Prediction of Coronary and Cerebrovascular Morbidity and Mortality by Direct Continuous Ambulatory Blood Pressure Monitoring in Essential Hypertension

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Background—The goal of this study was to assess the prognostic value of ambulatory versus clinic blood pressure measurement and to relate cardiovascular risk to ambulatory systolic and diastolic blood pressure levels.

Methods and Results—The study population consisted of 688 patients 51±11 years of age who had undergone pretreatment 24-hour intra-arterial ambulatory blood pressure monitoring on the basis of elevated clinic blood pressure. A total of 157 first events were recorded during a 9.2±4.1-year follow-up period. The predictive value of a regression model containing age, sex, race, body mass index, smoking, diabetes mellitus, fasting cholesterol level, and previous history of cardiovascular disease was significantly improved by the addition of any ambulatory systolic or diastolic blood pressure parameter (whether 24-hour, daytime, or nighttime mean) or pulse pressure, whereas inclusion of baseline clinic blood pressure variables did not enhance the prediction of events. The most predictive models contained the ambulatory systolic blood pressure parameters. In the model containing 24-hour mean ambulatory systolic blood pressure ($P=0.001$), age ($P<0.001$), male sex ($P<0.001$), South Asian origin ($P=0.008$), diabetes mellitus ($P=0.05$), and previous cardiovascular disease ($P<0.001$) were additional independent predictors of events. Whereas 24-hour ambulatory systolic blood pressure was linearly related to the incidence of both coronary and cerebrovascular events, 24-hour ambulatory diastolic blood pressure exhibited a positive linear relationship with cerebrovascular events but a curvilinear relationship with coronary events.

Conclusions—Ambulatory blood pressure is superior to clinic measurement for the assessment of cardiovascular risk; there is no reduction in coronary risk at lower levels of ambulatory diastolic blood pressure. (Circulation. 1999;100:1071-1076.)

Key Words: blood pressure ■ prognosis ■ cardiovascular diseases

Over the last 50 years, it has become increasingly recognized that isolated clinic blood pressure measurements may not be adequately representative of the daily blood pressure load away from the medical environment. With frequent readings taken during routine daily activities, 24-hour ambulatory blood pressure monitoring offers a more valid assessment of an individual's true blood pressure level. Consequently, cross-sectional studies have generally shown ambulatory blood pressure to be more closely related to target organ damage than clinic-based measurements, but longitudinal data are limited. The intra-arterial method of ambulatory blood pressure monitoring is a powerful research tool and remains the reference standard by which noninvasive monitors are validated. It provides beat-to-beat measurements of blood pressure over a 24-hour period in truly ambulant patients and therefore represents the most accurate measure of the daily hemodynamic burden imposed by blood pressure. In contrast, noninvasive auscultatory and oscillometric monitors rely on intermittent recordings at predetermined time intervals, and these may not be accurate during unrestricted physical activity. The aims of this study were to assess the prognostic value of ambulatory versus clinic blood pressure measurement for the prediction of subsequent morbid events in patients with essential hypertension and to relate the risk of all-cause, coronary, and cerebrovascular events to the level of ambulatory systolic and diastolic blood pressure.

