Office and Ambulatory Blood Pressure Are Independently Associated With Albuminururia in Older Subjects With Type 2 Diabetes

Andrew Moran, Walter Palmas, Thomas G. Pickering, Joseph E. Schwartz, Lesley Field, Ruth S. Weinstock, Steven Shea

Abstract—Blood pressure strongly predicts microalbuminuria and later progression to renal failure in people with diabetes. Ambulatory blood pressure monitoring seems to be superior to office blood pressure in predicting progression to microalbuminuria in type 1 diabetes. The associations of ambulatory blood pressure with office blood pressure and microalbuminuria in type 2 diabetes remain unclear. We studied the association of office blood pressure taken with an automated device and ambulatory blood pressure with spot urine albumin:creatinine ratio in 1180 older people with type 2 diabetes participating in the Informatics for Diabetes Education and Telemedicine Study. Office and awake systolic blood pressure were independently associated with albuminuria ($P<0.001$ for both) in a multivariate linear regression analysis that adjusted for age, gender, duration of diabetes, hemoglobin A1c, number of antihypertensive medications, and use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. Twelve percent of participants had well-controlled office blood pressure but not ambulatory blood pressure, whereas 14% had well-controlled ambulatory but not office blood pressure. The prevalence of microalbuminuria and macroalbuminuria in these subgroups was intermediate between those with well-controlled or uncontrolled blood pressure by both methods. We found, in a multiethnic group of older subjects with type 2 diabetes, that office systolic blood pressure and awake systolic ambulatory blood pressure exhibited independent associations with degree of albuminuria. (Hypertension. 2006;47:955-961.)

Key Words: blood pressure monitoring, ambulatory ■ diabetes mellitus ■ elderly

 Individuals with type 1 diabetes who are normotensive by office blood pressure (BP) measurement often present with microalbuminuria. Elevated sleep systolic BP, detected with 24-hour ambulatory BP (ABP) monitoring (ABPM), has been shown to be the best BP predictor of microalbuminuria in patients with type 1 diabetes, even in normotensive patients. Some studies of persons with type 2 diabetes have similarly found that elevated sleep systolic BP was the ambulatory measure with the strongest association with microalbuminuria and macroalbuminuria. In individuals with essential hypertension, ABP predicts cardiovascular events independent of office BP.

The relationship of office BP and ABP with microalbuminuria is not well characterized in older patients with type 2 diabetes mellitus. In patients with type 2 diabetes, microalbuminuria is associated with progression to overt nephropathy, atherosclerotic coronary artery disease, stroke, peripheral vascular disease, and cardiovascular mortality. BP is a major predictor of microalbuminuria in people with diabetes. Patients with type 2 diabetes are usually diagnosed with hypertension in the office before microalbuminuria is detected, and it is not clear whether ambulatory monitoring adds useful information to the assessment of BP in these patients. Previous studies of ABP in subjects with type 2 diabetes have been limited by small sample sizes or lack of office BP measurements. We, therefore, studied the relationship of ABP and office BP measured with an automated device to urine albumin:creatinine ratio (ACR) in a large, multiethnic sample of older people with type 2 diabetes. The purpose of this study was to evaluate the potential role of ABPM in the clinical assessment of patients with type 2 diabetes. We specifically sought to determine whether ABP measurements were associated with microalbuminuria and macroalbuminuria independent of office BP measured with an automated device.

