Ambulatory Blood Pressure and Urinary Albumin Excretion in Diabetic (Non–Insulin-Dependent and Insulin-Dependent) Hypertensive Patients Relationships at Baseline and After Treatment by the Angiotensin Converting Enzyme Inhibitor Trandolapril

Bernard Bauduceau, Nathalie Genès, Bernard Chamontin, Laurent Vaur, Maguy Renault, Sylvie Etienne, and Michel Marre

The aim of the present study was to examine the relationships between ambulatory blood pressure (ABPM) and urinary albumin excretion (UAE) in diabetic (non–insulin dependent [NIDDM] and insulin-dependent [IDDM]) hypertensives at baseline and after treatment by an angiotensin converting enzyme (ACE) inhibitor. After a 3-week placebo period, patients were treated for 16 weeks with trandolapril, 2 to 4 mg/day. The UAE and blood pressure (mercury sphygmomanometer and 24-h ABPM) were measured at baseline and repeated on trandolapril. Predictive factors of abnormal UAE (24-h UAE ≥30 mg) were determined using univariate and multivariate analysis (logistic regression). Predictors of UAE decrease were also searched. One hundred seventy-one patients entered the analysis. Baseline office BP was 164 ± 14/97 ± 6 mm Hg and 24-h BP was 142 ± 17/83 ± 10 mm Hg. Seventy-four patients (43%) had UAE ≥30 mg. Independent risk factors for abnormal UAE were nighttime diastolic BP (odds ratio [OR] = 4.1, confidence interval [CI] = 2.0 to 8.6, P = .0001), diabetes duration (OR = 2.4, CI = 1.1 to 5.0, P = .025), and presence of retinopathy (OR = 3.2, CI = 1.0 to 10.0, P = .047).

Conversely, office BP level was not significantly related to UAE. On treatment, office BP levels decreased to 143 ± 13/82 ± 8 mm Hg (P < .0001) and 24-h BP levels to 134 ± 17/78 ± 9 mm Hg (P < .0001). In the abnormal UAE group, UAE significantly decreased from 76 to 50 mg/day (P = .006). After treatment, independent predictive factors of abnormal UAE were: on-drug fasting plasma glucose (OR = 3.5, CI = 1.7 to 7.4, P = .0009) and on-drug nighttime diastolic BP (OR = 3.5, CI = 1.7 to 7.4, P = .001). The only predictor of UAE decrease was a 24-h systolic BP decrease (OR = 2.3, CI = 1.3 to 4.3, P = .007). We conclude that in diabetic hypertensives with abnormal UAE, trandolapril exhibited a sustained 24-h antihypertensive effect and provided a consistent reduction of microalbuminuria. This study confirmed the superiority of ABPM over clinical BP to predict target organ damage. Am J Hypertens 1998;11:1065–1073 © 1998 American Journal of Hypertension, Ltd.

KEY WORDS: Urinary albumin excretion, diabetes mellitus, angiotensin converting enzyme inhibitor, ambulatory blood pressure monitoring.

Received June 19, 1997. Accepted March 25, 1998.

From the Hôpital Bégin (BB), Saint Mandé; Medical Department, Laboratoires Roussel (NG, LV, SE), Paris; Hôpital Purpan (BC), Toulouse; Medical Department, HMR France (MR), Paris; and Centre Hospitalier Universitaire (MM), Angers; France.

Address correspondence and reprint requests to Pr. Bernard Bauduceau, Service d’Endocrinologie, Hôpital d’Instruction des Armées Bégin, 69 avenue de Paris, 94160 Saint Mandé, France.

© 1998 by the American Journal of Hypertension, Ltd.
Hypertension is frequently observed in diabetic patients. The relationship between hypertension and diabetes is complex. Hypertension is closely associated to the extent of renal injury and might aggravate several complications of diabetes such as coronary disease, arteriopathy, retinopathy, and nephropathy. Microalbuminuria is considered as an initial sign of glomerular injury in normotensive and hypertensive diabetic patients, as well as in patients with essential hypertension. In diabetes mellitus, microalbuminuria has been shown as a predictor of the progression of nephropathy, but also of cardiovascular morbidity and mortality. In essential hypertension, microalbuminuria has been positively correlated with markers of the severity of hypertension such as blood pressure level or target organ damage. Hypertensive patients with microalbuminuria could exhibit a higher prevalence of cardiovascular disease.