Methods

From January 1, 1979, to January 1, 1993, 723 patients were subjected to 24-hour intra-arterial ambulatory blood pressure monitoring at our institution; their demographic profile has recently been published. The racial composition of the patient population studied reflects the local population of the London boroughs of Harrow,
Brent, and Ealing, which includes mainly white subjects but also South Asian (Indian subcontinent) and African-Caribbean subjects. All patients were originally referred for the management of hypertension because of persistently elevated clinic blood pressure taken over a period of weeks to months in a primary care setting. At each hospital visit, a single blood pressure measurement was taken by a nurse or technician using the conventional auscultatory technique after 5 to 10 minutes of semisupine rest in a warm environment. The point of disappearance of auscultatory sounds was taken as the diastolic blood pressure. This was followed by a full medical history and physical examination by a physician. Secondary causes of hypertension were excluded, as far as possible, in all patients by measurement of serum urea, creatinine, and electrolytes and of urinary catecholamines; chest x-ray; and more recently, intravenous renal digital subtraction angiography. Baseline clinic blood pressure was taken as the mean of ≥2 untreated readings at separate clinic visits in the 4 weeks before or after the intra-arterial study. Those in whom clinic systolic blood pressure was ≥140 mm Hg or diastolic blood pressure was ≥90 mm Hg were required to undergo 24-hour intra-arterial ambulatory blood pressure monitoring within 2 months. Antihypertensive medication either had not been started or had been withdrawn in the 8 weeks preceding intra-arterial blood pressure monitoring. The method of 24-hour intra-arterial ambulatory blood pressure monitoring was approved by the Harrow Health Authority Ethical Committee, and patients were required to give written informed consent before the procedure. General practitioners were informed of test results, and antihypertensive therapy was generally recommended if 24-hour ambulatory systolic blood pressure was ≥140 mm Hg or diastolic blood pressure was ≥90 mm Hg. Treatment of lower ambulatory blood pressure readings was more conservative and discretionary. Subsequent assessment of blood pressure control and treatment was largely left to the individual general practitioners or hospital physicians and was based on clinic blood pressure measurements, in keeping with standard clinical practice.

Intra-Arterial Blood Pressure Monitoring

The technique of intra-arterial blood pressure recording used in this laboratory has been well documented, as has the method of analysis. Blood pressure was recorded from a fine brachial artery cannula with a specially designed transducer/perfusion unit and an Oxford Medilog Mark I tape recorder. The equipment was designed so that patients were fully ambulant and able to carry out their normal daily activities away from the hospital environment. The 24-hour tape recordings were analyzed on a custom-built hybrid computer by use of a program that calculated mean hourly blood pressure and heart rate. Mean (24-hour) systolic and diastolic intra-arterial blood pressures were calculated by averaging the 24-hour systolic and diastolic blood pressure readings. Blood pressure and heart rate variabilities were expressed as the SD of mean hourly systolic and diastolic blood pressures and heart rate, respectively. Daytime mean systolic and diastolic blood pressures were defined as the average of the hourly blood pressure readings from 6 AM to 10 PM; nighttime mean blood pressures, between 10 PM and 10 AM. The nocturnal decreases in systolic and diastolic blood pressures were calculated by subtracting respective nighttime mean from daytime mean blood pressure recordings. Nondippers were defined as those who did not exhibit a reduction in mean systolic and diastolic blood pressures by ≥10% from day to night; the remaining subjects were classified as dippers. The white-coat effects on systolic and diastolic blood pressures were defined as initial clinic blood pressure measurements minus respective daytime mean ambulatory readings.

Follow-Up Evaluation

The study patients have been intermittently reviewed over the years to record clinic blood pressure, drug therapy, and the occurrence of interim cardiovascular events. Ethical approval for the most recent follow-up, performed during an 18-month period from 1994 to 1996, was gained from the hospital ethics committee before patients or their family practitioners were contacted. To obtain complete mortality data, the dates and certified causes of interim deaths were obtained from the National Health Service Central Register, Southport, UK. Hospital records of all patients were also scrutinized. Survivors were invited to attend a follow-up evaluation for documentation of events, clinic blood pressure measurement on current treatment, serum creatinine estimation, and fasting cholesterol level determination. General practitioners of the nonattenders were sent a questionnaire for details about these patients.

Documented events consisted of noncardiovascular death, coronary death (myocardial infarction or ischemia, ventricular fibrillation, or cardiac failure), cerebrovascular death, peripheral vascular death, nonfatal myocardial infarction, nonfatal stroke, and coronary revascularization.

