

ORIGINAL ARTICLE

# Prognostic Value of Ambulatory Blood-Pressure Recordings in Patients with Treated Hypertension

Denis L. Clement, M.D., Ph.D., Marc L. De Buyzere, B.Sc., Dirk A. De Bacquer, Ph.D., Peter W. de Leeuw, M.D., Ph.D., Daniel A. Duprez, M.D., Ph.D., Robert H. Fagard, M.D., Ph.D., Peter J. Gheeraert, M.D., Luc H. Missault, M.D., Jacob J. Braun, M.D., Roland O. Six, M.D., Patricia Van Der Niepen, M.D., and Eoin O'Brien, M.D., Ph.D., for the Office versus Ambulatory Pressure Study Investigators\*

## ABSTRACT

### BACKGROUND

It is uncertain whether ambulatory blood-pressure measurements recorded for 24 hours in patients with treated hypertension predict cardiovascular events independently of blood-pressure measurements obtained in the physician's office and other cardiovascular risk factors.

### METHODS

We assessed the association between base-line ambulatory blood pressures in treated patients and subsequent cardiovascular events among 1963 patients with a median follow-up of 5 years (range, 1 to 66 months).

### RESULTS

We documented new cardiovascular events in 157 patients. In a Cox proportional-hazards model with adjustment for age, sex, smoking status, presence or absence of diabetes mellitus, serum cholesterol concentration, body-mass index, use or nonuse of lipid-lowering drugs, and presence or absence of a history of cardiovascular events, as well as blood pressure measured at the physician's office, higher mean values for 24-hour ambulatory systolic and diastolic blood pressure were independent risk factors for new cardiovascular events. The adjusted relative risk of cardiovascular events associated with a 1-SD increment in blood pressure was 1.34 (95 percent confidence interval, 1.11 to 1.62) for 24-hour ambulatory systolic blood pressure, 1.30 (95 percent confidence interval, 1.08 to 1.58) for ambulatory systolic blood pressure during the daytime, and 1.27 (95 percent confidence interval, 1.07 to 1.57) for ambulatory systolic blood pressure during the nighttime. For ambulatory diastolic blood pressure, the corresponding relative risks of cardiovascular events associated with a 1-SD increment were 1.21 (95 percent confidence interval, 1.01 to 1.46), 1.24 (95 percent confidence interval, 1.03 to 1.49), and 1.18 (95 percent confidence interval, 0.98 to 1.40).

### CONCLUSIONS

In patients with treated hypertension, a higher ambulatory systolic or diastolic blood pressure predicts cardiovascular events even after adjustment for classic risk factors including office measurements of blood pressure.

From the Departments of Cardiovascular Diseases (D.L.C., M.L.D.B., D.A.D., P.J.G.) and Public Health (D.A.D.B.), Ghent University, Ghent, Belgium; the Department of Medicine, University Hospital Maastricht, Maastricht, the Netherlands (P.W.L.); the Cardiovascular Division, University of Minnesota, Minneapolis (D.A.D.); the Hypertension and Cardiovascular Rehabilitation Unit, University of Leuven, Leuven, Belgium (R.H.F.); the Department of Cardiology, Algemeen Ziekenhuis St. Jan, Bruges, Belgium (L.H.M.); the Department of Internal Medicine, Vlietland Hospital, Schiedam, the Netherlands (J.J.B.); the Department of Internal Medicine and Hypertension, Vrije Universiteit Brussel, Brussels, Belgium (R.O.S., P.V.D.N.); and the Blood Pressure Unit and Arterial Disease, Assessment, Prevention, and Treatment Centre, Beaumont Hospital, Dublin, Ireland (E.O.). Address reprint requests to Dr. Clement at the Department of Cardiology and Angiology, University Hospital, De Pintelaan 185, B-9000 Ghent, Belgium, or at denis.clement@skynet.be.

\*The Office versus Ambulatory Blood Pressure (OvA) Study Investigators are listed in the Appendix.

N Engl J Med 2003;348:2407-15.

Copyright © 2003 Massachusetts Medical Society.

SEVERAL PROSPECTIVE CLINICAL STUDIES, as well as population-based studies, have indicated that the incidence of cardiovascular events is predicted by blood pressure as measured conventionally or with ambulatory methods, even after adjustment for a number of established risk factors.<sup>1-11</sup> In some of these studies, ambulatory measurements of blood pressure predicted cardiovascular events even after adjustment for conventional blood-pressure measurements.<sup>1,3,5,7,9,12</sup> However, in most of these studies, the majority of data on ambulatory blood pressure, which were used to predict end points, were recorded in initially untreated subjects or during a placebo run-in phase; in most cases, treatment was initiated afterward. There is a lack of data on the prognostic value of ambulatory blood-pressure monitoring in patients with treated hypertension in whom both ambulatory measurements of blood pressure and office-based measurements of blood pressure are recorded when patients are receiving active treatment — a scenario that more closely reflects daily clinical practice for many patients. An indication that ambulatory blood-pressure measurements during treatment are superior to office blood-pressure measurements in predicting cardiovascular risk came from a recent post hoc subanalysis involving 790 patients with treated hypertension.<sup>13</sup>

We conducted the prospective, multicenter Office versus Ambulatory Blood Pressure (OvA) study to address whether ambulatory blood pressure monitored in patients with treated hypertension could predict cardiovascular events and death even after adjustment for conventional office blood-pressure measurements. To this end, 1963 patients were prospectively enrolled and followed for approximately five years.

---

## METHODS

---

### STUDY DESIGN

The study protocol was approved by the institutional review boards of the Ghent University Hospital (Ghent, Belgium) and other participating centers. All patients gave written informed consent. All decisions concerning the study design, the collection, analysis, and interpretation of the data, and the intellectual content of the manuscript were made independently by the study committees, without the involvement of the pharmaceutical-industry sponsors.

