Ambulatory Blood Pressure 
An Independent Predictor of Prognosis in Essential Hypertension

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Abstract To determine the prognostic significance of ambulatory blood pressure, we prospectively followed for up to 7.5 years (mean, 3.2) 1187 subjects with essential hypertension and 205 healthy normotensive control subjects who had baseline off-therapy 24-hour noninvasive ambulatory blood pressure monitoring. Prevalence of white coat hypertension, defined by an average daytime ambulatory blood pressure lower than 131/86 mm Hg in women and 136/87 mm Hg in men in clinically hypertensive subjects, was 19.2%. Cardiovascular morbidity, expressed as the number of combined fatal and nonfatal cardiovascular events per 100 patient-years, was 0.47 in the normotensive group, 0.49 in the white coat hypertension group, 1.79 in dippers with ambulatory hypertension, and 4.99 in nondippers with ambulatory hypertension. After adjustment for traditional risk markers for cardiovascular disease, morbidity did not differ between the normotensive and white coat hypertension groups (P=.83). Compared with the white coat hypertension group, cardiovascular morbidity increased in ambulatory hypertension in dippers (relative risk, 3.70; 95% confidence interval, 1.13 to 12.5), with a further increase of morbidity in nondippers (relative risk, 6.26; 95% confidence interval, 1.92 to 20.32). After adjustment for age, sex, diabetes, and echocardiographic left ventricular hypertrophy (relative risk versus subjects with normal left ventricular mass, 1.82; 95% confidence interval, 1.02 to 3.22), cardiovascular morbidity in ambulatory hypertension was higher (P=.0002) in nondippers than in dippers in women (relative risk, 6.79; 95% confidence interval, 2.45 to 18.82) but not in men (P=.91). Our findings suggest that ambulatory blood pressure stratifies cardiovascular risk in essential hypertension independent of clinic blood pressure and other traditional risk markers including echocardiographic left ventricular hypertrophy. Cardiovascular morbidity is low in white coat hypertension and exceedingly high in women with ambulatory hypertension and absent or blunted blood pressure reduction from day to night. (Hypertension. 1994;24:793-801.)

Key Words • blood pressure monitoring, ambulatory • hypertension, essential • prognosis • hypotrophy, left ventricular • mortality • morbidity • echocardiography

Target-organ damage in essential hypertension is more closely associated with ambulatory than with clinic blood pressure (BP),1-3 and for any given value of clinic BP it is directly related to the mean levels4,5 and variability6,6 of ambulatory BP. Since target-organ damage is a powerful predictor of morbidity and mortality in hypertension,7,8 ambulatory BP might offer prognostic information beyond that provided by clinic BP. Only one large prospective study, based on daytime ambulatory BP readings, has been published concerning the prognostic significance of ambulatory BP in essential hypertension.17,18 On the other hand, an association between nighttime BP and target-organ damage, reflecting the potential detrimental effect of a persistent pressure overload, has been shown in several cross-sectional studies.6,19-23 In a small case-control study, we found preliminary evidence of a blunted nocturnal reduction of BP in hypertensive women, but not in men, with a major cardiovascular event over the subsequent years.24 Moreover, a history of stroke is more frequent in subjects with an absent or blunted nocturnal fall in BP than in those with normal diurnal BP rhythm.25

In 1986 we started the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study, a registry of morbidity and mortality in subjects with essential hypertension whose initial off-therapy diagnostic workup included 24-hour ambulatory BP monitoring according to a standardized protocol. The results of this study are reported here.