Several trials using different antihypertensive agents have been conducted in microalbuminuric patients with either essential hypertension or diabetes mellitus. Previously, it has been reported that angiotensin converting enzyme (ACE) inhibitors could be superior to other antihypertensives in reducing urinary albumin excretion. ACE inhibitors could exhibit a beneficial renoprotective effect on glomerular function and structure beyond that obtained by blood pressure reduction alone.

Blood pressure levels are usually evaluated by repeated measurements with mercury sphygmomanometer but they might be influenced by the phenomenon of white coat hypertension. Ambulatory blood pressure monitoring is a well-established method that allows the determination of circadian variations of blood pressure and the efficacy of antihypertensive treatment. Moreover ambulatory blood pressure monitoring has been found to be more closely related to target organ damage and to cardiovascular mortality, than casual blood pressure.

The aim of this study was to examine at baseline the relationships among ambulatory blood pressure and urinary albumin excretion (UAE) in diabetic hypertensive patients and to evaluate whether treatment by an angiotensin converting enzyme (ACE) inhibitor could modify this relationship.

METHODS

Patients Men and women aged 18 to 75 years with mild to moderate hypertension and diabetes mellitus were eligible to enter the study. At the end of a 3-week placebo run-in period, office diastolic blood pressure (DBP) had to be confirmed in the range 90 to 115 mm Hg. Ambulatory blood pressure levels at baseline were not used as inclusion criteria. Main exclusion criteria were 1) any serious chronic disease, 2) known hypersensitivity or contraindication to ACE inhibitors, 3) serum creatinine >150 μmol/L, and 4) concomitant antihypertensive medications. All patients gave their written informed consent and the protocol was approved by the Comité Consultatif de Protection des Personnes se prétendant à la Recherche Biomédicale de Toulouse, France.

Study Design This was an open multicenter study. After a 3-week placebo run-in period, eligible patients received trandolapril 2 mg once daily for 16 weeks. After 4 weeks of treatment, the dosage had to be increased to 4 mg once daily in nonresponder patients. If patients were still nonresponders at 8 weeks, 20 mg of furosemide had to be added to 4 mg of trandolapril.

Blood Pressure Measurements Office blood pressure was recorded both at the end of the placebo run-in period (to check that inclusion criteria had been met), after 4 and 8 weeks of treatment, and at the end of the active treatment period. Physicians were recommended to perform three consecutive measurements in the sitting position after a 10-min rest using a mercury sphygmomanometer. Systolic blood pressure (SBP) was defined by phase I and DBP by phase V Korotkoff sound. At each evaluation, the mean of three readings defined office SBP and DBP. Patients were defined as nonresponders if the DBP was >90 mm Hg or the DBP decreased by <10 mm Hg.

Ambulatory 24-h blood pressure monitoring (ABPM) was performed both at the end of the placebo period and at the end of the active treatment period. Ambulatory recordings were made using the SpaceLabs 90207 monitor (Redmond, WA). Four measurements per hour were programmed during both day and night. Diastolic blood pressure values greater than SBP values, DBP values lower than 40 mm Hg or more than 150 mm Hg, SBP values lower than 60 mm Hg or more than 250 mm Hg, and values with differential arterial pressures less than 10 mm Hg were excluded. Mean hourly BP was calculated as the average of the measurements in the clock-range ± 30 min. Recordings with less than 75% of hourly means available were discarded. Average SBP and DBP levels were determined for each of the following periods: 24h, daytime (7 am to 10 pm) and nighttime (10 pm to 7 am). Patients were defined as nondippers if the ratio of daytime BP level minus nighttime BP level over daytime BP level was <10% for both SBP and DBP. The prevalence of hypertension based on ambulatory monitoring was calculated using the threshold value of 139/87 mm Hg for 24-h BP. Therefore, patients with 24-h BP ≤139/87 mm Hg were considered as white coat hypertensives.