The prerequisite for inclusion was documented

hypertension at two separate visits within a two-year period before enrollment (visits 1 and 2). Hypertension was diagnosed if the mean of three sphygmomanometric readings of diastolic blood pressure (assessed as the fifth Korotkoff sound and obtained in the office, when the patient was sitting, after five minutes of rest) exceeded 90 mm Hg in a patient who was currently taking antihypertensive medication or 95 mm Hg in a patient who was not taking such medication. In order to be eligible, patients had to have been treated with antihypertensive drugs for at least three months by the time of the inclusion visit (visit 3). Patients of either sex who were 18 years of age or older were eligible. Criteria for exclusion included suspicion of secondary hypertension, insulin-treated diabetes mellitus, recent stroke (occurring within the previous three months), recent acute myocardial infarction, recent hospitalization for chronic heart failure, recent revascularization or planned cardiovascular intervention during the succeeding three months, a serum creatinine concentration of more than 2.5 mg per deciliter (220  $\mu$ mol per liter), chronic obstructive pulmonary disease, any coexisting diseases that might seriously reduce life expectancy, heart transplantation, use of experimental drugs, pregnancy, and refusal to undergo repeated follow-up visits and ambulatory blood-pressure monitoring. The choice of antihypertensive drugs was at the discretion of the physician, and physicians were repeatedly advised to follow current guidelines and to target a blood pressure of 140/90 mm Hg, as measured in the office while the patient was sitting.

### DATA COLLECTION

At visit 3, demographic data were recorded, as well as information about traditional cardiovascular risk factors, history of cardiovascular events, and current medications (antiplatelet, antidiabetic, lipid-lowering, and other cardiovascular drugs). Anthropometric data were collected, and a routine 12-lead electrocardiogram was obtained. At that time, a sample of venous blood was drawn to assess base-line factors. Immediately after visit 3, ambulatory blood pressure was recorded over a 24-hour period during the patient's normal daily activities, with the use of properly validated and calibrated monitors programmed to obtain readings at intervals of not more than 30 minutes between 8 a.m. and 8 p.m. and at intervals of not more than 60 minutes between 8 p.m. and 8 a.m. Raw data were sent to the coordinating center and were visually inspected by a technician

before being entered into the central data base. No specific editing criteria were applied to the blood-pressure readings. We planned to follow patients for up to 5.5 years.

**END POINTS**

The end-point committee identified all major end points by reviewing the patients' files and source documents or by requesting more detailed written information from the investigators; the committee was blinded with respect to all blood-pressure data. Cardiovascular events were validated according to the principles used in the Systolic Hypertension in Europe trial.<sup>14</sup> Stroke was defined as a neurologic deficit with symptoms continuing for more than 24 hours or leading to death with no apparent cause other than a vascular cause. Acute myocardial infarction was defined by the presence of two of the following: typical chest pain, electrocardiographic changes, and increased cardiac-enzyme concentrations. The definition of myocardial infarction did not include silent myocardial infarction. The definition of congestive heart failure required the presence of symptoms, clinical signs, and a need for treatment. Sudden death was defined as any death of unknown cause occurring immediately or within 24 hours after the onset of acute symptoms or any unwitnessed death for which no likely cause could be established on the basis of the medical history. Angina pectoris was diagnosed if there was chest pain and documented electrocardiographic signs of coronary ischemia or if there was a need for coronary revascularization in the absence of acute myocardial infarction. Patients recorded as having peripheral (noncoronary) vascular disease included those who underwent surgical or angioplastic procedures on the aorta or the arteries of the legs. Transient ischemic attacks were excluded from the statistical analysis.

**STATISTICAL ANALYSIS**

Statistical analyses were planned for the primary end point of fatal or nonfatal cardiovascular events and the secondary end points of fatal or nonfatal acute myocardial infarction or stroke, death from any cause, and death from cardiovascular causes. The study variables compared were the office blood pressure (the mean of the sphygmomanometric blood pressure readings at visit 3, obtained as described above) and the means of the 24-hour, daytime, and nighttime ambulatory measurements of systolic and diastolic blood pressure (also recorded

**Table 1. Characteristics of the Patients According to Category of Ambulatory Blood Pressure.\***

Characteristic	24-Hr Ambulatory Systolic Blood Pressure		P Value
	<135 mm Hg (N=1153)	≥135 mm Hg (N=810)	
<b>Risk factors</b>			
Age (yr)	56±13	57±13	0.002
Female sex (%)	51.9	44.0	<0.001
Body-mass index	28.0±4.7	27.8±4.6	0.27
Current smoking (%)	14.7	20.8	<0.001
Previous cardiovascular disease (%)	5.3	6.8	0.17
Diabetes mellitus (%)	8.6	14.4	<0.001
Total serum cholesterol concentration (mg/dl)	235±46	233±47	0.37
Use of lipid-lowering drugs (%)	11.4	12.0	0.72
<b>Office blood pressure (mm Hg)</b>			
Systolic	148±18	165±21	<0.001
Diastolic	91±10	96±12	<0.001
<b>Ambulatory blood pressure (mm Hg)</b>			
24-Hr systolic	123.5±7.7	148.8±11.8	<0.001
24-Hr diastolic	78.8±8.2	90.2±11.2	<0.001
Daytime systolic	128.8±9.2	153.7±12.9	<0.001
Daytime diastolic	83.8±9.1	94.8±11.9	<0.001
Nighttime systolic	113.2±10.4	138.0±15.6	<0.001
Nighttime diastolic	69.8±9.6	81.4±12.6	<0.001
Ratio of nighttime systolic to daytime systolic	0.88±0.09	0.90±0.09	<0.001
Ratio of nighttime diastolic to daytime diastolic	0.84±0.10	0.86±0.11	<0.001
<b>No. of events</b>			
Fatal or nonfatal cardiovascular event	56	101	<0.001
Fatal or nonfatal myocardial infarction or stroke	22	55	<0.001
Death from any cause	35	43	0.01

\* Plus-minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters. Previous cardiovascular disease includes stroke, transient ischemic attack, acute myocardial infarction, stable or unstable angina pectoris, peripheral vascular disease, and congestive heart failure. For 24-hour monitoring, nighttime is defined as midnight to 6 a.m., and daytime as 8 a.m. to 8 p.m. To convert values for cholesterol to millimoles per liter, multiply by 0.02586.

