OBJECTIVE We investigated the prognostic impact of 24-h blood pressure control in treated hypertensive subjects.

BACKGROUND There is growing evidence that ambulatory blood pressure improves risk stratification in untreated subjects with essential hypertension. Surprisingly, little is known on the prognostic value of this procedure in treated subjects.

METHODS Diagnostic procedures including 24-h noninvasive ambulatory blood pressure monitoring were undertaken in 790 subjects with essential hypertension (mean age 48 years) before therapy and after an average follow-up of 3.7 years (2,891 patient-years).

RESULTS At the follow-up visit, 26.6% of subjects achieved adequate office blood pressure control (<140/90 mm Hg), and 37.3% of subjects achieved adequate ambulatory blood pressure control (daytime blood pressure <135/85 mm Hg). Months or years after the follow-up visit, 58 patients suffered a first cardiovascular event. Event rate was lower (0.71 events/100 person-years) among the subjects with adequate ambulatory blood pressure control than among those with higher blood pressure levels (1.87 events/100 person-years) (p = 0.0026). Ambulatory blood pressure control predicted a lesser risk for subsequent cardiovascular disease independently of other individual risk factors (RR 0.36; 95% confidence intervals: 0.18 to 0.70; p = 0.003), including age, diabetes and left ventricular hypertrophy. Office blood pressure control was associated with a nonsignificant lesser risk of subsequent events (RR 0.63; 95% confidence intervals: 0.31 to 1.31; p = NS). In-treatment ambulatory blood pressure was more potent than pre-treatment blood pressure for prediction of subsequent cardiovascular disease.

CONCLUSIONS Ambulatory blood pressure control is superior to office blood pressure control for prediction of individual cardiovascular risk in treated hypertensive subjects. (J Am Coll Cardiol 2002; 39:878–85) © 2002 by the American College of Cardiology Foundation

Despite the awareness of the elevated cardiovascular risk associated with hypertension (1) and the availability of effective and well-tolerated antihypertensive drugs, only a minority of treated hypertensive subjects achieve adequate blood pressure (BP) control (2–4). Clinical studies indicate that many subjects with elevated BP are not treated aggressively by their doctors (3) and that long-term compliance with therapy may be poor (5). Lack of adequate BP control is a major clinical issue because it is well established that poor control of office BP during treatment predicts a high risk of future cardiovascular disease (6–9) and that in-treatment BP is more effective than pre-treatment BP for cardiovascular risk stratification (7–9).

A growing body of evidence indicates that 24-h ambulatory BP (ABP) measurements are superior to office BP measurements for cardiovascular risk stratification in subjects with essential hypertension (10,11). However, prognostic studies on 24-h ABP in hypertensive patients typically have been conducted in patients who were untreated at the time of ABP monitoring. Therefore, the potential for ABP to improve definition of individual risk in treated hypertensive subjects remains unexplored. The aim of the present study was to investigate the prognostic impact of BP control over 24 h in a large cohort of subjects with essential hypertension.

METHODS The PIUMA study. The Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study was established in June 1986 as an observational registry in initially untreated subjects with essential hypertension (12). Office BP had to be ≥140 mm Hg systolic and/or ≥90 mm Hg diastolic on at least three preliminary visits. Admission criteria included absence of previous antihypertensive treat-
Abbreviations and Acronyms

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ABP = ambulatory blood pressure
ACE = angiotensin-converting enzyme
BP = blood pressure
ECG = electrocardiography
LV = left ventricular
PIUMA = Progetto Ipertensione Umbria Monitoraggio Ambulatoriale

ment or treatment having been withdrawn for at least four weeks; no current or previous diagnosis of heart failure, coronary artery disease, significant valvular defects, secondary causes of hypertension; \( \geq 1 \) valid BP measurement per hour over the 24 h. Patients with cancer or other important pathologic conditions were excluded. Diabetes was not an exclusion criterion. Diagnosis of diabetes included a fasting glucose \( \geq 7.77 \) mmol/l (140 mg/dl) or current treatment with oral hypoglycemic drugs or insulin (13).