Methods

Study Population

The study population was composed of 1187 subjects diagnosed with essential hypertension who entered the PIUMA registry from June 1986 to July 1993 in three participating hospitals (Perugia, Città della Pieve, Castiglione del Lago). Admission criteria to the PIUMA registry included all of the following: (1) essential hypertension with sitting BP greater than or equal to 140 mm Hg systolic or 90 mm Hg diastolic on
at least three visits in the previous 3 weeks; (2) any previous antihypertensive drugs withdrawn for at least 4 weeks; (3) agreement within 5 mm Hg between a mercury column and automatic recorder in at least three consecutive BP measurements taken simultaneously on the same arm before ambulatory BP monitoring was begun; (4) at least one valid ambulatory BP reading per hour for the entire 24-hour period; and (5) absence of heart failure, valvular defects, or concomitant important disease. Previous cardiovascular events were not exclusion criteria from the study for subjects maintaining their full physical and working activities. The initial evaluation in the PIUMA study included a detailed medical history, a 12-lead electrocardiogram, blood test (serum urea nitrogen, serum creatinine, serum glucose, serum uric acid, serum cholesterol, serum sodium, potassium, calcium, and urinalysis), and, from October 1987, routine standard and Doppler echocardiographic studies. Diabetes mellitus was defined by any one of the following: a fasting blood glucose level greater than or equal to 140 mg/dL, a random nonfasting blood glucose level greater than or equal to 200 mg/dL, or the use of an oral hypoglycemic agent or insulin.

A cohort of 205 healthy normotensive subjects composed of members of the hospital staff, medical students, or training fellows (n=98) or subjects examined in our echocardiography laboratories for reasons different from hypertension (innocent systolic murmurs, palpitations, general checkup) volunteered to undergo the laboratory procedures established in the PIUMA registry and were included as a control group. To be eligible for inclusion, their clinic BP had to remain less than 140/90 mm Hg for at least three visits over a 3-week period in the absence of any treatment. All subjects gave informed consent to the study, which was conducted in accordance with the declarations of Helsinki and Tokyo.

Ambulatory BP Monitoring

Ambulatory BP was recorded using the fully automatic SpaceLabs units 5200, 90202, and 90207 set to take a measurement every 15 minutes throughout the 24 hours. The reading, editing, and analysis of data provided by the recorders were done by the SpaceLabs ABP5600, ABP90204, and ABP90209 interfaces. Systolic readings greater than 260 mm Hg or less than 70 mm Hg, diastolic readings greater than 150 mm Hg or less than 40 mm Hg, and pulse pressure readings greater than 150 mm Hg or less than 20 mm Hg were automatically discarded. The daytime period was defined as the interval between 6 AM and 10 PM and the nighttime period as between 10 PM and 6 AM. The spontaneous day-to-day variability of 24-hour, daytime, and nighttime ambulatory BP values had previously been assessed in some of these subjects.26

White coat hypertension was defined by a mean daytime ambulatory BP lower than 131/86 mm Hg in women and 136/87 mm Hg in men. These values are the 90th percentile of the distribution of daytime ambulatory BP in a normotensive population examined in our laboratory.27 A previous study from our group showed that echocardiographic left ventricular (LV) mass, taken as a surrogate measure of outcome,7 is normal in clinically hypertensive subjects with mean daytime ambulatory BP below these values.27 Nondippers were arbitrarily defined by a reduction in the mean systolic and diastolic BP values lower than 10% from day (6 AM to 10 PM) to night (10 PM to 6 AM), and the remaining subjects were classified as dippers. The division between dippers and nondippers was made on the basis of previous studies from our laboratory showing a different target-organ damage in the two groups.28

Echocardiographic Study of the LV

M-mode echocardiographic study of the LV was performed under cross-sectional control using commercially available machines according to standard laboratory procedures described previously.20,27 Only tracings with optimal visualization of interfaces and showing simultaneous visualization of septum, LV internal diameter, and posterior wall were considered adequate for determination of LV mass. With the use of the formula introduced by Devereux et al.,28 LV mass in grams was calculated as $0.80 \times 1.04 \times [(septal\ thickness+LV\ internal\ diameter+posterior\ wall\ thickness)^3-(LV\ internal\ diameter)^3]+0.6 \ g$ and normalized by body surface area. The cutoff point for LV hypertrophy was 125 g/m² in both genders. This value has been validated in two prospective studies of the independent prognostic value of echocardiographic LV hypertrophy,12,19 one of which was carried out on a mixed population of men and women.12 A division between absence and presence of LV hypertrophy at echocardiography may also be made using sex-specific height-adjusted values of LV mass, as done in the Framingham Heart Study.12,14 A Cornell voltage score greater than 2.0 mV in women or 2.8 mV in men20 defined LV hypertrophy by standard 12-lead electrocardiography.