UAE Measurements Urinary albumin excretion was measured both at the end of the placebo period and at...
the end of the active treatment period. At each time
point, a single 24-h urine collection was done. After
completion, volumes were measured and aliquots of
urine were taken from the 24-h collection. Thereafter,
urine aliquots were sent to a central laboratory for
dosage. UAE was measured by immunonephelomet-y. The high sensitivity and reproducibility of this
method has been previously reported. Urinary cre-
tatinine was also measured to ensure adequacy of UAE
measurements. Normoalbuminuria was defined as
24-h UAE ≤30 mg, microalbuminuria as 24-h UAE
ranging from 30 to 299 mg, and macroalbuminuria as
24-h UAE ≥300 mg. Fasting blood samples were
drawn and sent to central laboratory for measurement
of glycosylated hemoglobin (HbA1c) using HPLC and
for standard chemical tests (serum creatinine, kali-
emia, serum glucose).

Statistical Analysis  Data were expressed as mean ±
SD. As UAE did not follow a normal distribution, it
was expressed by its median and the 5th and 95th
percentiles. Subjects were categorized as having nor-
moalbuminuria (0 to 29 mg/day) or abnormal UAE
(≥30 mg/day). Differences between the two groups
were compared using Student’s t test for quantitative
variables and χ² test for qualitative variables (univari-
ate analysis). Multivariate logistic regression analysis
was used to estimate the independent association of
abnormal UAE with selected clinical variables (age,
gender, body mass index, duration of hypertension
and diabetes, complications), blood pressure levels
-office and ambulatory BP), and biological parameters
(seum creatinine, fasting serum glucose, and HbA1c).
These analyses were performed at baseline and after
treatment. Predictive factors of UAE decrease were
also analyzed by both univariate and multivariate
analyses. They were described by their odds ratio
(OR) and corresponding 95% confidence intervals
(CI). Statistical significance was considered for
P < .05. SAS statistical software (V6.08) (Cary, NC) was used
for all calculations.

RESULTS
One hundred seventy-one patients (mean age 62 ± 10
years, 54% men), with valid ABPM and UAE dosages,
completed the study. Noninsulin-dependent diabetes
was present in 95% of patients and insulin-dependent
diabetes in 5%. At baseline, mean office BP was 164 ±
14/97 ± 6 mm Hg and 24-h BP was 142 ± 18/81 ± 10
mm Hg. Forty-five patients (26%) were classified as
ambulatory hypertensives and 126 patients (74%) as
white coat hypertensives.

Ninety-seven patients (57%) had normoalbuminuria
and 74 patients (43%) exhibited UAE ≥30 mg/day. Among
them, 65 patients (38%) had microalbuminuria and
9 patients (5%) exhibited macroalbuminuria. Univari-
ate analysis compared the characteristics of pa-
tients with normoalbuminuria at baseline to those of
patients with abnormal UAE (Table 1). According to
this analysis, significant predictive factors of abnormal
UAE at baseline were: known diabetes duration, reti-
opathy, degree of metabolic control as determined by
HbA1c, and ambulatory BP levels. Nondipping was

### TABLE 1. CHARACTERISTICS OF PATIENTS ACCORDING TO BASELINE UAE LEVEL: UNIVARIATE ANALYSIS

<table>
<thead>
<tr>
<th></th>
<th>UAE &lt;30 mg/day</th>
<th>UAE ≥30 mg/day</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62 ± 9</td>
<td>61 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (% males)</td>
<td>51</td>
<td>58</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29 ± 4</td>
<td>30 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>7 ± 7</td>
<td>11 ± 9</td>
<td>.005</td>
</tr>
<tr>
<td>Fasting serum glucose (mmol/L)</td>
<td>8.3 ± 2.8</td>
<td>9.1 ± 3.2</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.3 ± 1.8</td>
<td>8.1 ± 2.2</td>
<td>.014</td>
</tr>
<tr>
<td>Hypertension duration (years)</td>
<td>6 ± 8</td>
<td>7 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Office SBP/DBP</td>
<td>164 ± 14/96 ± 6</td>
<td>164 ± 13/98 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>24-h SBP/DBP</td>
<td>136 ± 14/79 ± 9</td>
<td>149 ± 17/87 ± 10</td>
<td>.0001/.0001</td>
</tr>
<tr>
<td>Daytime SBP/DBP</td>
<td>141 ± 14/84 ± 10</td>
<td>152 ± 18/90 ± 10</td>
<td>.0001/.0002</td>
</tr>
<tr>
<td>Nighttime SBP/DBP</td>
<td>127 ± 17/71 ± 9</td>
<td>142 ± 20/81 ± 11</td>
<td>.0001/.0001</td>
</tr>
<tr>
<td>Nondippers (%)</td>
<td>22</td>
<td>46</td>
<td>.001</td>
</tr>
<tr>
<td>Retinopathy* (%)</td>
<td>9</td>
<td>26</td>
<td>.004</td>
</tr>
<tr>
<td>Arteritis (%)†</td>
<td>4</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>Angina (%)</td>
<td>5</td>
<td>5</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Retinopathy was defined as fundus oculi grade ≥2.
† Arteritis was defined as a previous history of intermittent claudication.