Methods
We studied a subset of patients enrolled in the Informatics for Diabetes Education And Telemedicine (IDEATel) Study.
is a federally funded study to assess telemedicine as a means of managing the care of older (age ≥55) Medicare beneficiaries with diabetes who reside in medically underserved areas of New York state. A detailed description of how the IDEATel cohort was assembled is published elsewhere. Exclusion criteria for the IDEATel study included end-stage renal disease; impairment of speech, hearing, vision, or cognition; and life-threatening comorbidities. The 2 IDEATel clinical centers are at Columbia University (New York, NY) and Upstate Medical University (Syracuse, NY). The study recruited 1665 participants (15% black/non-Hispanic, 49% white/non-Hispanic, and 35% Hispanic) who received fasting baseline examinations between December 2000 and October 2002. Participants took their usual daily medications (including antihypertensive medications) on the day of the baseline examination, and prescription drug use and smoking history were ascertained by an interviewer-administered questionnaire. Height, weight, and seated BP were measured; blood and spot urine samples were collected; and a 24-hour ABPM was performed. The 1180 participants who had baseline measurements of urinary albumin and creatinine, serum measurements of lipids and hemoglobin A1c, seated resting BP, and an ABPM of acceptable quality were included in this analysis. The study was approved by the Institutional Review Boards of Columbia University Medical Center and State University of New York Upstate Medical University using principles outlined in the Declaration of Helsinki and Title 45 of the US Code of Federal Regulations, all of the participants gave written informed consent, and all of the study procedures were in accordance with local institutional guidelines.

Laboratory Measures
Urinary albumin level was measured using the immunoprecipitin method (Diasorin) from a random spot urine sample collected at the examination. Values <5.7 mg/dL were assigned a value of 4.0 mg/dL. Urine creatinine level was measured using the picric acid colorimetric method. Both analyses were performed using a Roche/Hitachi 717 automated analyzer (Roche Diagnostics). The urine ACR (milligrams of albumin/grams creatinine) was calculated. Microalbuminuria was defined as an ACR of ≥30 mg/g but <300 mg/g. Macroalbuminuria was defined as an ACR ≥300 mg/g. HbA1c was analyzed by boronate affinity chromatography with the Primus CLC 385 (Primus). Biochemical analyses were performed at Penn Medical Laboratory (currently Medstar Medical Laboratory) in Washington, DC.

Office BP Measured With an Automated Device
Office BP was measured using the DinarMap Monitor Pro 100 (Critikon) automated oscillometric device following a standardized protocol. Cuff size was selected based on a measurement of the arm circumference. Three measurements were obtained at 1-minute intervals in a seated position after 5 minutes of rest, with the cuff at the level of the heart. The average of the second and third measurements was recorded as the resting BP. Uncontrolled office BP was defined as a systolic BP >130 mm Hg or diastolic BP >80 mm Hg.

ABPM
ABPM was performed using a Spacelabs 90207 oscillometric monitor (Spacelabs) following a published protocol. ABPM was recorded every 20 minutes for a 24-hour period with the machine programmed to deflate in 8-mm Hg bleed steps. A minimum of 6 valid awake readings and 4 valid sleep readings were required for the computation of awake and sleep ABP averages. Among the 1180 participants included in the analysis, the mean±SD for the number of valid awake and sleep BP readings were 40±9 and 24±6, respectively. Sleep and awake intervals were based on diary entries, which were confirmed by a telephone interview on the morning that the ABP monitoring ended. Nocturnal dipping was defined as the ratio of mean sleep:mean awake systolic BP <0.90. Nondipping was defined as a ratio of ≥0.90. Twenty-nine participants with a nocturnal dip of <0.80 were included in this analysis, because eliminating them from the analyses did not discernibly alter the results. We used the Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommendations regarding BP goals for diabetes and defined uncontrolled ABP as a mean awake systolic BP >130 mm Hg or a mean awake diastolic BP >80 mm Hg, the same values used to define uncontrolled office BP measured with an automated device. To assess the robustness of our findings, and because the JNC 7 definitions for essential hypertension based on awake ABP are 5 mm Hg lower than for office systolic and diastolic BP, we also tested a more stringent definition of uncontrolled BP as a mean awake systolic >125 mm Hg and or a mean awake diastolic BP >75 mm Hg.