Blood pressure was measured by a physician with a standard mercury sphygmomanometer in the outpatient office in a quiet environment, on subjects seated and relaxed for at least 10 min. The average of three measurements was used for analysis. Ambulatory BP was recorded using an oscillometric device (SpaceLabs 5200, 90202 and 90207, SpaceLabs, Redmond, Washington), set to take a reading every 15 min throughout the 24 h. The spontaneous day-to-day variability of ABP was assessed in some of these patients (14). Standard 12-lead electrocardiography (ECG) was recorded in all subjects at 25 mm/s and 1 mV/cm calibration. Left ventricular (LV) hypertrophy was tested using a score recently developed in our laboratory (Perugia score), which requires positivity of \( \geq 1 \) of the following three criteria: \( S V_3 + R aVL >2.4 \) mV (men) or \( >2.0 \) mV (women), left ventricular strain, a Romhilt-Estes score of \( \geq 5 \) points (15,16). None of the subjects was treated with digitalis.

Follow-up and assessment of end points. Follow-up was mostly handled by patients’ family doctors, in cooperation with the outpatient office of the referring hospital. Antihypertensive management was driven by office BP values recorded in the office. When PIUMA was established in 1986, most emphasis was given to diastolic BP control (<90 mm Hg). In the subsequent years, systolic BP control was increasingly pursued, as well, on the basis of emerging data on treatment benefits in isolated systolic hypertension (17). More recently, a BP target of <140 mm Hg systolic and 90 mm Hg diastolic has been endorsed. Although reports of ABP monitoring were open to patients and their family doctors, data were unlikely to affect therapeutic decisions because they were considered investigational findings not supported by operational guidelines. Also, the PIUMA protocol states that therapeutic decisions should be based on office BP measurements. Diuretics, \( \beta \)-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers and \( \alpha_1 \)-blockers, alone or in various combinations, were the antihypertensive drugs most frequently used. Periodic contact with family doctors and telephone interviews with patients were arranged to ascertain the vital status and the occurrence of major cardiovascular events.

The follow-up visit, which included standard laboratory tests, 12-lead ECG and office and 24-h ABP measurement, was undertaken after an average of 3.7 years (range 1 to 12) of follow-up. Protocol for BP measurement and other experimental procedures were the same as that in the baseline study. Because the aim of the present study was the assessment of subjects without previous cardiovascular events both at entry and on the follow-up visit, those who eventually developed an event before the follow-up visit were excluded. At the end of the visit, ongoing antihypertensive treatment was modified, if needed, according to the degree of individual office BP control and overall cardiovascular risk assessment.

Hospital record forms and other source documents of patients who died or suffered a cardiovascular event months or years after the follow-up visit were reviewed in conference by the authors of this study. The international standard criteria used to diagnose outcome events in the PIUMA study have been described elsewhere (12,16). Cardiovascular events included myocardial infarction, unstable angina with concomitant ischemic ECG changes, coronary artery surgery or angioplasty, sudden cardiac death, congestive heart failure requiring hospitalization, stroke and transient ischemic attack. Transient ischemic attack was diagnosed by a neurologist or internist in the presence of a rapid onset of a focal neurological deficit, lasting more than 30 s and <24 h and presumably due to ischemia. The PIUMA protocol required that the deficit be present during the qualifying clinical examination in order to be accepted and coded as a terminating event. Patients with stroke were hospitalized during the acute phase, and brain imaging and other diagnostic tests were carried out according to individual needs.

Data analysis. Statistical analysis was performed using SPSS (SPSS Inc., Chicago, Illinois) and SAS-Stat (SAS Institute, Cary, North Carolina). Parametric data are reported as mean ± standard deviation. For those subjects who experienced multiple events, survival analysis was based on the first event. Survival curves were calculated using Kaplan-Meier product-limit method and compared by the Mantel (log-rank) test. The effect of prognostic factors on survival was assessed by stepwise Cox model (18). We first tested a baseline model using the following variables: age (y), gender (male, female), family history of premature (<55 years in the father, <65 years in the mother) cardiovascular disease (no, yes), diabetes (no, yes), LV hypertrophy at ECG (no, yes), serum cholesterol (mmol/l), serum triglycerides (mmol/l), smoking habits (nonsmokers, current smokers), body mass index (kg/m²), antihypertensive treatment at the follow-up visit (coded under four categories: lifestyle measures alone, diuretics and \( \beta \)-blockers alone or
Results are reported in Table 2. After controlling for age, diabetes and LV hypertrophy by multivariate analysis, ABP control achieved adequate control of office BP; 295 subjects (37.3%) achieved control of ABP. Overall, 32% of the subjects were using lifestyle measures alone and 68% were being treated with antihypertensive drugs. Of these, 268 received monotherapy with diuretics (n = 19), β-blockers (n = 50), ACE inhibitors (n = 100) or angiotensin II antagonists (n = 17), calcium channel blockers (n = 64) or other drugs (n = 18). The remaining subjects were treated with various drug combinations, mostly ACE inhibitors plus diuretics. Office BP and 24-h ABP at the entry visit and at follow-up visit are reported in Figure 1. From the baseline to the follow-up visit, office BP decreased from 156/98 mm Hg to 145/91 mm Hg, and 24-h ABP from 137/87 mm Hg to 128/81 mm Hg (all p < 0.01). At the follow-up visit, systolic BP was higher in the subset with subsequent cardiovascular events than in that without events (office systolic BP: 150 vs. 145 mm Hg, 24-h systolic BP: 135 vs. 127 mm Hg; both p < 0.05). Diastolic BP did not differ significantly between the two groups (90 vs. 90 mm Hg; 84 vs. 81 mm Hg). Pulse pressure was higher in the subset with subsequent cardiovascular events than in that without events (office pulse pressure: 59 vs. 54 mm Hg; 24-h pulse pressure: 51 vs. 46 mm Hg, both p < 0.05).