Clinical Follow-up

After initial evaluation, all hypertensive subjects included in the PIUMA registry were followed-up in the outpatient clinic of the referring hospital or by their family doctors and were treated with the aim of reducing clinic BP below 140/90 mm Hg using standard lifestyle and pharmacological measures. The PIUMA protocol recommends that, in the absence of universally established normative values on ambulatory BP measures, therapeutic strategies should be based on clinic BP. Ambulatory BP reports remained accessible to patients and their doctors, but these data were unlikely to significantly influence therapeutic decisions, being generally considered as investigational findings of unproved clinical utility. Diuretics, β-blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, and α-blockers, alone or in various combinations, were the antihypertensive drugs most frequently used.

Telephone interviews were conducted to ascertain the incidence of major complications of hypertension. All interviews were conducted directly with the subjects without knowledge of the results of ambulatory BP monitoring and were followed by a clinical visit whenever the subjects consented. The same procedures were performed in the control group. Periodic clinical visits could be performed in approximately 30% of hypertensive subjects.

Hospital record forms were collegially reviewed by the authors of this study for the subjects who died from any cause or developed a major fatal or nonfatal cardiovascular event. Cardiovascular events included myocardial infarction, stroke, sudden death, angina pectoris, coronary revascularization, transient cerebral ischemic attack, aortoiliac occlusive disease, documented thrombotic occlusion of a retinal artery, and progressive cardiac or renal failure. Myocardial infarction was diagnosed on the basis of at least two of three standard criteria (typical chest pain, electrocardiographic QRS changes, transient elevation of myocardial enzymes by more than twofold the upper normal laboratory limits). Angina pectoris was defined by chest pain accompanied by typical ischemic changes on the electrocardiogram (1 mm of horizontal or downsloping ST depression during exercise test in the absence of digoxin and without ST depression at rest; 1 mm of horizontal or downsloping ST depression lasting 1 minute or longer during Holter monitoring). Sudden death was defined as a witnessed death that occurred within an hour after the onset of acute symptoms, with no history that violence or accident played any role in the fatal outcome. Stroke was diagnosed on the basis of rapid onset of localizing neurological deficit lasting 24 hours or longer in the absence of any other disease process explaining the symptoms. Transient ischemic attack was defined by the diagnosis, made by a physician, of any sudden focal neurological deficit that cleared completely in less than 24 hours.

Statistical Analysis

The outcome events studied were cardiovascular morbidity (fatal plus nonfatal events) and mortality. Event rates are
presented as the number of events per 100 patient-years based on the ratio of the observed number of events to the total number of patient-years of exposure. For subjects who experienced multiple nonfatal events, the analysis included only the first event. Survival curves were estimated using the Kaplan-Meier product-limit method and compared by the Mantel (log-rank) test. The effect of prognostic factors on survival was evaluated by the Cox semiparametric regression model. The assumption of proportional hazards over time was verified before the analyses were performed and was met by all covariates. The assumption concerning linearity of continuous covariates was also verified before analysis. We pursued two lines of inquiry. First, we tested the independent significance of white coat hypertension in the entire cohort of normotensive and hypertensive subjects grouped into four categories: clinical normotension; white coat hypertension; ambulatory hypertension, dippers; and ambulatory hypertension, nondippers. The covariates included in the Cox model were age (<40 years, 40 to 60 years, >60 years), sex (men, women), clinic diastolic BP, clinic pulse pressure (to account for the levels of systolic BP), smoking habits (current smokers, previous smokers, never smokers), previous cardiovascular events (no, yes), diabetes mellitus (no, yes), serum cholesterol (<5.2 mmol/L, 5.2 to 6.5 mmol/L, >6.5 mmol/L), and body mass index (body weight in kilograms divided by height squared in meters ≤27, >27). LV hypertrophy was included either as electrocardiographic (no, yes) or echocardiographic (no, yes). Second, we tested the independent significance of the dippers-nondippers classification in the subset with ambulatory hypertension. Besides the above-mentioned covariates, average 24-hour ambulatory systolic and diastolic BP values were included in this model.

All analyses including echocardiographic LV hypertrophy among the covariates were limited to the subset (n=1070) with adequate echocardiographic tracings for determination of LV mass.