**Table 2. Relative Risks Associated with Office and Ambulatory Measurements of Systolic and Diastolic Blood Pressure at Entry.\***

Blood-Pressure Measurement	Fatal or Nonfatal Cardiovascular Event (N=157)	Fatal or Nonfatal Myocardial Infarction or Stroke (N=77)	Death from Any Cause (N=78)
	<i>relative risk (95% confidence interval)</i>		
<b>Systolic</b>			
Office	1.48 (1.25–1.75)	1.22 (0.95–1.59)	1.40 (1.10–1.78)
24-Hr	1.50 (1.27–1.78)	1.51 (1.19–1.92)	1.18 (0.94–1.48)
Daytime	1.47 (1.24–1.74)	1.54 (1.21–1.96)	1.18 (0.94–1.50)
Nighttime	1.40 (1.20–1.65)	1.30 (1.03–1.65)	1.18 (0.94–1.49)
<b>Diastolic</b>			
Office	1.40 (1.16–1.68)	1.14 (0.86–1.52)	1.27 (0.98–1.64)
24-Hr	1.32 (1.11–1.57)	1.41 (1.10–1.80)	1.22 (0.96–1.55)
Daytime	1.35 (1.13–1.61)	1.45 (1.13–1.86)	1.22 (0.95–1.56)
Nighttime	1.26 (1.06–1.50)	1.28 (0.99–1.65)	1.22 (0.96–1.56)

\* Relative risks are for each 1-SD increment in blood pressure and were adjusted for sex, age, body-mass index, smoking status, presence or absence of diabetes mellitus, serum cholesterol concentration, use or nonuse of lipid-lowering drugs, and presence or absence of cardiovascular complications at entry. Cardiovascular events include myocardial infarction or sudden death, stroke, new episodes of angina pectoris, congestive heart failure, and peripheral vascular disease (affecting the aorta or peripheral arteries). For 24-hour monitoring, nighttime was defined as midnight to 6 a.m., and daytime as 8 a.m. to 8 p.m.

at visit 3). Daytime ambulatory blood pressure was defined as that between 8 a.m. and 8 p.m., and nighttime ambulatory blood pressure as that between midnight and 6 a.m.<sup>15–18</sup> We initially screened 2232 patients, but because of protocol violations (in 10 patients), technical failure (in 41 patients with poor-quality ambulatory blood-pressure recordings and 6 patients with an insufficient number of readings to allow statistical analysis), or inadequate clinical follow-up (in 212 patients), a total of 269 patients had to be excluded from final analyses, yielding 1963 eligible patients (88 percent). In all 1963 patients, office measurements of blood pressure, ambulatory measurements of blood pressure, and adequate follow-up documentation were available.

The distributions of base-line characteristics in the group of patients with cardiovascular events and the group without cardiovascular events were compared with the use of Fisher's exact test for proportions and the t-test or the Mann-Whitney U test for continuous variables. Cox proportional-hazards

models were used to estimate relative risks (with 95 percent confidence intervals) for events associated with a 1-SD increment in blood pressure, with adjustment for sex, age, body-mass index (the weight in kilograms divided by the square of the height in meters), smoking status, presence or absence of diabetes mellitus, serum cholesterol concentration, use or nonuse of lipid-lowering drugs, and history of cardiovascular events. All statistical analyses were performed with the use of SAS software, version 6.12 (SAS Institute).

## RESULTS

### CHARACTERISTICS OF THE PATIENTS

The median duration of follow-up was 5 years (range, 1 to 66 months). The event committee validated first cardiovascular events during follow-up in 157 patients (combined incidence of fatal and nonfatal cardiovascular events, 12.8 per 1000 person-years). Fatal events occurred in 78 patients (incidence, 6.1 deaths per 1000 person-years), and 38 of these events were cardiovascular events. Patients who had cardiovascular events were older than those who did not have such events ( $P<0.001$ ), were more likely to be male ( $P<0.001$ ), and had a higher prevalence of diabetes mellitus ( $P<0.001$ ) and previous cardiovascular disease ( $P<0.001$ ). In addition, they had higher cholesterol levels ( $P=0.001$ ) and a higher rate of use of lipid-lowering drugs ( $P<0.001$ ). Characteristics of the patients according to category of ambulatory systolic blood pressure ( $<135$  mm Hg or  $\geq 135$  mm Hg) are summarized in Table 1. The higher category of ambulatory blood pressure was associated with older age, male sex, current smoking, presence of diabetes mellitus, and higher office blood pressures. Fatal and nonfatal cardiovascular events and death from any cause were also more frequent among patients with an ambulatory systolic blood pressure of 135 mm Hg or higher.

### OFFICE AND AMBULATORY BLOOD PRESSURES AS PREDICTORS OF RISK

Cox proportional-hazards analysis for each outcome variable was performed with the use of fixed clock-time definitions of both daytime and nighttime ambulatory blood pressure. Table 2 shows the relative risks (and 95 percent confidence intervals) associated with a 1-SD increment in blood pressure after adjustment for sex, age, body-mass index, smoking status, presence or absence of diabetes mellitus, serum cholesterol concentration, use or

nonuse of lipid-lowering drugs, and presence or absence of a history of cardiovascular events. Both of office and ambulatory measurements of systolic and diastolic blood pressure significantly predicted the primary end point of fatal or nonfatal cardiovascular events. Table 3 summarizes the relative risks associated with each 1-SD increment in ambulatory measurements of systolic and diastolic blood pressure after additional adjustment for office blood pressure. For the primary end point, 24-hour and daytime ambulatory systolic and diastolic blood pressure predicted outcome even after adjustment for office blood pressure. The mean 24-hour blood-pressure measurements at base line for patients who had a cardiovascular event and those who did not are shown in Figure 1. Results were similar for the end point of fatal or nonfatal myocardial infarction or stroke (Table 3).

