Adverse Prognostic Significance of New Diabetes in Treated Hypertensive Subjects

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Abstract—Diabetes may develop in nondiabetic hypertensive subjects during treatment, but the long-term cardiovascular implications of this phenomenon are not clear. We determined the prognostic value of new diabetes in hypertensive subjects. In a long-term cohort study, 795 initially untreated hypertensive subjects, 6.5% of whom with type 2 diabetes, underwent diagnostic procedures including 24-hour ambulatory blood pressure (BP) monitoring and electrocardiography (ECG). Procedures were repeated after a median of 3.1 years in the absence of cardiovascular events. Follow-up duration was 1 to 16 years (median 6.0). New diabetes occurred in 5.8% of subjects initially without diabetes. Antihypertensive treatment included a diuretic in 53.5% of these subjects, versus 30.4% of those in whom diabetes did not develop \( P=0.002 \). Plasma glucose at entry \( P=0.0001 \) and diuretic treatment on follow-up \( P=0.004 \) were independent predictors of new diabetes. Subsequent to the follow-up visit, a first cardiovascular event occurred in 63 subjects. Event rate in nondiabetic subjects at both visits, new diabetes, and diabetes at entry were 0.97, 3.90, and 4.70×100 person-years, respectively \( P=0.0001 \). After adjustment for several confounders, including 24-hour ambulatory BP, the relative risk of events was 2.92 \( (95\% \text{ CI: } 1.33 \text{ to } 6.41; P=0.007) \) in the group with new diabetes and 3.57 \( (95\% \text{ CI: } 1.65 \text{ to } 7.73; P=0.001) \) in the group with previous diabetes, when compared with the group persistently free of diabetes. In treated hypertensive subjects, occurrence of new diabetes portends a risk for subsequent cardiovascular disease that is not dissimilar from that of previously known diabetes. \( \text{Hypertension. 2004;43:963-969.} \)

Key Words: hypertension ■ echocardiography ■ hypertrophy ■ blood pressure ■ epidemiology ■ diuretics

The coexistence of hypertension and diabetes is frequent.\(^1\) Type 2 diabetes accounts for >90% of these cases\(^2\) and cardiovascular risk is markedly increased when hypertension and diabetes coexist.\(^3\)–\(^5\) Despite the evidence of the excess risk associated with the coexistence of hypertension and type 2 diabetes, very limited information exists on the prognostic significance of new diabetes in treated hypertensive subjects. The issue is clinically relevant because widely used antihypertensive agents such as thiazide diuretics and \( \beta \)-blockers may increase blood glucose.\(^6\)–\(^8\) Some intervention trials showed a lesser incidence of diabetes in hypertensive subjects treated with drugs different from diuretics and \( \beta \)-blockers.\(^9\)–\(^12\)

In this study, we investigated the prognostic value of new type 2 diabetes in a cohort of hypertensive subjects without previous cardiovascular events who repeated some diagnostic procedures before and during treatment. After the follow-up study, subjects continued to be followed-up for detection of major cardiovascular events. Nondiabetic subjects who developed diabetes during treatment and those with established diabetes at entry were compared in their subsequent incidence of cardiovascular events with the nondiabetic subjects who remained free of diabetes.

Methods

The Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study\(^13\)–\(^15\) is an observational registry of morbidity and mortality in initially untreated subjects with essential hypertension. The study was initiated on June 1986. Entry criteria included an office blood pressure \((\text{BP})\) \( \geq140 \text{ mm Hg systolic and/or } \geq90 \text{ mm Hg diastolic} \) at least 3 visits and absence of secondary causes of hypertension, previous cardiovascular disease, and life-threatening conditions. \( \text{BP} \) was measured by a physician with a mercury sphygmomanometer, with subjects sitting and relaxed for at least 10 minutes. Three measurements were averaged for analysis. Systolic and diastolic BPs were identified by Korotkoff phases I and V. Standard 12-lead ECG was recorded at 25 mm/s and 1 mV/cm calibration. Subjects with complete right or left bundle branch block, previous myocardial infarction, Wolff-Parkinson-White syndrome, and atrial fibrillation were excluded. None of the subjects was being treated with digitalis. Diagnosis of left ventricular (LV) hypertrophy by electrocardiography was made using the Perugia score.\(^16\)\(^,\)\(^17\) The modified Cornell voltage was obtained through a received-operator characteristics (ROC) curve analysis.\(^16\) Ambulatory BP was recorded using an oscillometric device (SpaceLabs 5200, 90202, and 90207; SpaceLabs, Redmond, Wash), and measurements were automatically taken every 15 minutes throughout the 24 hours. Reproducibility of ambulatory BP readings in our patients has been assessed in a previous study.\(^18\)