Adjusted relative risks (RR) for the significant Cox model factors were calculated as the antilogarithm of the b| coefficient (e^b|). Ninety-five percent confidence intervals (CI) around the RR estimate were obtained from the formula e^b|±1.96×SE(b^|), where SE is the standard error of b. In two-tailed tests, probability values less than .05 were considered statistically significant. SAS statistical software version 6.08 was used for analyses.

Results

Study Population

We obtained complete follow-up data from 1380 of the 1392 subjects who entered the study from June 1986 to July 1993 (99.1%). The mean duration of follow-up was 3.2 years (range, 0.5 to 7.5). An echocardiographic study of the LV was attempted in 1233 subjects, and tracings were of adequate quality for determination of LV mass in 1070 (87%).

Table 1 presents the clinical characteristics in the normotensive group, in the white coat hypertension group, and in dippers and nondippers with ambulatory hypertension. Prevalence of white coat hypertension was 19.2%. The distribution of antihypertensive treatments differed between the white coat hypertension and ambulatory hypertension groups (χ2=56.6, P<.0001). In fact, 29% of subjects with white coat hypertension were under drug treatment, as opposed to 56% of subjects with ambulatory hypertension (nonpharmacological measures, diuretics or β-blockers alone or combined, angiotensin-converting enzyme inhibitors or calcium antagonists alone or combined, various drug combinations and unknown treatments in 71%, 9%, 13%, 7%, and 0%, respectively, of subjects in the white coat group compared with 43%, 10%, 24%, 22%, and 1% of subjects in the ambulatory hypertension group). Table 2 shows the clinical characteristics in dippers and nondippers with ambulatory hypertension divided by gender.

Cardiovascular Morbidity

We documented 89 cardiovascular events (21 fatal and 68 nonfatal). Among fatal events, there were 10 strokes, 5 myocardial infarctions, and 6 sudden cardiac deaths. As for nonfatal events, there were 19 subjects with stroke, 7 with transitory ischemic attack, 10 with myocardial infarction, 8 with new-onset angina and ischemic electrocardiographic changes (3 of whom underwent coronary revascularization), 7 with new-onset congestive heart failure, 11 with aortoiliac occlusive disease, 2 with thrombotic occlusion of a retinal artery, and 4 with renal failure requiring dialysis. The distribution of antihypertensive treatments did not differ between the subjects who suffered a cardiovascular morbid event and those who did not (nonpharmacological measures, diuretics or β-blockers alone or combined, angiotensin-converting enzyme inhibitors or calcium antagonists alone or combined, various drug combinations or unknown treatments in 52%, 9%, 24%, 15%, and 0%, respectively, in those with events versus 53%, 10%, 20%, 16%, and 1% in those without events; P=NS).

As shown in Fig 1 (left), there were 4 events in the normotensive group (0.47 per 100 patient-years), 3 events in the white coat hypertension group (0.49 per 100 patient-years), 37 events in dippers with ambulatory hypertension (1.79 per 100 patient-years), and 45 events in nondippers with ambulatory hypertension (4.99 per 100 patient-years). Comparison between survival curves (Fig 1, right) was highly significant (P<.0001). In the Cox analysis (Table 3), the risk of cardiovascular morbid events did not differ between the normotensive and white coat hypertension groups (P=.83). Compared with the white coat hypertension group, cardiovascular morbidity increased in ambulatory hypertension in dippers (RR, 3.70; 95% CI, 1.13 to 12.5), with a further increase of morbidity in nondippers (RR, 6.26; 95% CI, 1.92 to 20.32). These differences held after adjustment for the other significant covariates in the model including age, diabetes mellitus, previous cardiovascular events, and clinic pulse pressure. In contrast, clinic diastolic BP, smoking, serum cholesterol, body mass index, and echocardiographic LV hypertrophy did not yield statistical significance.