We also examined separately the cerebrovascular and coronary outcomes (although this was not a prespecified aim, and the numbers were small). Systolic blood pressure as measured in the office independently predicted the risk of cerebrovascular events (36 patients had such an event; relative risk associated with a 1-SD increment in office systolic blood pressure, 1.50 [95 percent confidence interval, 1.08 to 2.08]), and ambulatory blood pressure was not predictive of the risk of cerebrovascular events after adjustment for office blood pressure. However, 24-hour and daytime ambulatory systolic blood pressure predicted the risk of coronary events (which occurred in 42 patients) even after adjustment for office blood pressure (relative risk associated with a 1-SD increment in ambulatory systolic blood pressure, 1.63 [95 percent confidence interval, 1.10 to 2.42] and 1.68 [95 percent confidence interval, 1.14 to 2.48], respectively). None of the ambulatory blood-pressure variables predicted the risk of death from any cause (Tables 2 and 3) or death from cardiovascular causes (which occurred in 38 patients; data not shown).

As compared with patients with a mean 24-hour systolic blood pressure of less than 135 mm Hg, patients with a 24-hour ambulatory systolic blood pressure of 135 mm Hg or higher had a relative risk of cardiovascular events, with adjustment for office blood pressure and other potential confounders, of 1.74 (95 percent confidence interval, 1.15 to 2.63). Figure 2 further illustrates the higher incidence of cardiovascular events with higher ambulatory blood-pressure measurements among patients in each of three categories of office systolic blood

**Table 3. Relative Risks Associated with Ambulatory Blood-Pressure Measurements after Additional Adjustment for Office Blood Pressure at Entry.\***

Blood-Pressure Measurement	Fatal or Nonfatal Cardiovascular Event (N=157)	Fatal or Nonfatal Myocardial Infarction or Stroke (N=77)	Death from Any Cause (N=78)
<i>relative risk (95% confidence interval)</i>			
<b>Systolic</b>			
24-Hr	1.34 (1.11–1.62)	1.52 (1.16–2.00)	1.03 (0.79–1.33)
Daytime	1.30 (1.08–1.58)	1.56 (1.19–2.05)	1.03 (0.79–1.34)
Nighttime	1.27 (1.07–1.51)	1.25 (0.97–1.62)	1.06 (0.82–1.36)
<b>Diastolic</b>			
24-Hr	1.21 (1.01–1.46)	1.41 (1.08–1.85)	1.16 (0.90–1.49)
Daytime	1.24 (1.03–1.49)	1.46 (1.11–1.92)	1.15 (0.89–1.49)
Nighttime	1.18 (0.98–1.40)	1.25 (0.96–1.64)	1.17 (0.91–1.50)

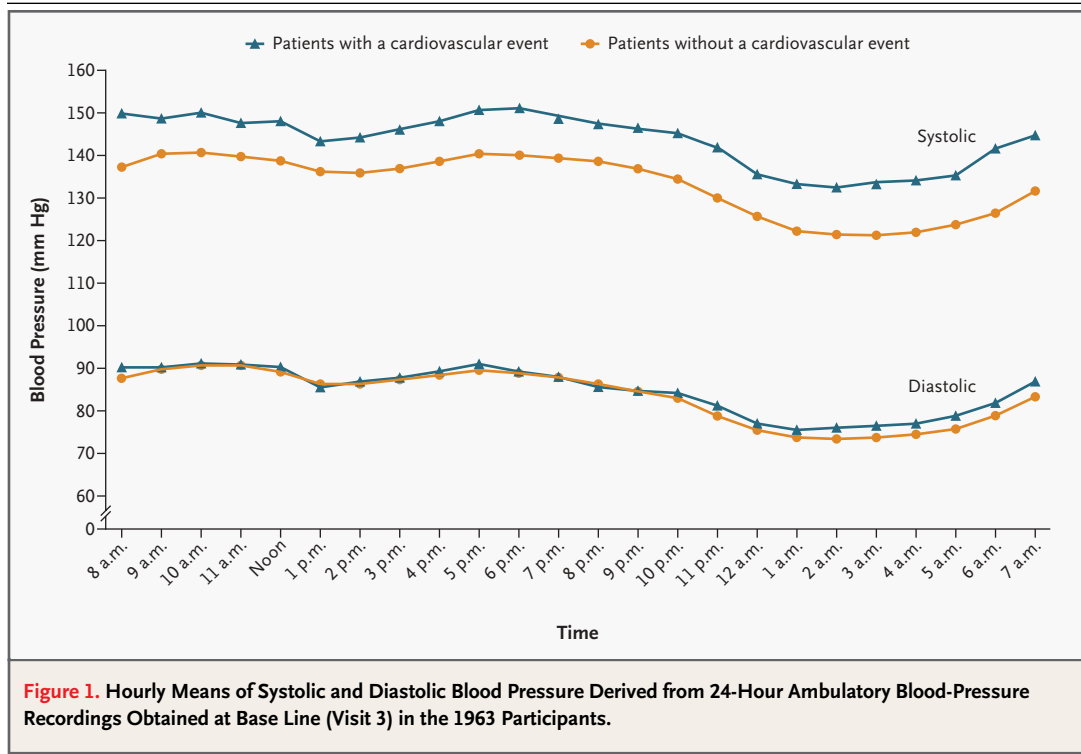
\* Relative risks are for each 1-SD increment in blood pressure and were adjusted for sex, age, body-mass index, smoking status, presence or absence of diabetes mellitus, serum cholesterol concentration, use or nonuse of lipid-lowering drugs, presence or absence of cardiovascular complications at entry, and office blood pressure at entry (ambulatory systolic blood pressure was adjusted for office systolic blood pressure, and ambulatory diastolic blood pressure was adjusted for office diastolic blood pressure). Cardiovascular events include myocardial infarction or sudden death, stroke, new episodes of angina pectoris, congestive heart failure, and peripheral vascular disease (affecting the aorta or peripheral arteries). For 24-hour monitoring, nighttime was defined as midnight to 6 a.m., and daytime as 8 a.m. to 8 p.m.

pressure (<140 mm Hg, 140 to 159 mm Hg, and ≥160 mm Hg).