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Diabetes was diagnosed using the American Diabetes Association criteria\(^\text{19}\) of a fasting plasma glucose of 7.0 mmol/L (126 mg/dL) or higher on repeated occasions or current antidiabetic therapy, whereas impaired fasting glucose (IFG) was defined by a fasting plasma glucose 6.1 to 6.9 mmol/L (110 to 125 mg/dL).\(^\text{19}\)

### Follow-Up

Follow-up of patients was the responsibility of family doctors and our hospital staff. Treatment was tailored individually and based on lifestyle and pharmacological measures. Thiazide diuretics, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium-channel blockers, and α₁-blockers, alone or combined, were the antihypertensive drugs most frequently used.

A comprehensive follow-up examination, which included standard laboratory tests, 12-lead ECG, and 24-hour ambulatory BP monitoring in all subjects, was undertaken after a median of 3.2 years. Current antihypertensive treatment was not discontinued and drugs regularly used at least over the past 3 months were recorded. Protocol for experimental procedures was the same as that in the baseline studies. None of the patients had a cardiovascular morbid event develop at the time of the follow-up visit. Subsequent to the follow-up visit, periodic contacts with family doctors and phone interviews with patients were arranged to ascertain the vital status and the occurrence of major cardiovascular events.

The total duration of follow-up until event or censoring was up to 16 years (median 6).

### End Points

For assessment of end points, hospital record forms and other source documents of patients who died or had a cardiovascular event were reviewed in conference by the authors of this study. Details about the international standard criteria used to diagnose outcome events in the PIUMA study have been reported in previous reports.\(^\text{14,15}\)

### Data Analysis

Statistical analysis was performed using SPSS (SPSS Inc, Chicago, Ill) and SAS-Stat (SAS Institute, Cary, NC). Parametric data are reported as mean±SD. The Student t test was used to compare the baseline with the follow-up visit. Comparisons between the groups with absence of diabetes, new diabetes, and previous diabetes were made using the 1-way ANOVA. In case of significant F values for trends, the Tukey test was used for multiple comparisons between the groups. A logistic regression analysis was performed to determine the independent predictors of new diabetes. For this analysis, use of antihypertensive drugs was sorted into nonmutually exclusive categories. Subjects receiving multidrug therapy were assigned to multiple categories according to the component drugs.

For survival analyses, event-free curves were estimated using Kaplan-Meier product-limit method and compared by the Mantel-Haenszel test. For the subjects who experienced multiple events, survival analysis was based on the first event. The independent effect of several prognostic factors on survival was tested by stepwise Cox model.\(^\text{20}\) Two dummy variables were generated to simultaneously compare the nondiabetic subjects on both examinations (reference group) with that with new-onset diabetes or previous diabetes. BP entered the model as either office BP or average 24-hour ambulatory BP, and that yielding the best improvement of the −2 likelihood ratio was retained.\(^\text{20}\) Other tested variables were age, gender (men, women), body mass index (kg/m²), total cholesterol (mmol/L), serum triglycerides (mmol/L), LV hypertrophy by ECG, family history of cardiovascular disease at age younger than 55 in the father or younger than 65 in the mother (no, yes), smoking habits (nonsmokers, current smokers), and type of drug treatment at the follow-up visit. The glycemic control was analyzed either as fasting plasma glucose (mmol/L) or as IFG (yes, no). In 2-tailed tests, \(P<0.05\) was considered statistically significant.

### Results

Table 1 shows the main characteristics of the whole population (N=795). There was a clinically consistent and statistically significant reduction in the office and ambulatory BP from the baseline to the follow-up study (all \(P<0.01\)). There was also a small, albeit significant, reduction the heart rate (all \(P<0.05\)). At the follow-up study, 5.8% (n=43) of the 743 initially nondiabetic subjects had diabetes. Estimated incidence of new diabetes was 1.9% per year.

