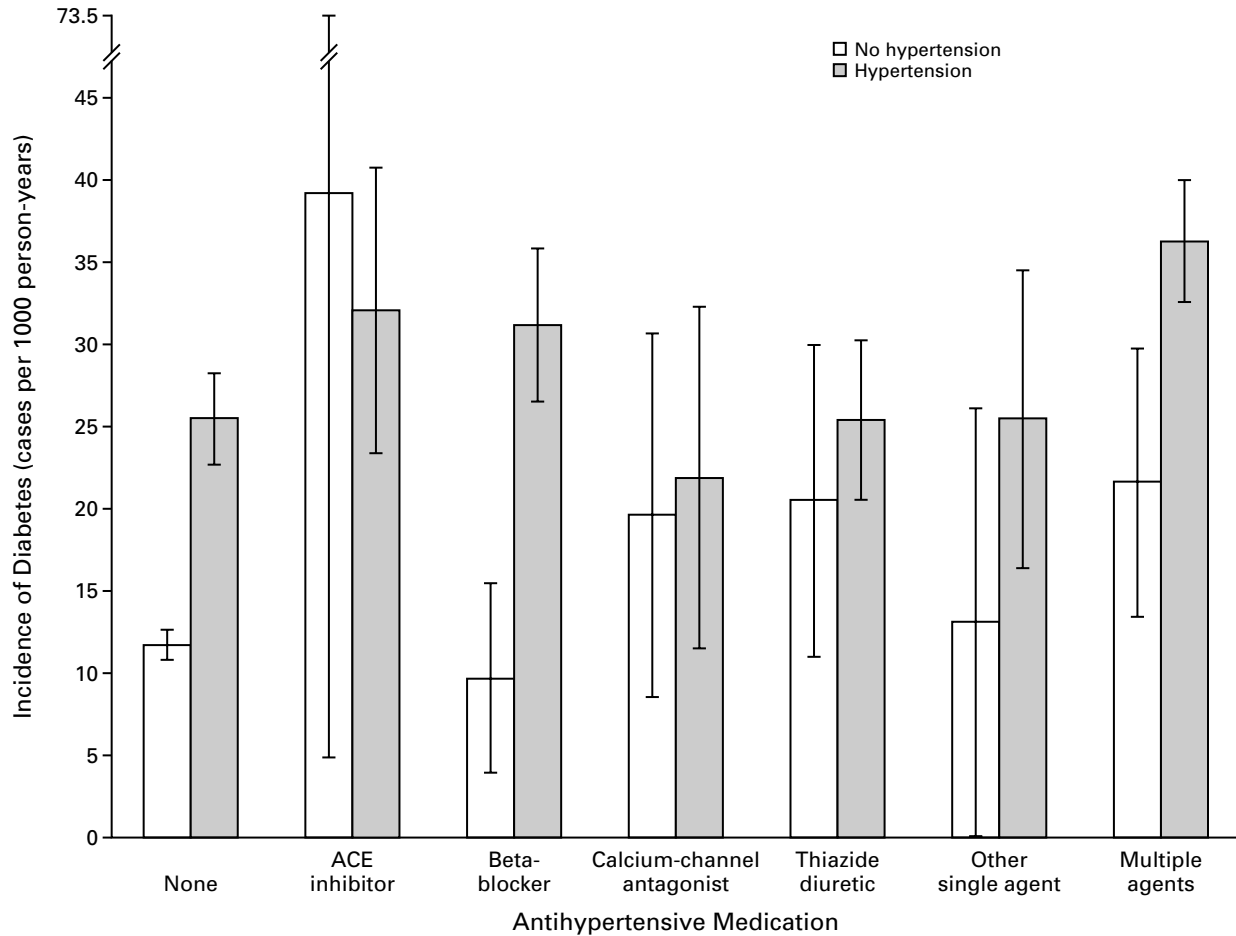


Figure 1. Incidence of Type 2 Diabetes Mellitus among 12,550 Adults According to the Presence or Absence of Hypertension and Antihypertensive Drug Treatment.

The number of new cases of type 2 diabetes mellitus per 1000 person-years is shown for the entire six-year follow-up period. Subjects without hypertension who were taking antihypertensive agents presumably took them for other indications, such as angina pectoris (treated with beta-blockers) or lower-extremity edema (treated with thiazide diuretics). ACE denotes angiotensin-converting enzyme. I bars indicate 95 percent confidence intervals.