Statistical Analysis
Variables that were positively skewed were log transformed. Group comparisons were made using the χ² test for categorical variables and I-way ANOVA for continuous variables that approximated a normal distribution. The nonparametric Mann-Whitney or Kruskall-Wallis test was used for highly skewed continuous variables. A P value for trend was calculated for comparisons of continuous variables and ordinal variables across quartiles of office systolic BP measured with an automated device. Pearson correlation coefficients were calculated between log-transformed ACR and continuous independent variables. Multivariate linear regression was performed with log-transformed ACR as the dependent variable. The covariates included in the regression model were age, gender, body mass index (BMI), duration of diabetes, hemoglobin A1c, number of antihypertensive medications, and use of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). Total cholesterol, high-density lipoprotein cholesterol, and triglycerides were omitted from the final models, because their inclusion did not materially change the findings. First, a model including the covariates and office systolic BP measured with an automated device was estimated. Next, mean awake systolic ABP was entered into the model. This ABP measure was chosen because it was bivariately associated with log-transformed ACR and independent of office systolic BP. Sleep systolic BP was added to test for an independent association with ACR above and beyond office BP and awake ABP. A similar method was followed for the logistic regression analysis, in which the dependent variable was defined as microalbuminuria or macroalbuminuria (ACR ≥30 mg/g) versus normoalbuminuria (ACR <30 mg/g). A model with office systolic BP and the other covariates used in the linear regression model was estimated first, and then awake systolic ABP was added in a second step. Because previous studies excluded subjects with macroalbuminuria (ACR ≥300 mg/g), we estimated both linear and logistic regression models that excluded participants with an ACR ≥300 mg/g. We evaluated differences in the association between awake systolic ABP and ACR in linear regression models estimated with and without macroalbuminuria subjects by performing a postestimation analysis that identified influential observations. The linear regression models were repeated with groups of influential observations eliminated (dropping observations with an absolute value of DFBETA for awake systolic BP >0.10).

In addition, participants were grouped into 4 categories of BP control: well-controlled BP by both office BP measured with an automated device and ABPM, well-controlled office BP but uncontrolled ABPM, uncontrolled office BP but well-controlled ABPM, and uncontrolled BP by both office and ambulatory measurement. For both ambulatory and office BP, well-controlled BP was defined as a systolic BP ≤130 mm Hg and a diastolic BP ≤80 mm Hg. The relationship between categories of BP control and categories of urinary ACR (normoalbuminuria, microalbuminuria, and macroalbuminuria) was tested using a χ² test. This analysis was then repeated using a more stringent criterion to define well-controlled BP by ABPM: ≤125 mm Hg systolic and ≤75 mm Hg diastolic. To assess for the possibility that differences in the distribution of covariates across the BP control categories might influence prevalence in microalbuminuria or macroalbuminuria, we estimated a logistic regression model with microalbuminuria or macroalbuminuria as the
dependent variable (as defined above); BP control category as the primary predictor; and age, gender, BMI, duration of diabetes, hemoglobin A1c, number of antihypertensive medications, and use of ACE inhibitor or ARB as covariates.

Two-tailed $P$ values are reported for all of the tests. Statistical analyses were performed using SPSS (SPSS) and Stata statistical software (Stata Corp).

Results

Of the 1665 subjects randomized in IDEATel, 485 were excluded from this analysis: 36 because of missing urine albumin measurement, 416 because they did not undergo ABP monitoring or had <6 awake ABP readings, and 33 because they had <4 sleep ABP readings. The 1180 subjects included in this analysis tended to be older and more frequently men and to have lower office BP measured with an automated device, a higher BMI, and a lower ACR. The 2 groups were similar regarding diabetes duration, HgbA1c, and the proportion treated for hypertension.

The mean age of our sample was 71 years; 59% were women, 13% were black, and 38% were Hispanic. The mean duration of diabetes was 11.1 years, the mean hemoglobin A1c was 7.4% (range, 5% to 15%), the mean BMI was 31 kg/m², the mean office systolic BP measured with an automated device was 141 mm Hg (range, 84 to 233 mm Hg), and the median ACR was 19.7 mg/g. Eighty percent were taking antihypertensive medications, 62% were taking an ACE inhibitor or ARB, and 70% lacked the normal fall in nocturnal BP (“nondippers”). The prevalence of nondipping among subjects with normoalbuminuria, microalbuminuria, and macroalbuminuria was 68%, 71%, and 77%, respectively.