### Comparisons Between the Groups

At entry, nondiabetic subjects with future diabetes showed a more elevated 24-hour ambulatory systolic and diastolic BP, a greater prevalence of LV hypertrophy, and increased glucose levels (all \(P<0.05\)) compared with subjects with normal glucose tolerance who remained free of diabetes (Table 2). In particular, a condition of IFG was present in 42% of subjects with future diabetes and 7% of those in whom diabetes did not develop (\(P<0.001\)). Subjects with diabetes at entry differed in several aspects from those in whom diabetes did not develop. These included an older age, an increased body mass index, higher values of office and 24-hour ambulatory systolic BP and greater prevalence of LV hypertrophy, increased serum glucose, and lower HDL cholesterol (all \(P<0.05\)). At the follow-up visit, the subjects with new-onset diabetes showed a higher 24-hour systolic BP and a greater prevalence of LV hypertrophy (all \(P<0.05\)), in addition to increased serum glucose (\(P<0.05\)), when compared with those in whom diabetes did not develop.

### Antihypertensive Treatment

At the follow-up visit, the proportion of subjects being treated with lifestyle measures only, diuretic, and/or β-blockers,
alone or combined, ACE inhibitors, and/or calcium-channel blockers alone or combined, or various drug associations was 30.4%, 11.1%, 19.2%, and 39.2%, respectively. More than 90% of diuretic users received hydrochlorothiazide or chlorthalidone in a dose range of 12.5 to 25.0 mg per day. The subjects in whom diabetes developed were exposed to diuretics (P<0.01), calcium-channel blockers (P<0.05), and ACE inhibitors (P<0.05) more frequently than those in whom diabetes did not develop (Figure 1). In a logistic regression analysis (Figure 2), glucose concentration at the baseline visit (P<0.0001) and exposure to diuretics at the follow-up visit (P=0.004) were the sole independent predictors of new-onset diabetes. The logistic model was defined by the following equation: Y = 2.483 × glucose concentration at entry (mmol/L) + 0.937 × exposure to diuretics (0=no; 1=yes) − 16.81.

Treatment with drugs different from diuretics and other potential predictors of new diabetes, including age, office and ambulatory blood pressure, body mass index, smoking status, and other metabolic parameters, were not significantly different between the groups (Table 2).

Figure 1. Distribution of antihypertensive treatments at the follow-up visit in nondiabetic subjects, subjects with new-onset diabetes, and subjects with previously known diabetes.
BP, and prevalence of LV hypertrophy, did not achieve significance in the logistic model.

**Cardiovascular Events**

Months or years after the follow-up visit, there were 63 first cardiovascular events, 4 of which were fatal (3 subjects with heart failure, 1 with stroke). The 795 study subjects contributed 4777 person-years of observation over the entire study period up to terminating event or censoring (median 6.0 years), and the overall event rate was 1.32 per 100 person-years. There were 18 subjects with stroke, 13 with myocardial infarction, 10 with transient ischemic attack, 15 with new-onset coronary artery disease, 2 with heart failure requiring hospitalization, 1 with new-onset aorto-iliac occlusive disease verified at angiography, 1 with occlusion of the retinal artery, and 3 with renal failure requiring dialysis.

Event-free survival curves and crude event rates are shown in Figure 3. In nondiabetic subjects in both studies, new-onset diabetes and diabetes at entry event rate (per 100 person-years) was 0.97, 3.90, and 4.70, respectively (log-rank test: \( P=0.0001 \) for trend). Survival curves did not differ between the subjects with new-onset diabetes and those with diabetes at entry (\( P=NS \)).

**Multivariate Analysis**

In the Cox model (Table 3), the relative risk of events was 2.92 (95% CI: 1.33 to 6.41; \( P=0.007 \)) in the subjects with new-onset diabetes, and 3.57 (95% CI: 1.65 to 7.73; \( P=0.001 \)) in those with diabetes at entry as compared with nondiabetic subjects. These findings remained significant after adjustment for age, LV hypertrophy, and average 24-hour systolic BP at the follow-up visit (all \( P<0.01 \)). None of the other tested variables (see the section Data Analysis) achieved significance, including IFG at the baseline or follow-up visits, serum triglycerides, cigarette smoking, and type of antihypertensive treatment. When office and ambulatory BP were forced in the same model, office BP did not achieve significance. For each 1.58 mmol/L increase in serum glucose at the follow-up visit, the independent risk of subsequent events increased by 23% (95% CI: 4 to 46; \( P=0.013 \)). Figure 4 shows the age-adjusted 5-year risk of cardiovascular events in nondiabetic subjects, subjects with new diabetes, and subjects with previous diabetes. Risk estimates have been developed at different levels of 24-hour systolic BP and for absence and presence of LV hypertrophy.

**Figure 2.** Probability of new diabetes in relation to baseline glucose concentration and treatment with a diuretic.

**Figure 3.** Cardiovascular events in treated hypertensive subjects without diabetes (group A), new-onset diabetes (group B), and previously known diabetes (group C).