BMI, body mass index; HbA1c, glycosylated hemoglobin; SBP, DBP, systolic and diastolic blood pressure, respectively; UAE, urinary albumin excretion.
Abbreviations as in Table 1.

significantly more frequent in patients with abnormal UAE. In white coat hypertensives, median UAE was lower than in ambulatory hypertensives (44 mg/day vs 22 mg/day, P = .008). Conversely, age, sex, body mass index, hypertension duration, and office blood pressure were not significantly related to baseline UAE level. In the multivariate analysis (Table 2), only three factors emerged as independent predictive factors of abnormal UAE: nighttime DBP, retinopathy, and diabetes duration. Nighttime DBP was the first predictive factor: patients with nighttime DBP ≥ 75 mm Hg had a fourfold increased risk of abnormal UAE compared to patients having nighttime DBP < 75 mm Hg (P < .0001). Presence of retinopathy multiplied the risk by 3 (P = .047) and duration of diabetes ≥ 5 years doubled this risk (P = .025).

At the end of the 16-week treatment period, 120 patients (70.2%) were still on 2 mg of trandolapril, 34 patients (19.9%) on 4 mg of trandolapril, and 17 patients (9.9%) were receiving 4 mg of trandolapril and 20 mg of furosemide. There was no difference in treatment distribution between the normoalbuminuric group and the abnormal UAE group.

After 16-week treatment mean office BP levels decreased to 143 ± 13/82 ± 8 mm Hg (P < .0001) and 24-h BP level to 134 ± 17/78 ± 9 mm Hg (P < .0001). On-drug office and ambulatory BP level of patients according to UAE at baseline are shown in Table 3. Baseline and on-drug ambulatory BP levels of both groups are represented in Figures 1 and 2. In the two groups, office and ambulatory BP decreased significantly. However, on-drug ambulatory BP levels still remained higher in the abnormal UAE group when compared to the normoalbuminuric patients (all P < .05).

In the normoalbuminuric group, UAE increased slightly although the median was unchanged. In the abnormal UAE group, UAE significantly decreased from 76 to 50 mg/day (P = .006). Among normoalbuminuric patients at baseline, 12 patients (12%) exhibited UAE ≥ 30 mg/day on trandolapril. Conversely, 21 patients (28%) with abnormal UAE at baseline recovered normoalbuminuria (P = .0002). Univariate analysis compared the characteristics of patients with normoalbuminuria on treatment to those of patients with abnormal UAE on treatment (Table 4). According to this analysis, significant predictive factors of abnormal UAE on treatment were: diabetes duration, retinopathy, degree of metabolic control as determined by on-drug HbA1c, and fasting serum glucose, on-drug 24-h, daytime, nighttime SBP and DBP levels. In white coat hypertensives, UAE levels still remained lower when compared to ambulatory hypertensives (33 vs 20 mg/day, P = .01). On-drug office SBP level was also

TABLE 2. PREDICTORS OF ABNORMAL UAE AT BASELINE: RESULTS OF THE MULTIVARIATE ANALYSIS

<table>
<thead>
<tr>
<th>Ranking</th>
<th>Predictive Factor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nighttime DBP</td>
<td>4.1</td>
<td>2.0–8.6</td>
<td>.001</td>
</tr>
<tr>
<td>2</td>
<td>Diabetes duration</td>
<td>2.4</td>
<td>1.1–5.0</td>
<td>.025</td>
</tr>
<tr>
<td>3</td>
<td>Retinopathy</td>
<td>3.2</td>
<td>1.0–10.0</td>
<td>.047</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nighttime DBP</td>
<td>4.1</td>
<td>2.0–8.6</td>
<td>.001</td>
</tr>
<tr>
<td>Diabetes duration</td>
<td>2.4</td>
<td>1.1–5.0</td>
<td>.025</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>3.2</td>
<td>1.0–10.0</td>
<td>.047</td>
</tr>
</tbody>
</table>