In the subset with available echocardiographic tracings, the risk associated with echocardiographic LV hypertrophy bordered on statistical significance (RR, 1.73; 95% CI, 0.98 to 3.04; P=.057). Prevalence of LV hypertrophy at echocardiography among subjects with essential hypertension was 25.7%. The highest cardiovascular morbidity among subjects with echocardiographic LV hypertrophy occurred in nondippers with ambulatory hypertension; conversely, the lowest rate of events among subjects with normal LV mass occurred in the subjects with white coat hypertension (Fig 2). Therefore, cardiovascular risk stratification based on these three categories of ambulatory BP provided a stronger predictivity than stratification based on the two categories of presence and absence of echocardiographic LV hypertrophy. However, when the multivariate analysis was restricted to the subset with ambulatory hyperten-
TABLE 1. Baseline Characteristics of Essential Hypertensive and Normotensive Control Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Essential Hypertensive Subjects</th>
<th>Normotensive Subjects</th>
<th>White Coat Hypertension</th>
<th>Ambulatory Hypertension</th>
<th>Ambulatory Hypertension</th>
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<td>n</td>
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<tr>
<td>Mean age, y</td>
<td>796 Hypertension Vol 24, No 6 December 1994</td>
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<tr>
<td>Male sex, %</td>
<td></td>
<td>50 (12)†‡</td>
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<tr>
<td>Diabetes mellitus, %</td>
<td></td>
<td>47</td>
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<tr>
<td>Current smokers, %</td>
<td></td>
<td>22</td>
<td></td>
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<tr>
<td>Previous cardiovascular events, %</td>
<td></td>
<td>27</td>
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<tr>
<td>Body mass index, kg • m~2</td>
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<td>26 (4)</td>
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<tr>
<td>Clinic BP, mm Hg</td>
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<td>26 (4)</td>
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<tr>
<td>Systolic</td>
<td>126 (9)†‡</td>
<td>124 (6)†</td>
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<tr>
<td>Diastolic</td>
<td>79 (7)**</td>
<td>79 (5)†</td>
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<tr>
<td>Mean 24-hour ambulatory BP, mm Hg</td>
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<tr>
<td>Systolic</td>
<td>119 (9)†</td>
<td>110 (10)†</td>
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<tr>
<td>Diastolic</td>
<td>75 (7)†</td>
<td>67 (7)†</td>
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<tr>
<td>Mean daytime ambulatory BP, mm Hg</td>
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<tr>
<td>Systolic</td>
<td>123 (9)†</td>
<td>110 (10)†</td>
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<tr>
<td>Diastolic</td>
<td>79 (8)†</td>
<td>79 (5)†</td>
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<tr>
<td>Mean nighttime ambulatory BP, mm Hg</td>
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<tr>
<td>Systolic</td>
<td>110 (11)†</td>
<td>110 (10)†</td>
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<tr>
<td>Diastolic</td>
<td>67 (8)†</td>
<td>67 (7)†</td>
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<tr>
<td>Serum cholesterol, mmol/L</td>
<td>5.22 (1.06)</td>
<td>5.39 (1.18)</td>
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<tr>
<td>Serum triglycerides, mmol/L</td>
<td>1.67 (0.94)</td>
<td>1.67 (1.11)</td>
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<tr>
<td>Serum glucose, mmol/L</td>
<td>5.89 (1.91)</td>
<td>5.56 (1.20)†</td>
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<tr>
<td>Serum uric acid, mmol/L</td>
<td>268 (84)†</td>
<td>278 (78)†</td>
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<tr>
<td>Subset with adequate echocardiographic tracings</td>
<td>256 (84)†</td>
<td>278 (78)†</td>
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</table>

BP indicates blood pressure; LV, left ventricular. Values are mean (SD).

*P<.01 vs white coat hypertension.
†P<.01 vs ambulatory hypertension, nondippers.
‡P<.01 vs normotensive controls.

sion (Table 4), cardiovascular risk was higher in nondippers than in dippers in women (RR, 6.79; 95% CI, 2.45 to 18.82; P=.0002) but not in men (P=.91) (Fig 3), and these differences held after adjustment for the other independent covariates in the model including age, sex, and echocardiographic LV hypertrophy (RR versus absence of hypertrophy, 1.82; 95% CI, 1.02 to 3.22; P=.039). All the other risk markers for cardiovascular disease, including average 24-hour systolic and diastolic BP values, were not statistically significant.