A higher pulse pressure (calculated as the systolic pressure minus the diastolic pressure) was also predictive of cardiovascular events (data not shown). However, neither office nor ambulatory measurements of pulse pressure independently predicted the risk of cardiovascular events according to a model including the ambulatory systolic or diastolic blood pressure. Neither the ratio of nighttime systolic blood pressure to daytime systolic blood pressure nor the ratio of nighttime diastolic blood pressure to daytime diastolic blood pressure was an independent predictor of the risk of cardiovascular events (data not shown).

DISCUSSION

The results of our large-scale prospective study demonstrate that, after adjustment for classic risk factors including office blood pressure, the 24-hour ambulatory blood pressure provided additional



prognostic information concerning cardiovascular events, including a combined outcome of nonfatal or fatal myocardial infarction or stroke. However, this measure did not predict the risk of death from any cause.

The findings of our study, in which all ambulatory measurements of blood pressure were obtained in treated patients, are consistent with those of previously published outcome studies,<sup>1-11</sup> in which ambulatory blood-pressure measurements were obtained in untreated or placebo-treated subjects at the time of inclusion in the study.

In the substudy of the Systolic Hypertension in Europe trial addressing ambulatory blood pressure,<sup>9</sup> about 800 patients underwent ambulatory blood-pressure monitoring during the placebo run-in period before undergoing randomization to placebo or active treatment. In the placebo group, ambulatory systolic blood pressure predicted cardiovascular complications after cumulative adjustments for age, sex, smoking status, presence or absence of previous cardiovascular complications, residence or nonresidence in western Europe, and conventional blood-pressure measurements. The participants in that study were elderly patients with isolated systolic hypertension, and in contrast to our

study, that study showed that ambulatory blood pressure did not predict the outcome in the active-treatment group.

Earlier data based on semiautomatic ambulatory blood-pressure monitoring demonstrated the potential value of ambulatory blood pressure in discriminating between hypertensive patients at high cardiovascular risk and those at lower risk; these data showed that such discrimination was possible on the basis of the variance in the daytime ambulatory blood pressure, which was not explained by readings obtained in the clinic.<sup>1,12</sup> In that study, for technical reasons, no nighttime monitoring was performed, which resulted in incomplete documentation of the 24-hour profile.

Among referred patients with hypertension included in the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale prospective registry, the base-line ambulatory blood pressure measured before treatment began was an independent predictor of the risk of cardiovascular events.<sup>8,19,20</sup> In that study, the authors focused on the increased risk associated with a blunted nocturnal decrease in blood pressure but did not directly compare office blood pressure measured in treated patients with ambulatory blood pressure. A post hoc subgroup analysis

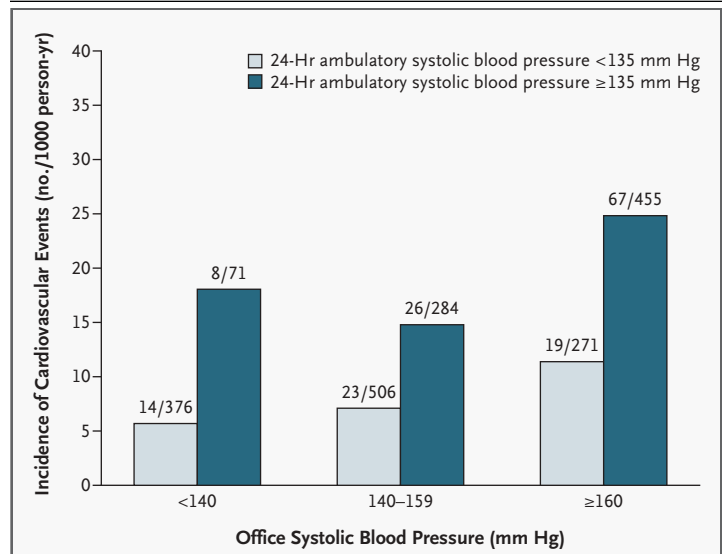
suggested an association between the ambulatory blood pressure in patients whose blood pressure was adequately controlled by treatment and a reduced risk of cardiovascular events that was independent of other traditional risk factors.<sup>13</sup> Office blood-pressure values in treated patients were not significantly related to cardiovascular risk. However, the design of that study differed substantially from our protocol. The authors recorded 24-hour blood pressure with ambulatory monitoring in treated patients an average of 3.7 years after their enrollment in the registry and did not study fatal events.

In a large sample of a Japanese community comprising both treated and untreated subjects, ambulatory blood pressure also predicted the risk of fatal cardiovascular events, even after adjustment for age, sex, risk factors, medication, cardiovascular history, and conventional blood pressure.<sup>3,21,22</sup> In a study of 688 patients with hypertension followed for more than nine years, the ambulatory intraarterial blood pressure recorded before treatment began was predictive of cardiovascular risk. In our study, a noninvasive approach to ambulatory monitoring of blood pressure was used.

The prognostic value of ambulatory blood pressure has also been assessed in a small study of patients with treatment-refractory hypertension.<sup>5</sup> Higher values for ambulatory blood pressure more accurately predicted future cardiovascular events than did clinic-based measurements of blood pressure. The mean blood pressure among patients in that study was considerably higher than the mean pressure in our study. In general, the patients we studied could not be considered to have true refractory hypertension, although it is possible that a small proportion of our patients presented with drug-resistant hypertension.