**Table 3. Independent Predictors of Cardiovascular Events**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Comparison (95% Confidence Intervals)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>11 y (1 SD) 1.57 (1.16–2.12)</td>
<td>0.004</td>
</tr>
<tr>
<td>Average 24-h SBP</td>
<td>14 mm Hg (1 SD) 1.52 (1.12–2.06)</td>
<td>0.009</td>
</tr>
<tr>
<td>LV hypertrophy</td>
<td>Yes vs No 2.44 (1.23–4.58)</td>
<td>0.006</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>New-onset diabetes</td>
<td>2.92 (1.33–6.41)</td>
<td>0.007</td>
</tr>
<tr>
<td>Previously known</td>
<td>3.57 (1.65–7.73)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Other tested variables (see the section Data Analysis) did not achieve statistical significance. SBP indicates systolic blood pressure; SD, standard deviation.
Discussion

This study provides new data on the adverse impact of new-onset diabetes in treated hypertensive subjects. Approximately 2 of 100 initially nondiabetic subjects had diabetes develop every year. Pretreatment blood glucose and exposure to diuretics during follow-up were independent predictors of new diabetes. After accounting for robust covariates, including age, 24-hour ambulatory BP, and LV hypertrophy, subjects with new-onset diabetes and those with a previous diagnosis of diabetes were almost 3-times as likely to have subsequent cardiovascular disease over a long follow-up period than those who remained free of diabetes.

Clinical Value of New-Onset Diabetes in Hypertensive Subjects

Although it is well established that the coexistence of diabetes and hypertension portends a 2- to 3-fold higher risk of cardiovascular disease, surprisingly few data exist on the prognostic impact of new-onset diabetes in initially nondiabetic subjects. In a longitudinal study of 685 middle aged hypertensive men, subjects with diabetes at entry were 2-times as likely to have coronary heart disease than those without diabetes. New-onset diabetes developed in 1.3% of participants per year, and these subjects were 1.5-times as likely to have subsequent coronary events than those without diabetes. However, such excess risk was not statistically significant because of the wide confidence intervals that crossed the unit. Because definition of outcome was restricted to coronary heart disease, and because diabetes was defined according to the World Health Organization criteria, these factors may have decreased the power of the study to detect a significant relation of new-onset diabetes to subsequent cardiovascular disease. In a long-term study, Alderman et al showed a 2-fold higher cardiovascular risk in hypertensive subjects with a history of diabetes and a direct association between in-treatment blood glucose and subsequent cardiovascular events. However, the independent prognostic value of new-onset diabetes in initially nondiabetic subjects was not examined. In a longitudinal cohort study from Sweden, the risk of myocardial infarction after age 60 was predicted by the increase in blood glucose between the ages of 50 and 60 in a subgroup of hypertensive men mostly treated with diuretics and β-blockers. Risk of infarction was greater in this group than in a composite group of normotensive and hypertensive subjects not receiving drug treatment. Unfortunately, data analysis focused on the association between increase in blood glucose, antihypertensive treatment, and outcome, and failed to estimate the independent prognostic impact of potentially important covariates, such as the severity of hypertension and new-onset diabetes.

The Present Study

The subjects with future diabetes had features of increased cardiovascular risk at entry and during follow-up when compared with subjects without diabetes. Because of such imbalance, the association between new-onset diabetes and outcome was tested with simultaneous adjustment for age, average 24-hour systolic BP, and incidence of LV hypertrophy at the follow-up study. Other important covariates including serum triglycerides and an IGT status did not achieve significance in the multivariate model. Notably, the incidence of cardiovascular events did not differ between the subjects with new diabetes and those with diabetes at entry.