Outcome events. Subsequently to the follow-up visit, 58 subjects developed a first cardiovascular event. There were 14 subjects with myocardial infarction, 13 with new-onset angina and ST segment changes (2 of whom underwent coronary bypass surgery), 2 with heart failure requiring hospitalization, 15 with stroke and 8 with transient ischemic attack, 2 with occlusive arterial vascular disease and 4 with renal failure requiring dialysis. Event rate was 0.71 ± 0.10 patient-years in the subset who had achieved ABP control (11 events out of 295 patients) versus 1.87 in the subset with higher ABP (47 events out of 495 patients) (p = 0.0026). Figure 2 shows the incidence of cardiovascular events in treated hypertensive subjects with and without adequate control of ambulatory blood pressure. Office BP control was associated with a nonsignificant lesser risk of subsequent cardiovascular events (0.98 vs. 1.16 events × 100 patient-years; p = 0.12).

Multivariate analysis. Results are reported in Table 2. After controlling for age, diabetes and LV hypertrophy by ECG, achieved ABP control independently predicted a considerably lesser risk for subsequent cardiovascular events (relative risk 0.36; 95% confidence intervals: 0.18 to 0.70; p = 0.003). In contrast, office BP control did not achieve significance (relative risk 0.63; 95% confidence intervals: 0.31 to 1.31; p = NS). When both office and ABP control were forced in the same model, only ABP control achieved significance (p = 0.003). In-treatment systolic (p = 0.003)
and diastolic (p = 0.006) ABP levels were also independent predictors of subsequent events; office BP levels were not (all p = NS). For every 12-mm Hg (1 SD) increase in 24-h systolic BP at the follow-up visit, there was an independent 49% increase in the risk of future cardiovascular events, and for every 8-mm Hg (1 SD) increase in 24-h diastolic BP, there was an independent 47% increase of events. None of the other tested variables (see data analysis) achieved statistical significance. Pre-treatment 24-h pulse pressure achieved significance (p = 0.026); pre-treatment 24-h systolic BP bordered significance (p = 0.07).

Figure 3 shows the progressive rise in the age-adjusted five-year risk of cardiovascular disease from the bottom to the top quartile of in-treatment 24-h ABP, according to the presence or absence of diabetes and LV hypertrophy.

Division points for quartiles are 120, 127 and 134 mm Hg for 24-h systolic BP and 75, 81 and 86 mm Hg for 24-h diastolic BP. The age- and risk-factor adjusted increase in cardiovascular disease risk with progressively higher values of pre-treatment and in-treatment ABP is shown in Figure 4. For any given increment in 24-h ABP, the age- and risk-factor adjusted five-year event risk increased in a steeper fashion with in-treatment than with pre-treatment levels, both systolic and diastolic.

**DISCUSSION**

The present study increases our understanding of the prognostic value of ABP in treated hypertensive subjects by showing that ABP achieved during treatment is a more
potent determinant of the risk of cardiovascular disease than achieved office BP.