(95 percent confidence interval, 0.69 to 1.13). Similarly, an association between beta-blocker use and the risk of diabetes was observed in person-year analyses that accounted for changes in medication after three years: the number of new cases of diabetes per 1000 person-years among subjects taking a beta-blocker was 33.6; among those taking a thiazide, 27.5; and among those not taking any medication, 26.3. Finally, in fully adjusted, multiple linear regression models in which the change in the fasting serum glucose concentration from base line to year 3 was used as the dependent variable, subjects taking an ACE inhibitor or a calcium-channel antagonist had small decreases in this variable (decreases in the fasting serum glucose concentration of 0.55 and 0.41 mg per deciliter [0.031 and 0.023 mmol per liter], respectively; $P < 0.01$); subjects taking a thiazide diuretic

had a small increase (0.24 mg per deciliter [0.013 mmol per liter], $P < 0.01$); and subjects taking a beta-blocker had no significant change (an increase of 0.11 mg per deciliter [0.006 mmol per liter], $P = 0.21$).

The association between the risk of diabetes and use of beta-blockers did not appear to be confounded by heart rate, since the mean (\pm SE) base-line heart rate among the 84 initially untreated subjects with hypertension who went on to receive beta-blockers was similar to that among the 334 initially untreated subjects who went on to receive other antihypertensive agents (70.4 ± 1.1 and 70.2 ± 0.5 beats per minute, respectively). Weight gain did not appear to mediate the excess risk of diabetes associated with beta-blocker use in subjects with hypertension: from base line to the six-year follow-up visit, this subgroup had a mean gain in body-mass index that was virtually iden-

TABLE 3. RISK OF DIABETES MELLITUS AMONG 3804 SUBJECTS WITH HYPERTENSION, ACCORDING TO CATEGORY OF ANTIHYPERTENSIVE MEDICATION.*

ANTIHYPERTENSIVE MEDICATION	HAZARD RATIO (95% CONFIDENCE INTERVAL)		
	MODEL 1	MODEL 2	MODEL 3
None	1.0	1.0	1.0
ACE inhibitor	0.99 (0.73–1.35)	0.96 (0.71–1.31)	0.98 (0.72–1.34)
Beta-blocker	1.26 (1.03–1.52)†	1.25 (1.03–1.52)†	1.28 (1.04–1.57)†
Calcium-channel antagonist	1.17 (0.85–1.62)	1.16 (0.84–1.60)	1.17 (0.83–1.66)
Thiazide diuretic	0.95 (0.77–1.17)	0.93 (0.76–1.15)	0.91 (0.73–1.13)

*Model 1 adjusted for age, sex, race, and use of other antihypertensive medications. Model 2 adjusted for the variables included in model 1, as well as body-mass index, waist-to-hip ratio, level of education, smoking status, alcohol use, and physical-activity level. Model 3 adjusted for the variables included in model 2, as well as systolic blood pressure, diastolic blood pressure, fasting serum insulin concentration, and the presence or absence of hypercholesterolemia, cardiovascular disease, pulmonary disease, renal insufficiency, and a family history of diabetes. ACE denotes angiotensin-converting enzyme.

† $P < 0.05$ for the comparison with subjects taking no antihypertensive medication.

tical to that in subjects with hypertension who were taking no medication (0.20 ± 0.08 and 0.20 ± 0.05 , respectively), and this gain was less than that in subjects taking any other antihypertensive medication (0.43 ± 0.04).

DISCUSSION

In this prospective cohort study, we found that type 2 diabetes mellitus was almost 2.5 times as likely to develop in subjects with hypertension as in subjects with normal blood pressure. After accounting for the excess risk of diabetes in subjects with hypertension, we found that those who took a thiazide diuretic, ACE inhibitor, or calcium-channel antagonist were not at increased risk of diabetes. The risk of diabetes was 28 percent greater among those who took beta-blockers than among those who took no medication, without regard to the presence or absence of hypertension, sociodemographic characteristics, health-related behavior, family history with respect to diabetes, and a variety of coexisting conditions. The strengths of our study included its use of a large number of subjects drawn from the general population, the collection of extensive data on potential confounders, a standardized method of identifying new cases of diabetes, and the ability to compare several categories of antihypertensive medication simultaneously.

Nonetheless, several limitations of our study should be kept in mind. First, information regarding doses of drugs and the duration of treatment was not available. Second, the power to detect moderate effects of calcium-channel antagonists was limited because of the small numbers of subjects taking these agents. Third, the categories of medication we used were broad, and we were therefore unable to examine differences within the categories (e.g., cardioselective as compared with nonselective beta-blockers). Finally,

we cannot completely exclude the possibility that our results may have been influenced by prescribing patterns related to a perceived risk of diabetes. For example, physicians may have prescribed ACE inhibitors to patients thought to be at high risk for diabetes and thiazides to those thought to be at low risk. However, such confounding would not explain our finding of an increase in risk associated with the use of beta-blockers, which have generally been thought to increase the risk of diabetes. Moreover, our study accounted for a wide array of clinically relevant factors that might have affected physicians' perception of the risk of diabetes, such as greater adiposity, a high heart rate, and coexisting conditions.