Clinical and laboratory characteristics of the participants were compared across 4 categories of office systolic BP measured with an automated device (Table 1). Those in the higher categories of resting systolic BP were older, had a higher median ACR and a higher prevalence of microalbuminuria and macroalbuminuria, were more likely to be taking antihypertensive medications, and were more likely to take ACE inhibitors or ARBs. Hemoglobin A1c, BMI, and smoking history were similar across categories.

We examined the bivariate correlations of ABP with log-transformed ACR and with office systolic BP measured with an automated device (Table 2). Office systolic BP correlated most strongly with log-transformed ACR. Of the ABP measures, awake and 24-hour systolic BP correlated most strongly with log-transformed ACR, and those measures also correlated strongly with office systolic BP. Sleep systolic BP correlated slightly less with log-transformed ACR and office systolic BP. Percentage of nocturnal dip was not associated with the log-transformed ACR ($r = -0.03; p = 0.26$) nor was dipping status significantly associated with category of albuminuria (normoalbuminuria, microalbuminuria, and macroalbuminuria; $\chi^2 P = 0.14$).

The multivariate linear regression analysis showed that office systolic BP measured with an automated device was significantly associated with ACR, after adjusting for all of the covariates ($p < 0.001$). When awake systolic BP was added to the model, both office systolic BP and awake systolic BP were independently associated with urine ACR ($p < 0.001$ for both; Table 3). When sleep systolic BP was added to the model along with office and awake systolic BP, it was not associated with urine ACR ($p = 0.98$). Both office systolic BP and awake systolic BP remained significantly associated with ACR when subjects ($n = 113$) with an ACR $\geq 300$ (macroalbuminuria) were excluded from the analysis ($p < 0.001$ for office systolic BP; $p = 0.04$ for awake systolic ABP). To assess the robustness of our findings, influential data points were identified by postestimation analyses in the 2 final linear regression models, with and without macroalbuminuric subjects, respectively, and then were excluded from the models. Eliminating influential observations ($n = 10$) from the model that included all of the subjects did not alter the $\beta$ coefficients or the $P$ values substantially. After influential observations ($n = 11$) were removed from the model excluding ACR $\geq 300$ mg/g, the $\beta$ coefficient for awake mean systolic BP changed from 0.003 to 0.002, and the $P$ value changed from 0.04 to 0.10.

We also studied the association of office systolic BP measured with an automated device with 2 levels of albuminuria (<30 mg/g or $\geq 30$ mg/g) in a logistic regression model that adjusted for the same covariates used in the linear model. The odds ratio [95% confidence interval (CI)] for the association between office BP and microalbuminuria or macroalbuminuria was 1.4 (95% CI, 1.3 to 1.5) for every 10 mm Hg increase in resting office systolic BP ($p < 0.001$). We then added awake systolic BP to the model. The odds ratio for the association of awake systolic BP with microalbuminuria or macroalbuminuria was 1.4 (95% CI, 1.3 to 1.6) for every 10 mm Hg increase in awake systolic BP ($p < 0.001$). In this model, the odds ratio for office systolic BP remained significant (OR, 1.2; 95% CI, 1.1 to 1.3; $p < 0.001$). In other words, after adjusting for covariates, a participant with an office systolic BP of 150 mm Hg had 2.0 times the odds (95% CI, 1.5 to 2.9) of having microalbuminuria or macroalbuminuria compared with a participant with an office systolic BP of 110 mm Hg, and a participant with an awake systolic BP of 150 mm Hg had 4.1 times the odds (95% CI, 2.6 to 6.6) compared with a participant with an awake systolic BP of 110 mm Hg. The odds ratios from the logistic model remained significant when participants with macroalbuminuria were excluded [OR for the association with microalbuminuria, 1.2 (95% CI, 1.1 to 1.3) for each 10 mm Hg increase in office systolic BP ($p = 0.002$); and 1.4 (95% CI, 1.2 to 1.5) for each 10 mm Hg increase in awake systolic BP ($p < 0.001$)].