Cardiovascular Mortality

Fig 4 shows survival curves for fatal cardiovascular events. There was only 1 event in the normotensive group, no events in the white coat hypertension group, and 9 and 11 events, respectively, in dippers and nondippers with ambulatory hypertension. Comparison between survival curves (Fig 4) was highly significant (P<.002). Cardiovascular mortality could not be tested in the Cox multivariate analysis because the limited number of fatal events (n=21) precluded the inclusion in the model of more than two independent variables.34

Discussion

Ambulatory BP was an independent predictor of cardiovascular risk. Cardiovascular morbidity was lower in white coat than in ambulatory hypertension and not dissimilar between the white coat hypertension group and the normotensive group. Furthermore, it was higher
in nondippers than in dippers among women with ambulatory hypertension.

White coat hypertension, defined by persistent clinic hypertension despite normal BP during usual daily life,\textsuperscript{35,36} may be the result of an alerting reaction associated with the clinic measurement of BP,\textsuperscript{37} possibly leading to misclassification of hypertension in some actually normotensive individuals.\textsuperscript{36,37} Ambulatory BP\textsuperscript{38} and self-measured BP\textsuperscript{39} have been used to investigate the prevalence and clinical characteristics of white coat hypertension. In the absence of prospective studies, the normal ranges of variability of ambulatory and self-measured BP used to define white coat hypertension are currently derived from cross-sectional analyses of reference populations.\textsuperscript{38-40} Echocardiographic LV mass, an independent prognostic predictor in this study and in other studies,\textsuperscript{40-43} and similar in this and other studies,\textsuperscript{27,41,42} but not in all,\textsuperscript{43} to that of healthy individuals with normal clinic BP. Our findings provide prospective evidence that white coat hypertension, defined by an average daytime ambulatory BP less than 131/86 mm Hg in women or 136/87 mm Hg in men, is an independent predictor of low cardiovascular risk, even after adjustment for traditional risk markers for cardiovascular disease including, for example, clinic BP (which was lower in the white coat group than in the ambulatory hypertension group), age, diabetes, previous cardiovascular events, clinic pulse pressure, serum cholesterol, and echocardiographic LV hypertrophy. These results are consistent with preliminary data by Pickering\textsuperscript{36} who reported a lower incidence of cardiovascular morbid events in clinically hypertensive subjects with white coat hypertension than in those with higher levels of ambulatory BP. The independent prognostic significance of clinic pulse pressure is consistent with the results of a recent prospective study.\textsuperscript{44}