**Previous studies with ABP.** The prognostic value of ABP has been previously tested in several event-based studies in subjects who were untreated at the time of execution of ABP monitoring (12,20–23). However, although those studies provide strong evidence of the clinical value of this diagnostic technology for cardiovascular risk stratification in untreated hypertensive subjects (12,20–23), their applicability to treated subjects remains unproved. Only a few, small longitudinal studies with ABP monitoring have been carried out in treated hypertensive populations. In one of these studies (24), 86 patients with poorly controlled hypertension under drug treatment were followed for 4 years, and during this period 21 patients suffered a first cardiovascular event. Event rate was higher (p < 0.02) in the upper (13.6 events/100 patient-years) than in the middle (9.5 events/100 patient-years) and lowest (2.2 events/100 patient-years) quartiles of ABP.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Increment</th>
<th>Relative Risk (95% Confidence Intervals)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline model</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Age</td>
<td>10 years</td>
<td>1.41 (1.07–1.85)</td>
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<tr>
<td>Diabetes</td>
<td>Yes vs. no</td>
<td>3.38 (1.66–6.91)</td>
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<tr>
<td>LV hypertrophy</td>
<td>Yes vs. no</td>
<td>2.16 (1.22–3.80)</td>
<td>0.008</td>
</tr>
<tr>
<td>Full model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office BP control*</td>
<td>Yes vs. no</td>
<td>0.64 (0.31–1.31)</td>
<td>NS</td>
</tr>
<tr>
<td>Ambulatory BP control**</td>
<td>Yes vs. no</td>
<td>0.36 (0.18–0.70)</td>
<td>0.003</td>
</tr>
<tr>
<td>Pre-treatment office SBP</td>
<td>1 SD (18 mm Hg)</td>
<td>1.07 (0.81–1.42)</td>
<td>NS</td>
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<tr>
<td>Pre-treatment office DBP</td>
<td>1 SD (9 mm Hg)</td>
<td>0.92 (0.72–1.18)</td>
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</tr>
<tr>
<td>Pre-treatment office PP</td>
<td>1 SD (17 mm Hg)</td>
<td>1.16 (0.86–1.57)</td>
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<tr>
<td>Pre-treatment 24-h SBP</td>
<td>1 SD (14 mm Hg)</td>
<td>1.27 (1.00–1.91)</td>
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</tr>
<tr>
<td>Pre-treatment 24-h DBP</td>
<td>1 SD (10 mm Hg)</td>
<td>1.05 (0.78–1.41)</td>
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<td>Pre-treatment 24-h PP</td>
<td>1 SD (9 mm Hg)</td>
<td>1.31 (1.04–1.65)</td>
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<td>NS</td>
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<td>In-treatment office PP</td>
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<td>1.01 (0.77–1.33)</td>
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<td>1.49 (1.14–1.92)</td>
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<td>In-treatment 24-h PP</td>
<td>1 SD (8 mm Hg)</td>
<td>1.21 (0.94–1.56)</td>
<td>NS</td>
</tr>
</tbody>
</table>

The different blood pressure components were added one at a time to the baseline model, and the associated relative risk is adjusted for the baseline model.

*Office BP < 140 mm Hg systolic and 90 mm Hg diastolic; **Average daytime ambulatory BP < 135 mm Hg systolic and 85 mm Hg diastolic (17). BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure; SD = standard deviation.

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**Figure 3.** Age-adjusted (Cox model) five-year risk of cardiovascular (CV) disease at different levels of 24-h in-treatment systolic and diastolic blood pressure (BP), diabetes and left ventricular (LV) hypertrophy. The calculated risk corresponds to the median within each quartile.
tertiles of daytime diastolic BP. This study was the first to suggest the prognostic value of ABP in treated patients with resistant hypertension, but results cannot be extended to a general population of treated hypertensive subjects with variable degrees of BP control. A cohort study in 116 treated hypertensive subjects followed for 31 months confirmed the prognostic value of ABP, but results are limited by the small sample size (25). A longitudinal general population study from Japan (26), a study in patients with symptomatic lacunar infarcts (27) and a study in patients with type II diabetes (28) provided additional evidence of the prognostic value of ABP. However, because those studies included both treated and untreated subjects and were performed in a variety of clinical settings, results cannot be reliably extended to the specific context of treated subjects with essential hypertension.