Some limitations of our study should be noted. We did not have the necessary information to adjust adequately for a family history of coronary artery disease, urinary albumin excretion, levels of low-density lipoprotein cholesterol or high-density lipoprotein cholesterol, levels of physical activity, or dietary measures. Thus, we could not account for the effect of these variables on cardiovascular outcomes.

The results of our study clearly demonstrate the limitations of office readings as they are routinely obtained. In our study, three blood-pressure readings from a single office visit were averaged for use as a measure of office blood pressure. By contrast, in the Systolic Hypertension in Europe study, conventional blood pressure was calculated on the ba-



**Figure 2. Incidence of Cardiovascular Events According to Category of Office Systolic Blood Pressure.**

All blood-pressure values were obtained at the inclusion visit. Among patients in all three categories of office systolic blood pressure, a 24-hour ambulatory systolic blood pressure of 135 mm Hg or higher predicted a higher incidence of cardiovascular events than a 24-hour ambulatory systolic blood pressure of less than 135 mm Hg. The unadjusted relative risk of a cardiovascular event associated with a 24-hour ambulatory systolic blood pressure of 135 mm Hg or higher as compared with a 24-hour ambulatory systolic blood pressure of less than 135 mm Hg was 3.19 (95 percent confidence interval, 1.34 to 7.59) among patients with an office systolic blood pressure of less than 140 mm Hg, 2.09 (95 percent confidence interval, 1.19 to 3.66) among patients with an office systolic blood pressure of 140 to 159 mm Hg, and 2.21 (95 percent confidence interval, 1.33 to 3.68) among patients with an office systolic blood pressure of 160 mm Hg or higher. After adjustment for sex, age, body-mass index, smoking status, presence or absence of diabetes mellitus, serum cholesterol concentration, use or nonuse of lipid-lowering drugs, and presence or absence of cardiovascular complications at entry, the corresponding relative risks were 2.80 (95 percent confidence interval, 0.80 to 9.85), 1.82 (95 percent confidence interval, 0.92 to 3.56), and 2.31 (95 percent confidence interval, 1.26 to 4.22). Numbers above the bars are the number of patients in the specific subgroup with a cardiovascular event over the total number of patients in that subgroup.

sis of six readings (two readings from each of three visits).<sup>9,14</sup> Fagard et al.<sup>23</sup> demonstrated that the correlations between left ventricular mass and clinic blood pressure and between left ventricular mass and ambulatory blood pressure became much closer when clinic readings were better standardized and when the readings were averaged over more than one visit. That study suggests that for direct comparisons between conventional and ambulatory measurements of blood pressure, it is best to use repeated, standardized conventional readings ob-

tained at prespecified intervals. The use of protocols that are not well standardized in the assessment of the office blood pressure may lead to a high degree of variance in this measure, particularly among treated patients such as those in our study.

Another weakness of routine blood-pressure measurement that may have influenced our results is that the effects of drugs (e.g., peak and trough effects) may have had a greater influence on the variance in office readings than on that in 24-hour ambulatory readings. Our study was not designed to address the effects of individual drugs or classes of drugs; therefore, patients were allowed to take all classes of drugs, which were administered at the discretion of their physicians.

Patients enrolled in our study were not optimally treated, as judged by their office readings at visit 3 (only 25 percent had an office systolic blood pressure below 140 mm Hg). Yearly follow-up visits failed to show improvement (data not shown), although participating physicians were continuously asked to adhere more closely to the target office blood pressure of 140/90 mm Hg. It is well recog-

nized<sup>24,25</sup> that in follow-up visits in observational studies, the proportion of patients with adequately controlled blood pressure is still far from optimal. In this sense, our study is a more accurate reflection of everyday practice than are studies in which blood pressure is better controlled.

Our study shows that 24-hour ambulatory blood pressure predicts the risk of cardiovascular events even after adjustment for classic risk factors including office blood pressure. The next step will be to determine the role of ambulatory blood-pressure monitoring in clinical practice and whether the cost-benefit ratio favors adding such monitoring to the standard care of patients with treated hypertension.<sup>26,27</sup>

Supported by the Flemish Science Foundation (Fonds voor Wetenschappelijk Onderzoek-Vlaanderen), the University of Ghent, the University Hospital of Ghent, AstraZeneca, Boehringer Ingelheim, Roche, Pfizer, Servier-Eutherapie Benelux, the Rotary Club Ghent, and the Stichting Gezondheidszorg Nollet.

We are indebted to Mrs. Linda Packet for her help in administering the study and her help in the preparation of the manuscript, and to Mrs. Gerda Bollaert and Mrs. Marleen Van Hecke for their logistic help during the study.

#### APPENDIX

The Office versus Ambulatory Blood Pressure (OvA) study was conducted under the auspices of the European Society of Hypertension, the European Society of Cardiology, and the Belgian Hypertension Committee. The following investigators were responsible for the coordination of the participating clinicians (an asterisk denotes deceased): *Trial coordinator* — D. Clement; *National coordinators* — L. Caparovski\* (Republic of Macedonia), M. Carrageta (Portugal), R. Cifkova (Czech Republic), J.P. Degaute (Belgium), P. de Leeuw (the Netherlands), M. Lapinski (Poland), J.M. Mallion (France), E. O'Brien (Ireland), P. Palatini (Italy), J.L. Rodicio (Spain); *Coordinators of Belgian general practices* — J. Beys, K. Bruyneel, M. Bury, D. De Clercq, D. Defrance, J. Deheneffe, Y. Deheneffe, P. De Jaegher, A. Friart, L. Geutjens, M. Gysbrechts, A. Herman, M. Kahan, A. Kassab, L. Labaki, P. Lafontaine, J. Lalmand, H. Lesseliers, D. Mertens, E. Mievis, E. Robbens, R. Six, C. Stevens, Y. Streulens, J. Thoeng, P. Timmermans, P. Van Der Niepen, A. Van Dorpe, E. Van Houwe, P. Van Iseghem, P. Vermeersch; *Protocol Committee* — D.L. Clement, A. Coats, J. Conway,\* G. Mancina, E. O'Brien; *End-Point Committee* — P. de Leeuw, R. Fagard (chairs), D. Duprez and P. Gheeraert (associate members); *Publication Committee* — D.L. Clement, M. De Buyzere, P. de Leeuw, R. Fagard, E. O'Brien; *Data Monitoring Committee* — D. De Bacquer (statistical analysis), M. De Buyzere, L. Missault, L. Packet; *Ethics Committee* — W. Birkenhäger, M. Bogaert, A. Zanchetti.