We found that the risk of diabetes mellitus among subjects taking a thiazide diuretic was not greater than that among those taking no medication. Most previous observational studies have found an increased risk of diabetes among those taking thiazide diuretics,^{19,21,23,24} but many of those studies failed to account for the presence or absence of hypertension,^{19,21,23} which is a strong predictor of diabetes.⁴⁴ In addition, many studies examined the use of thiazide diuretics in combination with other antihypertensive medications.^{19,21,24,45,46} In those studies, the use of diuretics may have been a marker of the severity of hypertension.

Early clinical trials of antihypertensive therapy examined glucose intolerance rather than diabetes as an outcome. Two early trials^{17,20} found a hyperglycemic effect associated with the use of thiazide diuretics, but several other trials^{18,22,32,33} did not: these included the trial conducted by the European Working Party on High Blood Pressure in the Elderly,²² which studied a combination of triamterene and hydrochlorothiazide; the Treatment of Mild Hypertension study,³² which studied chlorthalidone or one of five other

drugs; the Systolic Hypertension in the Elderly Program,³³ which studied chlorthalidone with or without atenolol or reserpine; and the Oslo study,¹⁸ which studied hydrochlorothiazide with or without methyldopa. However, the early trials included subjects taking larger daily doses of medications (e.g., hydrochlorothiazide at 50 to 200 mg²⁰) than those used in the later trials.

We identified a 28 percent increase in the risk of diabetes associated with the use of beta-blockers. Previous observational studies have also identified this risk but have usually found higher estimates of relative risk: for instance, in one study, subjects who took propranolol had up to 6.1 times the risk of diabetes of those who did not.²⁵

Previous clinical trials of beta-blockers have yielded mixed results. The Veterans Administration Cooperative Study Group on Antihypertensive Agents²⁰ found that propranolol had a hyperglycemic effect that persisted for one month after the discontinuation of drug treatment that had lasted one year. The Medical Research Council Working Party on Mild to Moderate Hypertension¹⁷ found that the rate of withdrawal from the study because of hyperglycemia was higher in the propranolol group than in the placebo group, but this difference was not statistically significant. In the Oslo study,¹⁸ the fasting serum glucose concentration in the group treated with propranolol in combination with a thiazide diuretic was significantly higher than that in the placebo group, whereas there was no difference in serum glucose concentrations between a group treated only with a thiazide diuretic and the placebo group. In neither the Treatment of Mild Hypertension study³² nor the Systolic Hypertension in the Elderly Program³³ was an increased risk of hyperglycemia or diabetes found for subjects taking beta-blockers; however, acebutolol was used in the former study and atenolol was used in combination with a thiazide diuretic in the latter. Differences in these results may stem from differences in the dosage of medication, the type of beta-blocker used (e.g., cardioselective as compared with non-selective), and the duration of treatment.

Treatment with beta-blockers has been associated with weight gain⁴⁷ and with attenuation of the beta-receptor-mediated release of insulin by pancreatic beta cells,⁴⁸ both of which may be risk factors for diabetes. In our study, however, the use of beta-blockers was not associated with either weight gain or hyperinsulinemia.

We found that the use of an ACE inhibitor or a calcium-channel antagonist was not associated with a significant increase in the risk of diabetes. Metabolic studies have consistently shown that ACE inhibitors have little or no effect on insulin resistance in patients with diabetes.⁴⁹ Similarly, most metabolic studies have found that calcium-channel antagonists, with the possible exception of nifedipine, do not have an effect on

insulin resistance in subjects with essential hypertension.⁴⁹ In a large, case-control study based on pharmacy-claims data, Gurwitz et al.²³ found an increased risk of diabetes associated with both ACE inhibitors and calcium-channel antagonists. However, no stratification or adjustment was performed for the presence or absence of hypertension or for body-mass index. Data from clinical trials with respect to these classes of drugs are limited. In the Treatment of Mild Hypertension study, neither enalapril nor amlodipine significantly influenced fasting serum glucose concentrations after four years of follow-up.³²

Our results have three main implications. First, the association between hypertension and the development of diabetes should prompt research on shared risk factors and alert clinicians that there is an easily identified group at high risk for diabetes. Second, concern about increasing the risk of diabetes should not discourage physicians from prescribing thiazide diuretics for the treatment of hypertension in adults. Third, the use of beta-blockers appears to increase the risk of diabetes, but this adverse effect must be weighed against the proven benefits of beta-blockers in reducing the risk of cardiovascular events.

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APPENDIX

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