Role of BP control. There is ample evidence from previous studies that achieved BP is an important predictor of cardiovascular risk in treated hypertensive subjects (6–9). In the International Prospective Primary Prevention Study in Hypertension (7), for every 5-mm Hg reduction in diastolic BP from before to during treatment, there was an independent 24% reduction of cardiac events and a 63% reduction in cerebrovascular events. In that study, pre-treatment BP was not a statistically significant predictor of outcome (7). In the Glasgow Blood Pressure Clinic, long-term mortality rate in 3,783 treated hypertensive subjects was directly associated with the BP reduction induced by treatment, even after controlling for age, gender and pre-treatment BP (8). In the Department of Health and Social Security Hypertension Care Computing Project, long-term mortality rate in 2,855 hypertensive subjects was not predicted by pre-treatment BP; it was by in-treatment BP (9). In our study, the proportion of subjects who achieved an adequate control of office BP, defined by a sphygmomanometric BP <140 mm Hg systolic and <90 mm Hg diastolic, was 26.6%, in agreement with a 28% control rate in a previous survey from northern Italy (4). Subjects with adequate control of their office BP showed a 36% lesser risk of future cardiovascular events compared with those with higher BP, but such reduction was not statistically significant because of the wide confidence intervals, possibly due to the limited sample size. However, the subjects with adequate control of ABP, defined by an achieved daytime ABP <135 mm Hg systolic and <85 mm Hg diastolic (19), showed a 64% reduction (95% confidence interval 30% to 82%) in the risk of future cardiovascular events when compared with subjects with higher ABP levels. Furthermore, in-treatment ABP, but not pre-treatment ABP or pre-treatment or in-treatment office BP, independently predicted the subsequent occurrence of adverse cardiovascular events.

These data provide substantial evidence that achieved ABP is a potent determinant of subsequent outcome and that its potency is superior to that of pre-treatment ABP and that of pre-treatment or in-treatment office BP. The higher prevalence of ABP control when compared with office BP control (26.6 vs. 37.3; p < 0.001) could be ascribed to the persistence of a white-coat effect even during the follow-up visit, as demonstrated by Parati et al. (29). However, the definition of “adequate” ABP control could also play a role. In this study, adequate ABP control was defined by an average daytime ABP <135 mm Hg systolic and <85 mm Hg diastolic, as suggested by an ad hoc panel of the American Society of Hypertension (19). The prevalence of subjects with adequate ABP control defined by using lower or higher limits may be expected to decrease or increase, respectively. For example, when using a cut-off value for 24-h ABP normality of 123/77 mm Hg (4), prevalence of our subjects with ABP control was 19.6%.

Study limitations. Because the PIUMA study sample includes only Caucasian subjects, caution is needed in extrapolating our results to different ethnic groups. Another limitation, which applies to all the observational cohort studies, is the lack of control for occasional changes in the
antihypertensive regimen over time. The planned exclusion of subjects with cardiovascular events before the follow-up visit including an ABP monitoring could have been a potential source of selection of our sample. Finally, we relied on a single follow-up visit to estimate the degree of BP control over the entire follow-up period.

Implications. Our findings do not imply that 24-h ABP monitoring should be used routinely in all treated subjects with essential hypertension. The Joint National Committee VI (30), the World Health Organization/International Society of Hypertension Committee (31) and the British Hypertension Society (32) provided a list of clinical conditions in which ABP monitoring might be clinically useful. These conditions may be grouped under all four areas of suspected white-coat hypertension, excessive BP variability over the same or different clinical visits, symptoms suggesting interhypotensive episodes in the presence or absence of antihypertensive treatment; apparent resistance to multiple drug treatment (30–32). Yet the present study and growing numbers of other surveys are providing evidence that ABP is more potent than sphygmomanometric BP for cardiovascular risk stratification in both treated and untreated subjects with essential hypertension (10,11). The stage is now set for intervention trials aimed to establish whether a management of hypertension based on results of ABP is superior, in terms of prevention of organ damage or cardiovascular events, to a traditional management based on office BP. In a recent study, adjustment of antihypertensive treatment based on ABP values instead of office BP values led to a less intensive drug treatment with comparable effects on BP control and left ventricular mass (33). Intervention trials should also include assessment of the prognostic value of self-measured home BP, which was not possible in the context of the present study.

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Reprint requests and correspondence: Dr. Paolo Verdecchia, Dipartimento Malattie Cardiovascolari, Università di Perugia-Ospedale R. Silvestrini, Località S. Andrea delle Fratte, 06156 Perugia, Italy. E-mail: verdec@tin.it. verdec@med.unipg.it.

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