\begin{table}
\centering
\begin{tabular}{lcccc}
\hline
Characteristic & \multicolumn{2}{c}{Men} & \multicolumn{2}{c}{Women} \\
 & Dippers & Nondippers & Dippers & Nondippers \\
\hline
\textbf{n} & 342 & 137 & 351 & 129 \\
\textbf{Mean age, y} & 50 (12) & 56 (11)* & 52 (12) & 60 (14)* \\
\textbf{Diabetes mellitus, %} & 7 & 12 & 7 & 22* \\
\textbf{Current smokers, %} & 31 & 36 & 16 & 10 \\
\textbf{Previous cardiovascular events, %} & 2.6 & 5.8 & 1.5 & 6.2* \\
\textbf{Body mass index, kg \cdot m\textsuperscript{-2}} & 27.5 (3) & 27.4 (4) & 26.0 (4) & 27.1 (5) \\
\textbf{Clinic BP, mm Hg} & & & & \\
\textbf{Systolic} & 156 (18) & 163 (19)* & 161 (18) & 169 (19)* \\
\textbf{Diastolic} & 98 (9) & 98 (11) & 98 (10) & 97 (11) \\
\textbf{Mean 24-hour ambulatory BP, mm Hg} & & & & \\
\textbf{Systolic} & 141 (13) & 150 (14)* & 139 (12) & 149 (17)* \\
\textbf{Diastolic} & 90 (8) & 93 (9)* & 87 (8) & 89 (10) \\
\textbf{Mean daytime ambulatory BP, mm Hg} & & & & \\
\textbf{Systolic} & 146 (13) & 151 (14)* & 144 (13) & 149 (16)* \\
\textbf{Diastolic} & 95 (8) & 95 (10) & 100 (8) & 91 (10) \\
\textbf{Mean nighttime ambulatory BP, mm Hg} & & & & \\
\textbf{Systolic} & 128 (13) & 146 (15)* & 125 (15) & 146 (18)* \\
\textbf{Diastolic} & 79 (9) & 90 (9)* & 75 (9) & 86 (10)* \\
\textbf{Serum cholesterol, mmol/L} & 5.69 (1.12) & 5.60 (1.07) & 5.46 (0.98) & 5.50 (1.30) \\
\textbf{Serum triglycerides, mmol/L} & 1.56 (1.28) & 1.64 (0.83) & 1.84 (1.05) & 1.86 (1.14)* \\
\textbf{Serum glucose, mmol/L} & 5.54 (1.31) & 6.15 (2.04) & 5.63 (1.02) & 5.85 (1.22)* \\
\textbf{Serum uric acid, mmol/L} & 242 (76) & 271 (89) & 316 (74) & 335 (88)* \\
\textbf{Subset with adequate echocardiographic tracings} & & & & \\
\textbf{n} & 283 & 105 & 289 & 81 \\
\textbf{Interventricular septum thickness, cm} & 1.23 (0.3) & 1.24 (0.3) & 1.04 (0.2) & 1.20 (0.3)* \\
\textbf{LV internal diameter, cm} & 5.1 (0.5) & 5.3 (0.7) & 4.8 (0.5) & 4.9 (0.5) \\
\textbf{Posterior wall thickness, cm} & 1.1 (0.2) & 1.1 (0.2) & 0.9 (0.2) & 1.0 (0.2)* \\
\textbf{LV mass, g \cdot m\textsuperscript{-2}} & 118 (35) & 124 (32) & 99 (26) & 120 (33)* \\
\hline
\end{tabular}
\caption{Baseline Characteristics of Subjects with Ambulatory Hypertension Subdivided Into Dippers and Nondippers in Either Gender}
\end{table}
There was a significant independent association between blunted nocturnal reduction of BP and cardiovascular morbidity in women, but not in men, with ambulatory hypertension. These results extend those of a smaller case-control analysis from the PIUMA registry. The mechanisms by which a persistent pressure overload, expressed by a blunted nocturnal reduction in BP, may increase cardiovascular risk are incompletely understood. There is evidence of increased LV mass, more advanced silent cerebrovascular damage, and more frequent history of stroke in hypertensive nondippers compared with dippers. Thus, for any given level of daytime BP, a persistent pressure overload might increase the progression of hypertensive organ damage and thereby predict a higher incidence of cardiovascular events. The greater cardiovascular risk in nondippers compared with dippers remained statistically significant after adjustment for the average 24-hour systolic and diastolic BP values. This removes the potential objection that the worse outcome in nondippers may be more closely associated with a higher average BP over the 24 hours than with an altered diurnal BP rhythm by itself. In a previous reproducibility study, 73% of hypertensive patients remained in the same dipper/nondipper category over two ambulatory sessions carried out 3 to 5 days apart, whereas the other 27% moved from one group to another.