Previous Studies

In some randomized trials, the incidence of new diabetes was higher in the subjects allocated to diuretics and β-blockers than in those allocated to different drugs. Incidence was 6.9% versus 6.1% (P=0.04), respectively, in the Captopril Prevention Project (CAPPP), 7.7% versus 5.6% (P=0.001), respectively, in the Intervention as a Goal in Hypertension Treatment study (INSIGHT), and 8% versus 6% (P=0.001), respectively, in the Losartan Intervention for End-point Reduction (LIFE) study. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the incidence of new diabetes at the end of the study was 11.6% in the chlorthalidone group, 9.8% in the amloidipine group (P=0.04), and 8.1% in the lisinopril group (P<0.001). In contrast, the incidence of new diabetes in the Swedish Trial in Old Patients with Hypertension-2 (STOP-2) study was 11.4% in the group randomized to diuretics and/or β-blockers, 10.7% in the group...
randomized to ACE inhibitors, and 10.5% in the group randomized to calcium-channel blockers \((P=0.77)\). Also, in the Nordic Diltiazem (NORDIL) study, incidence of new diabetes did not differ between the group randomized to diuretics and \(\beta\)-blockers and that randomized to diltiazem (4.6% versus 4.0%; \(P=0.14\)). Other randomized studies did not provide sufficient data to assess the incidence of new-onset diabetes in the different groups. Several possible reasons including the relatively short duration of follow-up and the usually small absolute difference in the incidence of new diabetes between the groups may have precluded the disclosure of a significant adverse prognostic impact of such phenomenon. The long duration of follow-up (up to 16 years) of our study and its observational nature were possible reasons that allowed disclosure of the clinical complications of new diabetes.

Predictors of New-Onset Diabetes

Compared with nondiabetic subjects, those with future diabetes showed a higher blood glucose at baseline and a more frequent use of diuretics at follow-up. ACE inhibitors and calcium-channel blockers were also given more frequently in the subjects who had new diabetes than in those who did not, but neither of these 2 classes of drugs achieved significance in the multivariate analysis. Unexpectedly, exposure to \(\beta\)-blockers was not associated with a greater risk of new diabetes. The more intensive therapy in the subjects with new diabetes was probably dictated by the worst risk profile in this group. These findings are consistent with a large Survey of Medicaid enrollees, which showed an association between multidrug treatment for hypertension and initiation of therapy for diabetes. Regarding diuretics, the adverse effects of these agents on glucose tolerance is well known. From a comprehensive review of literature, Ramsay et al observed that diuretics may exert substantial adverse effects on metabolic control in subjects with diabetes, whereas the extent of their influence on clinical diabetes and related cardiovascular complication in nondiabetic subjects remain unclear. The logical suggestion was that diuretics remain valuable first-line agents in nondiabetic subjects, whereas alternative options should be considered, whenever possible, in diabetics. Such a view is supported by the findings of Aldermann et al, who documented an independent association between use of diuretics and subsequent cardiovascular disease in hypertensive subjects with diabetes, but not in nondiabetics. Recently, the Seventh Report of the Joint National Committee of Prevention, Detection and Treatment of High Blood Pressure (JNC 7) did not endorse such a position and included diuretics among the first-line agents even in subjects in whom diabetes and hypertension coexist.

Because the effects of diuretics on blood glucose are related to the dose of these drugs, not to the levels of blood glucose, subjects with IFG may be more likely to have new diabetes when exposed to drugs that worsen glucose tolerance. A condition of IFG is by itself a condition of increased cardiovascular risk, particularly in subjects with hypertension, and approximately half of our subjects with new diabetes showed IFG when they entered the study. However, IFG was not an independent predictor of outcome after correction for new-onset diabetes, whereas pretreatment blood glucose was a strong predictor of new diabetes independently of the use of diuretics.

It is important to remark that the occurrence of new diabetes was an independent predictor of cardiovascular risk, whereas the use of diuretics, albeit predictive of new diabetes, did not show any independent relation with the subsequent cardiovascular events. These findings underscore the need for implementing aggressive strategies on the various aspects of the metabolic syndrome targeted to prevent occurrence of new diabetes in hypertensive subjects.

Limitations of the Study

Because our population was 100% white, caution is needed in extrapolating our results to different ethnic groups. Another limitation, inherent to observational cohort studies, is the lack of control for occasional changes in antihypertensive regimen over time. Furthermore, we could not assess the predictive value of insulin resistance on the development of new diabetes because plasma insulin was dosed only in a subset of patients. Finally, the potential impact of diet, physical activity, and socio-economic status on the development of new diabetes could not be evaluated.

Perspectives

New diabetes is an important clinical problem that occurs in \(\approx2\%\) of treated hypertensive subjects per year. Pretreatment plasma glucose and diuretic treatment on follow-up are independent predictors of new diabetes. New diabetes has an increased risk for cardiovascular disease and its adverse prognostic impact is not dissimilar from that of previously known diabetes. Subjects with new-onset diabetes and those with a previous diagnosis of diabetes are almost 3-times as likely to have subsequent cardiovascular disease over a long follow-up period than are those who remain free of diabetes. Hypertensive subjects with plasma glucose in the high-normal range and those treated with diuretics should be monitored with care to prevent occurrence of new diabetes.

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References


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