In a subsequent analysis of office BP measured with an automated device and awake ABP measurements, we tested the association between the level of albuminuria and different definitions of well-controlled BP (Table 4). We defined office and awake ABP control as a mean systolic BP $\leq 130$ mm Hg and mean diastolic BP $\geq 80$ mm Hg. Fifty-three percent of subjects had uncontrolled BP by both methods, and these participants had the highest prevalence of microalbuminuria and macroalbuminuria. Twelve percent of the participants had adequate BP control by resting office measurements but uncontrolled BP by ABPM, and 14% had adequate BP control by ABP measurement but were found to have uncontrolled BP in the office. For these subjects with controlled BP by one but not the other method, the prevalence of microalbuminuria and macroalbuminuria was intermediate compared with subjects with uncon-
trolled or controlled BP by both methods (overall $\chi^2 = 109; P < 0.001$). There was a significant trend for the odds ratios for microalbuminuria or macroalbuminuria across categories of BP control ($P$ for trend $< 0.001$, adjusted for covariates; Table 4).

Participants with uncontrolled BP by both office and ambulatory methods and participants with controlled ABP but not office BP had the same prevalence of ACE inhibitor or ARB use (66%) and a similar prevalence of taking any antihypertensive medication (84% and 79%, respectively). Subjects with controlled office BP but not ABP had a prevalence of ACE inhibitor or ARB use (51%) and any antihypertensive use (72%) that was lower than subjects with BP control by both methods (56% for ACE inhibitors or ARB and 79% for any antihypertensive medication). Subsequently, we recategorized our participants by defining well-controlled BP by ABPM more stringently, as mean awake systolic BP
Studies of subjects with essential hypertension have demonstrated that ABP predicts cardiovascular events above and beyond office BP\(^3,6\) and that ABPM can add to office BP management.\(^2\) Previous research in diabetes has found relationships between higher ABP and microalbuminuria in patients with diabetes\(^2,3,22-30\) or essential hypertension.\(^3\) Studies in younger subjects with type 1 diabetes have found that sleep ABP predicts the development of microalbuminuria even in subjects with normal office BP\(^2\) and that nocturnal BP correlated directly with pathological evidence of renal injury.\(^3\) In a cross-sectional study, Equiluz-Bruck et al\(^1\) showed that middle-aged subjects with type 2 diabetes and microalbuminuria had significantly higher night systolic BP than nondiabetic, normoalbuminuric hypertensive controls, but their sample size was small, and office BP measurements were not obtained. Torffvit et al\(^4\) reported an association of both day and night ABP with albuminuria and biopsy evidence of glomerular pathology in patients with type 2 diabetes, but they did not include office BP measurements. Nielsen et al\(^30\) in a longitudinal study of 23 patients with type 2 diabetes, found no baseline differences in BP between normoalbuminuric and microalbuminuric subjects but found that change in 24-hour BP, and less-so change in office systolic BP, correlated with change in urine albumin excretion over time. In our analysis, office systolic BP measured with an automated device and awake systolic ABP were each independently associated with degree of albuminuria.