TABLE 3. EFFECTS OF TRANDOLAPRIL ON OFFICE, AMBULATORY BLOOD PRESSURE AND UAE

<table>
<thead>
<tr>
<th></th>
<th>UAE &lt;30 mg/day (n = 97)</th>
<th></th>
<th>UAE ≥30 mg/day (n = 74)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>On-drug</td>
<td>P</td>
<td>Baseline</td>
</tr>
<tr>
<td>Office</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>164 ± 14</td>
<td>141 ± 14</td>
<td>&lt;.0001</td>
<td>164 ± 13</td>
</tr>
<tr>
<td>DBP</td>
<td>96 ± 6</td>
<td>81 ± 7</td>
<td>&lt;.0001</td>
<td>98 ± 7</td>
</tr>
<tr>
<td>24-h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>136 ± 14</td>
<td>129 ± 15</td>
<td>&lt;.0001</td>
<td>149 ± 17</td>
</tr>
<tr>
<td>DBP</td>
<td>79 ± 9</td>
<td>76 ± 5</td>
<td>&lt;.0001</td>
<td>87 ± 10</td>
</tr>
<tr>
<td>Daytime</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>141 ± 14</td>
<td>133 ± 15</td>
<td>&lt;.0001</td>
<td>152 ± 18</td>
</tr>
<tr>
<td>DBP</td>
<td>84 ± 10</td>
<td>80 ± 9</td>
<td>&lt;.0001</td>
<td>90 ± 10</td>
</tr>
<tr>
<td>Nighttime</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>127 ± 17</td>
<td>121 ± 18</td>
<td>&lt;.0001</td>
<td>142 ± 20</td>
</tr>
<tr>
<td>DBP</td>
<td>71 ± 9</td>
<td>67 ± 9</td>
<td>&lt;.0001</td>
<td>81 ± 11</td>
</tr>
<tr>
<td>UAE median (5th to 95th percentiles)</td>
<td>17 (9–27)</td>
<td>17 (10–41)</td>
<td>.04</td>
<td>76 (30–1011)</td>
</tr>
</tbody>
</table>

No between-group difference was observed for BP decrease (Student’s t-test).

UAE change was significantly different (P = .0001) between the two groups (Wilcoxon test).

Abbreviations as in Table 1.
associated with abnormal UAE. After multivariate analysis, only two factors emerged as predictive factors of abnormal UAE on trandolapril: on-drug fasting serum glucose and on-drug nighttime DBP (Table 5). Patients with on-drug fasting serum glucose ≥ 8 mmol/L had a 3.5-fold increased risk of abnormal

FIGURE 1. Circadian variations of blood pressure in patients with abnormal urinary albumin excretion (UAE): systolic (SBP) and diastolic (DBP) blood pressures at baseline and after treatment.

FIGURE 2. Circadian variations of blood pressure in normoalbuminuric patients: systolic (SBP) and diastolic (DBP) blood pressures at baseline and after treatment.
UAE compared to patients with serum glucose <8 mmol/L (P = .0009). On-drug nighttime DBP multiplied also the risk by 3.5 (P = .001).

Predictive factors of UAE changes were searched. Patients were divided into two groups according to UAE change: group 1 patients with UAE decrease (n = 82) and group 2 patients with no change in UAE or UAE increase (n = 89). Univariate analysis showed the following potential predictive factors of UAE decrease: 24-h SBP (P = .007), daytime SBP (P = .078), daytime DBP (P = .078), and HbA1c changes (P = .09). After multivariate analysis, the only predictive factor of UAE decrease was 24-h SBP decrease; patients with a 24-h SBP decrease of >7.5 mm Hg were more likely to present with an UAE decrease when compared to patients with a 24-h SBP decrease ≤7.5 mm Hg (OR = 2.3, CI 95% = 1.3 to 4.3, P = .007).