In addition, the following investigators participated in the study: *University Hospital Leuven, Campus Gasthuisberg, Leuven, Belgium* — R. Fagard, J. Staessen; *St. Jozefziekenhuis, Turnhout, Belgium* — I. Bekaert; *Centre Hospitalier Universitaire Tivoli, La Louviere, Belgium* — P. Dupont; *University Hospital, Ghent, Belgium* — D. Duprez; *Universitaire Instelling Antwerpen, Antwerp, Belgium* — J. Denekens, F. Rademakers; *Algemeen Ziekenhuis Stuivenberg, Antwerp, Belgium* — R. Lins; *Hôpital Saint Luc, Brussels, Belgium* — J.F. De Plaen; *Private cardiologists and general practitioners, Belgium* — H. Antonneau, L. Arcache, D. Barina, S. Bartholomeeusse, M. Barvais, I. Bayon, A. Bellucci, L. Berghmans, A. Berghs, A. Bernard, K. Bertels, G. Binet, L. Bleyen, J. Bogaert, F. Bolly, L. Bonami, D. Bonhomme, M. Bonhomme, A. Boogaerts, H. Boufessile, J. Boxus, B. Brichard, L. Brill, M. Brinker, C. Busellato, J. Busschaert, J. Cambier, P. Capiou, A. Carlier, J. Caudelier, P. Cayman, H. Cerfontaine, P. Ceurvelts, P. Chapelle, G. Charlier, G. Clerinx, E. Cloot-Snyders, S. Coene, A. Collin, D. Content, M. Content, M. Coopmans, P. Cornelis, J.M. Crespeigne, M.J. Cuvelier, G. Ledoux, J. Ledune, P. Leemans, A. Lefebvre, C. Lefebvre, P. Lenaerts, D. Lesage, R. Lietaer, L. Louette, J. Luyts, R. Maes, M. Maex, S. Manceaux-Thirion, G. Marco, J. Marquet-Lochegnies, R. Martens, J. Masureel, F. Maudens, P. Maudens, J.P. Meurant, E. Meys, A. Migeotte, A. Mignot, M. Minnaert, J. Moerman, J.P. Monette, A. Monoyer, A. Moonen, Y. Moons, A. Moreels, J.F. Mouvet, N. Neiman, J. Neven, F. Nollomont, J. Nuyten, W. Onsea, M. Pareit, E. Peeters, G. Peeters, L. Peremans, J.L. Perilleux, L. Phang, D. Plessers, M. Poot, D. Quertinier, J.P. Ralet, M. Rase, J.C. Reichling, R. Remmen, P. Robert, J.P. Rochet, F. Roelands, M. Roland, J.Y. Rousseau, M. Saey, F. Sas, D. Scheveneels, L. Schillemans, E. Schreurs, B. Seront, J. Sette, M. Simons, P. Simons, P. Sisani, J. Smekens, J.F. Soupart, J.F. Spiertz, A. Spilsteyns, F. Spirlet, J. Sprengers, J. Staelens, D. Strens, H. Stuer, C. Swinne, D. Taes, M. Talloen, M. Temmerman, P. Thibaut, D. Thiry, H.T. Tran, T. Tran Duy, Y. Urbain, P. Van Berkel, L. Van Boxelaer, J. Van Brabant, B. Van Damme, I. Van De Velde, A. Van De Weyer, F. Van Den Broek, G. Van Den Bussche, L. Van Den Eeckhout, W. Van Den Eede, B. Van den Eynden, H. Van Der Veken, W.



Van Dievel, W. Van Doninck, S. Van Enis, L. Van Eupen, C. Van Haren, L. Van Heyste, L. Van Hoecke, G. Vankerckhoven, F. Van Lint, J. Van Lint,\* J. Van Maele, E. Van Maerken, A.J. Van Oostveldt, C. Van Parijs, W. Van Peer, P. Van Royen, P. Van Severen, D. Van Troyen, P. Van Vlaenderen, L. Vanneste, G. Vereecken, A. Verheyen, V. Verstreken, J.P. Vervaeke, M. Vervaeke, M. Vrijdag, R. Vroonen, L. Vuylsteke, M. Vydts, C. Weber, A. Wery, S. Weyens, J. Willaert, L. Willaert, J.J. Zeiger; Institute for Clinical and Experimental Medicine, Prague, Czech Republic — R. Cifkova; Centre Hospitalier Universitaire, Grenoble, France — S. Boutelant, J.M. Mallion; Hôpital Universitaire La Milettrie, Poitiers, France — D. Herpin; Charitable Infirmary, Dublin, Ireland — E. Breslin, C. Gavin, E. O'Brien; Ospedale San Giovanni Di Dio, Florence, Italy — R. Laureano; Clinica Medica, Pavia, Italy — E. Marchesi; Ospedale Civile, San Daniele, Italy — L. Mos; Università degli Studi di Palermo, Palermo, Italy — S. Novo; Clinica Medica, Padua, Italy — P. Palatini; General Hospital Silvestrini, Perugia, Italy — C. Porcellati, P. Verdecchia; Academy of Medicine, Warsaw, Poland — M. Lapinski, J. Lewandowski; Hospital Universidade de Coimbra, Coimbra, Portugal — G. Pego; Instituto de Cardiologia Preventiva, Almada, Portugal — M. Carrageta; Hospital de la Santa Creu, Sant Pau, Barcelona, Spain — A. Roca Cusachs; Hospital 12 Octubre, Madrid — J.L. Rodicio; University Hospital, Skopje, Republic of Macedonia — L. Caparovski,\* N. Gjorgov; Vlietland Ziekenhuis, Schiedam, the Netherlands — J.J. Braun; Ikaziaziekenhuis, Rotterdam, the Netherlands — A. Dees; and Academisch Ziekenhuis Maastricht, Maastricht, the Netherlands — P. de Leeuw.