The association between sleep ABP and degree of albuminuria in patients with type 2 diabetes in our study was weaker than that observed by others.\(^3,4\) Office systolic BP and mean awake systolic BP, rather than sleep BP, may be stronger determinants of microalbuminuria and macroalbuminuria in this group of older subjects with type 2 diabetes, because the majority of the cohort had established hypertension, and elevated sleep BP may be a precursor to hypertension only in younger subjects. Alternatively, the weaker association of sleep, compared with awake ABPM with ACR, could be because of a high prevalence of nondipping: 70% of our participants exhibited less than a 10% dip in nocturnal BP. The prevalence of nondipping was higher than in past studies of populations with essential hypertension (25%)\(^33\) and young patients with type 1 diabetes (43%)\(^2\) but consistent with an earlier study by Equiluz-Bruck et al\(^3\) that measured ABP in a cohort with type 2 diabetes. In that study, with 72 subjects and a mean age of 60 years, the prevalence of nondipping was 43% in subjects with normoalbuminuria, 67% with microalbuminuria, and 80% with macroalbuminuria, whereas the corresponding percentages in our cohort were 68%, 71%, and 77%. Both studies found a higher prevalence of nondipping in those with a greater degree of albuminuria. Although the prevalence of nondipping was similar in the 2 studies, it was comparatively higher in our study. Possible explanations may be that our group was older, because the estimates of the earlier study were based on a smaller sample, because of measurement error on our part or theirs or because the populations were different in other respects. The higher prevalence of nondipping observed in our cohort of older participants with type 2 diabetes may be explained by age, diabetes, BP medication use (80%), treat-

### TABLE 2. Bivariate Correlations of Office BP Measured With an Automated Device and ABPMs With (Log-Transformed) Urinary ACR and Office Systolic BP in 1180 Subjects With Type 2 Diabetes, the IDEATel Study, New York, 2001–2002

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pearson Correlation With ACR</th>
<th>P Value</th>
<th>Pearson Correlation With Office Systolic BP</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office SBP</td>
<td>0.32</td>
<td>&lt;0.001</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Office DBP</td>
<td>0.13</td>
<td>&lt;0.001</td>
<td>0.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sleep SBP</td>
<td>0.26</td>
<td>&lt;0.001</td>
<td>0.55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wake SBP</td>
<td>0.30</td>
<td>&lt;0.001</td>
<td>0.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-h SBP</td>
<td>0.30</td>
<td>&lt;0.001</td>
<td>0.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sleep DBP</td>
<td>0.07</td>
<td>0.01</td>
<td>0.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wake DBP</td>
<td>0.06</td>
<td>0.03</td>
<td>0.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-h DBP</td>
<td>0.08</td>
<td>0.01</td>
<td>0.31</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SBP indicates systolic BP; DBP, diastolic BP.

\(\leq 125\) mm Hg and mean awake diastolic BP \(\leq 75\) mm Hg. Although this change in the definition of BP control recategorized some participants, the categories in which BP was controlled by one but not the other BP measurement method again had a prevalence of microalbuminuria and macroalbuminuria that was intermediate between that of subjects with uncontrolled or controlled BP by both methods (overall \(\chi^2=88; P<0.001;\) data not shown).

### TABLE 3. Results of Multivariate Linear Regression Testing Associations With Urine ACR in 1180 Subjects With Type 2 Diabetes, IDEATel Study, New York, 2001–2002

<table>
<thead>
<tr>
<th>Variable</th>
<th>(\beta) Coefficient</th>
<th>SE</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.003</td>
<td>0.002</td>
<td>0.21</td>
</tr>
<tr>
<td>Female gender</td>
<td>-0.026</td>
<td>0.030</td>
<td>0.39</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>-0.003</td>
<td>0.002</td>
<td>0.24</td>
</tr>
<tr>
<td>Duration of diabetes, y</td>
<td>0.009</td>
<td>0.002</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin A1C, %</td>
<td>0.039</td>
<td>0.010</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Taking ACE inhibitor or ARB</td>
<td>0.014</td>
<td>0.037</td>
<td>0.71</td>
</tr>
<tr>
<td>No. of antihypertensive medications</td>
<td>0.046</td>
<td>0.016</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Office systolic BP measured with an automated device, mm Hg</td>
<td>0.005</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean awake systolic BP, mm Hg</td>
<td>0.005</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Elevated BP is a major and potentially reversible determinant of microalbuminuria and progression to renal failure in people with diabetes. We found, in a multiethnic group of older subjects with type 2 diabetes, that office systolic BP measured with an automated device and awake systolic ABP exhibited independent associations with degree of albuminuria. In addition, we found that 12% of the study sample had well-controlled BP based on office measurements but were poorly controlled when assessed by ABPM.

Acknowledgments

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References


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