DISCUSSION

The relationship between blood pressure levels and urinary albumin excretion in hypertensive diabetic patients has been studied in several trials. Office blood pressure levels have been inconsistently found to be higher in microalbuminuric patients when compared to those of normoalbuminuric patients. However, casual blood pressure has been found to be less closely related to microalbuminuria than ambulatory blood pressure. Bianchi et al24 have found a significant correlation between UAE and 24-h SBP but no significant correlation was present between UAE and office blood pressure. Palatini et al25 have compared office and ambulatory BP level among 53 microalbuminuric subjects and 744 normoalbuminuric; office BP levels were slightly higher in the microalbuminuric group, but this increase was only significant for DBP. Ambulatory SBP and DBP levels were found more significantly higher in the microalbuminuric group. Using logistic regression analysis, only 24-h SBP emerged as a predictive factor of overt microalbuminuria. Our study confirms that ambulatory BP is more strongly associated with abnormal UAE. These results are in accordance with previous studies showing that target organ damage and cardiovascular mortality correlate better with average 24-h blood pressure than with casual office blood pressure.17–20

A significant number of either hypertensive or diabetic patients fail to manifest the normal nocturnal decrease of blood pressure. They have been called nondippers. Several studies have shown that nondippers exhibit greater evidence of organ damage and a higher incidence of cardiovascular morbidity and mortality.20 Indeed these patients showed a higher prevalence of overt microalbuminuria as compared to nondippers.24,26–28 In our study the phenomenon of nondipping was more frequently found in patients with abnormal UAE. However, the level of nocturnal DBP seems to be more relevant than the daytime/

### TABLE 4. CHARACTERISTICS OF PATIENTS ACCORDING TO ON-DRUG UAE LEVEL: UNIVARIATE ANALYSIS

<table>
<thead>
<tr>
<th></th>
<th>UAE &lt;30 mg/day (n = 106)</th>
<th>UAE ≥30 mg/day (n = 65)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63 ± 9</td>
<td>60 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (% males)</td>
<td>52</td>
<td>57</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29 ± 4</td>
<td>30 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>8 ± 9</td>
<td>11 ± 8</td>
<td>.04</td>
</tr>
<tr>
<td>On-drug fasting serum glucose (mmol/L)</td>
<td>7.9 ± 2.5</td>
<td>10.3 ± 3.7</td>
<td>.0001</td>
</tr>
<tr>
<td>On-drug HbA1c (%)</td>
<td>7.3 ± 1.7</td>
<td>8.3 ± 2.0</td>
<td>.001</td>
</tr>
<tr>
<td>Hypertension duration (years)</td>
<td>6 ± 7</td>
<td>7 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>On-drug office SBP/DBP</td>
<td>142 ± 15/82 ± 8</td>
<td>146 ± 10/83 ± 8</td>
<td>.02/NS</td>
</tr>
<tr>
<td>On-drug 24-h SBP/DBP</td>
<td>131 ± 15/76 ± 8</td>
<td>141 ± 18/82 ± 11</td>
<td>.0002/.0002</td>
</tr>
<tr>
<td>On-drug daytime SBP/DBP</td>
<td>135 ± 15/80 ± 8</td>
<td>144 ± 18/85 ± 11</td>
<td>.0007/.005</td>
</tr>
<tr>
<td>On-drug nighttime SBP/DBP</td>
<td>121 ± 17/68 ± 9</td>
<td>135 ± 21/76 ± 11</td>
<td>.0001/.0001</td>
</tr>
<tr>
<td>On-drug nondippers (%)</td>
<td>23</td>
<td>42</td>
<td>.009</td>
</tr>
<tr>
<td>Retinopathy (%)</td>
<td>11</td>
<td>24</td>
<td>.02</td>
</tr>
<tr>
<td>Arteritis (%)</td>
<td>9</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>Angina (%)</td>
<td>6</td>
<td>5</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