### Table 3. Relative Risks for Cardiovascular Morbid Events in the Overall Population

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Relative Risk (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population (n=1392)</td>
<td></td>
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</tr>
<tr>
<td>Ambulatory BP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White coat hypertension vs clinical normotension</td>
<td>1.17 (0.25-5.33)</td>
<td>.83</td>
</tr>
<tr>
<td>Ambulatory hypertension, dippers vs white coat hypertension</td>
<td>3.70 (1.13-12.5)</td>
<td>.03</td>
</tr>
<tr>
<td>Ambulatory hypertension, nondippers vs white coat hypertension</td>
<td>6.26 (1.92-20.32)</td>
<td>.002</td>
</tr>
<tr>
<td>Age &gt;60 vs &lt;40 y</td>
<td>7.11 (1.65-30.60)</td>
<td>.008</td>
</tr>
<tr>
<td>40-60 vs &lt;40 y</td>
<td>3.22 (0.76-13.56)</td>
<td>.11</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present vs absent</td>
<td>2.02 (1.26-3.23)</td>
<td>.003</td>
</tr>
<tr>
<td>Previous cardiovascular events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present vs absent</td>
<td>3.11 (1.71-5.57)</td>
<td>.0002</td>
</tr>
<tr>
<td>Clinic pulse pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous variable exp(0.013x clinic pulse pressure)</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>LV hypertrophy at echocardiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present vs absent</td>
<td>1.73 (0.98-3.04)</td>
<td>.057</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; BP, blood pressure; and LV, left ventricular.
Our study does not permit the elucidation of mechanisms by which the women with increased ambulatory BP, basically at lower cardiovascular risk than men, were most sensitive to the detrimental effect of a persistent compared with an intermittent pressure overload. Echocardiographic LV mass has been shown to be greater in hypertensive nondippers than in dippers only in women, as evidenced also in the present study, but the possible confounding effect of LV hypertrophy and other independent risk markers, particularly diabetes, old age, and previous cardiovascular events (all of which were more frequent in female nondippers), on the different cardiovascular risk in dippers and nondippers between the genders was accounted for in the Cox multivariate analysis.

This study has two main limitations. First, only 30% of subjects had periodic visits during follow-up, so we could not assess the degree of BP control in a sufficiently large number of subjects. A multicenter prospective study designed to address this issue is currently ongoing in Italy. Second, although the size of the study allowed a separate analysis for total and fatal cardiovascular events, it did not allow a further differentiation between cardiac, cerebrovascular, and peripheral vascular events.

In general, because of the relatively low number of cardiovascular events (89 events), further assessment of the prognostic significance of ambulatory BP will need larger trials.

The present study differs with regard to some methodological points from that by Perloff and coworkers, the only large study published so far on the prognostic value of ambulatory BP. Compared with the present study, that by Perloff and coworkers did not include a control normotensive group. Moreover, the availability of automated ambulatory BP recorders allowed us to estimate the entire 24-hour BP profile, whereas BP monitoring could not be performed during the night in the study of Perloff et al because of the use of manually activated recorders. Furthermore, serum cholesterol, cigarette smoking, and echocardiographic LV hypertrophy were tested as covariates only in the present study. Importantly, Perloff and coworkers did not attempt to define subjects with “normal” ambulatory BP (ie, white coat hypertension) but only hypertensive subsets at different cardiovascular risk. Overall, our findings and those by Perloff and coworkers indicate that ambulatory BP stratifies cardiovascular risk more accurately than...
found that evaluation of white coat hypertension covers approximately 22% of current clinical indications for ambulatory BP monitoring by community- or hospital-based physicians. The second is the differentiation between dippers and nondippers among women with ambulatory hypertension.

A fundamental point of this study, inherent in any observational survey, is the lack of intervention on potentially important confounders, in our case the current medical approach to hypertension. Since the management of hypertensive subjects was based on their clinic BP, the possibility remains that the better prognosis in the white coat group may reflect a superior effect of treatment in these subjects owing, for example, to their lower clinic BP compared with the ambulatory hypertension group. On the other hand, the higher incidence of cardiovascular events in female nondippers could reflect an incomplete control of nighttime BP in these subjects.

Nonetheless, these observational data generate two main hypotheses for interventional studies. First, antihypertensive drug treatment might be withheld in subjects with white coat hypertension, particularly when organ lesions or other risk factors are absent. The good prognosis in our subjects with white coat hypertension supports this possibility, but a more detailed background will come from surveys of the natural history of this condition in the very long term. These studies should also compare the response to drug treatment with that to lifestyle measures in these subjects. A cost-effectiveness analysis comparing a single session of ambulatory BP monitoring with repeated standardized BP measurements in the physician's office is also warranted because the accuracy of the latter procedure may be comparable with that of ambulatory BP monitoring. Second, an additional new goal of antihypertensive treatment might become the reduction of increased nighttime BP. The high incidence of cardiovascular morbid events in female nondippers with ambulatory hypertension suggests the potential utility of a more aggressive therapeutic approach for these subjects whose status of nondippers carries an independent risk for future cardiovascular events. In this setting, ambulatory BP monitoring seems to be the only practical way to detect nighttime BP.

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