REFERENCES

1. Perloff D, Sokolow M, Cowan R. The prognostic value of ambulatory blood pressure. *JAMA* 1983;249:2792-8.
2. Zweiker R, Eber B, Schumacher M, Toplak H, Klein W. "Non-dipping" related to cardiovascular events in essential hypertensive patients. *Acta Med Austriaca* 1994; 21:86-9.
3. Ohkubo T, Imai Y, Tsuji I, et al. Prediction of mortality by ambulatory blood pressure monitoring versus screening blood pressure measurements: a pilot study in Ohasama. *J Hypertens* 1997;15:357-64.
4. Nakano S, Fukuda M, Hotta F, et al. Reversed circadian blood pressure rhythm is associated with occurrence of both fatal and nonfatal vascular events in NIDDM subjects. *Diabetes* 1998;47:1501-6.
5. Redon J, Campos C, Narciso ML, Rodicio JL, Pascual JM, Ruilope LM. Prognostic value of ambulatory blood pressure monitoring in refractory hypertension: a prospective study. *Hypertension* 1998;31:712-8.
6. Yamamoto Y, Akiguchi I, Oiwa K, Hayashi M, Kimura J. Adverse effect of nighttime blood pressure on the outcome of lacunar infarct patients. *Stroke* 1998;29: 570-6.
7. Khattar RS, Swales JD, Banfield A, Dore C, Senior R, Lahiri A. Prediction of coronary and cerebrovascular morbidity and mortality by direct continuous ambulatory blood pressure monitoring in essential hypertension. *Circulation* 1999;100:1071-6. [Erratum, *Circulation* 1999;100:1760.]
8. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Pede S, Porcellati C. Ambulatory pulse pressure: a potent predictor of total cardiovascular risk in hypertension. *Hypertension* 1998;32:983-8.
9. Staessen JA, Thijs L, Fagard R, et al. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. *JAMA* 1999;282:539-46.
10. Sander D, Kukla C, Klingelhöfer J, Winbeck K, Conrad B. Relationship between circadian blood pressure patterns and progression of early carotid atherosclerosis: a 3-year follow-up study. *Circulation* 2000;102:1536-41.
11. Kario K, Pickering TG, Matsuo T, Hoshida S, Schwartz JE, Shimada K. Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. *Hypertension* 2001;38:852-7.
12. Perloff D, Sokolow M, Cowan RM, Juster RP. Prognostic value of ambulatory blood pressure measurements: further analyses. *J Hypertens Suppl* 1989;7:S3-S10.
13. Verdecchia P, Reboldi G, Porcellati C, et al. Risk of cardiovascular disease in relation to achieved office and ambulatory blood pressure control in treated hypertensive subjects. *J Am Coll Cardiol* 2002;39:878-85.
14. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet* 1997;350:757-64.
15. Fagard R, Brguljan J, Thijs L, Staessen J. Prediction of the actual awake and asleep blood pressures by various methods of 24-h pressure analysis. *J Hypertens* 1996;14:557-63.
16. Pickering TG. How should the diurnal changes of blood pressure be expressed? *Am J Hypertens* 1995;8:681-2.
17. O'Brien E, Sheridan J, O'Malley K. Dippers and non-dippers. *Lancet* 1988;2:397.
18. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Gattobigio R, Porcellati C. Nocturnal pressure is the true pressure. *Blood Press Monit* 1996;1:Suppl 2:S81-S85.
19. Verdecchia P, Schillaci G, Gatteschi C, et al. Blunted nocturnal fall in blood pressure in hypertensive women with future cardiovascular morbid events. *Circulation* 1993; 88:986-92.
20. Verdecchia P, Porcellati C, Schillaci G, et al. Ambulatory blood pressure: an independent predictor of prognosis in essential hypertension. *Hypertension* 1994;24:793-801. [Erratum, *Hypertension* 1995;25:462.]
21. Ohkubo T, Hozawa A, Yamaguchi J, et al. Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasama study. *J Hypertens* 2002;20:2183-9.
22. Ohkubo T, Imai Y, Tsuji I, et al. Reference values for 24-hour ambulatory blood pressure monitoring based on a prognostic criterion: the Ohasama Study. *Hypertension* 1998;32:255-9.
23. Fagard RH, Staessen JA, Thijs L. Prediction of cardiac structure and function by repeated clinic and ambulatory blood pressure. *Hypertension* 1997;29:22-9.
24. De Henauw S, De Bacquer D, Fonteyne W, Stam M, Kornitzer M, De Backer G. Trends in the prevalence, detection, treatment and control of arterial hypertension in the Belgian adult population. *J Hypertens* 1998;16:277-84.
25. Mancia G, Bombelli M, Lanzarotti A, et al. Systolic vs diastolic blood pressure control in the hypertensive patients of the PAMELA population. *Arch Intern Med* 2002; 162:582-6.
26. Staessen JA, Byttebier G, Buntinx F, Celis H, O'Brien ET, Fagard R. Antihypertensive treatment based on conventional or ambulatory blood pressure measurement: a randomised controlled trial. *JAMA* 1997; 278:1065-72.
27. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC7 Report. *JAMA* 2003;289: 2560-72.

Copyright © 2003 Massachusetts Medical Society.