### TABLE 5. PREDICTORS OF ON-DRUG ABNORMAL UAE: RESULTS OF THE MULTIVARIATE ANALYSIS

<table>
<thead>
<tr>
<th>Ranking</th>
<th>Predictive Factor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>On-drug fasting serum glucose</td>
<td>3.51</td>
<td>1.7–7.4</td>
<td>.0009</td>
</tr>
<tr>
<td>2</td>
<td>Nighttime DBP</td>
<td>3.49</td>
<td>1.7–7.4</td>
<td>.001</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
nighttime blood pressure difference. At baseline, using multivariate analysis, nighttime DBP was the first predictive factor of abnormal UAE, whereas nondipping disappeared when adjusted for the other independent risk factors. This major role of nighttime blood pressure has been previously reported by Berrut et al.26,29 Apart from ambulatory BP factors, our study revealed that duration of diabetes and presence of retinopathy were weaker predictors of abnormal UAE. Known diabetes duration has been previously correlated with UAE in one study,30 but this relationship is not usually found. Relationships between abnormal UAE and clinical target organ damage, such as retinopathy30,31 and peripheral vascular disease,31,32 have been more consistently reported. In insulin-dependent diabetes mellitus (IDDM) patients, microalbuminuria is usually consequent to poor glycemic control and renal vascular lesions due to diabetes.33 In non–insulin-dependent diabetes mellitus (NIDDM) hypertensive patients, microalbuminuria can be attributed to diabetic glomerular lesions or to essential hypertension associated with diabetes. The results of this study support that diabetes control and duration can be important determinants for microalbuminuria in hypertensive NIDDM patients, in addition to coexisting hypertension. Other clinical variables, such as age, male gender, or body mass index, have been inconsistently reported,11,31 but were not found in our study.

Trandolapril is a long-acting ACE inhibitor. Several studies using ABPM have demonstrated a sustained BP decrease over 24 h and beyond.34,35 Its trough-to-peak ratio is constantly more than 50%. It has been demonstrated to provide a longer duration of action than other well-established ACE inhibitors such as enalapril36 and perindopril.37 This study confirms a true 24-h antihypertensive effect. However, because of the large number of ambulatory normotensive patients at baseline, the magnitude of blood pressure reduction was modest.

After 4 months of treatment, in the overall population, a slight but not significant decrease in the number of patients with abnormal UAE was observed. These results are mainly explained by the low prevalence of abnormal UAE at baseline. However, in the group of patients with abnormal UAE, a significant decrease on both median of UAE and number of microalbuminuric patients was found. These results are in accordance with those previously reported with either trandolapril38 or other ACE inhibitors.39

This study is the first one aiming to evaluate the predictive factors of abnormal UAE after treatment by an ACE inhibitor. The only two predictors were on-drug fasting serum glucose and on-drug nighttime DBP. Nocturnal blood pressure remained the most important predictor among ambulatory BP variables. However, its importance decreased after treatment, whereas diabetes metabolic control emerged as the first predictor. These results can be explained by the antihypertensive effect of trandolapril, which has decreased the ambulatory BP levels in most of the patients. Indeed, 24-h SBP decrease was the only independent determinant for UAE decrease. In the Diabetes Control and Complications Trial (DCCT) it has been shown that intensive treatment of insulin-dependent diabetes reduced the risk of diabetic complications including microalbuminuria. This was attributed to improved glycemic control, but the relationship between the degree of hyperglycemia and the risk of microalbuminuria was not examined.40 In a recent study the relationship between microalbuminuria and quality of diabetes glycemic control evaluated by glycated hemoglobin has been highlighted.41 In our study, the impact of poor glycemic control emerged when blood pressure was decreased by the treatment; poor metabolic control rather than an insufficient ambulatory BP control was the reason for persistent microalbuminuria in these patients.

In conclusion, in diabetic hypertensive patients with abnormal UAE, trandolapril exhibited a sustained 24-h antihypertensive effect and provided a consistent reduction of microalbuminuria. Independent risk factors for abnormal UAE were nighttime DBP, diabetes duration, and presence of retinopathy. After treatment, on-drug nighttime DBP was still a predictor of persistent UAE but fasting serum glucose emerged as the most important predictor. Moreover, the 24-h SBP decrease was the only independent determinant for UAE decrease. This study confirms the superiority of ambulatory blood pressure (especially nighttime blood pressure) over clinical blood pressure to predict target organ damage.

REFERENCES


27. Equiluz-Bruck S, Schnack C, Kopp HP, et al: Nondipp-


ulatory blood pressure monitoring in type I (insulin-


31. Marre M, Girault A, Vasmant D: Prévalence de la mi-


ity and albuminuria in type 2 diabetic patients: a three-


33. Mathiesen ER, Ronn B, Jensen T, Storm B, Deckert T: The relationship between blood pressure and urinary albumin excretion in the development of microalbu-


action by self blood pressure measurement. Am J Hypertens 1996;9:146A.