Statistical Analysis

The clinical variables analyzed included age, sex, race, body mass index, diabetes mellitus, smoking, fasting cholesterol level, and previous cardiovascular disease. The follow-up period was defined as the time interval between 24-hour intra-arterial ambulatory blood pressure monitoring and last follow-up in uncomplicated patients or the development of a first morbid event. Continuous variables were expressed as mean±SD, and categorical variables were given as the percentage of patients so affected. The study population was dichotomized into those with and without events. Comparison of clinical variables and blood pressure data between these 2 groups was made by univariate Cox proportional-hazards analysis. In multivariate analysis, a baseline Cox regression model containing age, sex (men versus women), race (South Asians versus whites and African-Caribbeans versus whites), smoking (smokers versus nonsmokers), diabetes mellitus, previous cardiovascular disease, and fasting cholesterol level was devised for predicting the time to experiencing a first event. A series of regression models was then created, individually adding each blood pressure parameter to the clinical variables to assess whether any of these parameters could enhance the predictive value of the model with the use of the likelihood ratio test. The χ² value obtained from this test represented the difference in the log likelihood between the baseline model and the model containing the blood pressure parameter; the higher the χ² value, the better the fit of the model for prediction of events. Quadratic functions of 24-hour mean ambulatory systolic and diastolic blood pressures and clinic systolic and diastolic blood pressures were also incorporated into the regression models to assess for curvilinearity between these variables and subsequent events. Hazard ratios with 95% CIs were derived for each variable, and a value of P<0.05 was considered significant.

Results

The study population consisted of 688 patients (440 men, 248 women) with follow-up data, of whom 528 were white, 106 were South Asian, and 54 were African-Caribbean. A total of 157 first events were recorded during a mean follow-up period of 9.2±4.1 years, including 32 noncardiovascular deaths, 27 coronary deaths, 10 cerebrovascular deaths, 4 peripheral vascular deaths, 46 nonfatal myocardial infarctions, 20 nonfatal strokes, and 18 coronary revascularization procedures.

Comparison of Demographic Data

Table 1 gives a comparison of the baseline demographic data in those with and without events. The group with events was significantly older and had a higher fasting cholesterol level than the group without events. A significantly greater proportion of men than women, smokers than nonsmokers, diabetics than nondiabetics, and those with than those without a previous history of cardiovascular disease experienced a subsequent event. In addition, proportionately fewer African-Caribbean subjects (9%) developed an end point compared with whites (23%; P<0.001) and South Asians (28%; P<0.001).
Comparison of Hemodynamic Data

Table 2 gives a comparison of the baseline blood pressure data in those with and without events. All components of systolic blood pressure and pulse pressure (initial clinic, 24-hour mean, daytime mean, and nighttime mean) were significantly greater in those who experienced a morbid event. The most discriminatory diastolic blood pressure parameter between the 2 groups was nighttime mean diastolic blood pressure. The group of patients with events had a significantly greater proportion of nondippers and smaller nocturnal decreases in both systolic and diastolic blood pressures compared with those without events. Heart rate variability was also significantly lower in those who developed a morbid end point.

Cardiovascular Risk According to Level of Ambulatory Systolic and Diastolic Blood Pressures

Table 3 and Figures 1 and 2 summarize the incidence of all-cause, coronary, and cerebrovascular events in the 688 patients according to strata of 24-hour mean ambulatory systolic and diastolic blood pressures, respectively. These indicate that
the relationships between 24-hour mean ambulatory systolic blood pressure and each category of event were approximately linear. In contrast, the pattern of risk for 24-hour mean ambulatory diastolic blood pressure was dependent on the type of event. For all-cause and coronary events, a plateau effect was observed in the event rates at lower levels of ambulatory diastolic blood pressure, indicating no risk reduction below a certain level of diastolic blood pressure. However, the relationship between ambulatory diastolic blood pressure and cerebrovascular events was essentially linear, with proportionate reductions in the incidence of fatal and nonfatal stroke with a lower the level of diastolic blood pressure.

Multivariate Analysis

Table 4 lists the blood pressure parameters that significantly improved the prediction of events when added individually to a baseline regression model containing clinical variables, with respective \( \chi^2 \) and probability values. Whereas ambulatory systolic and diastolic blood pressure parameters (whether 24-hour, daytime, or nighttime mean) and ambulatory pulse pressure provided independent information and significantly improved the fit of the model for the prediction of events, the addition of clinic blood pressure measurements to the baseline model did not enhance the prediction of events. The regression models with the best predictive value, as reflected by the \( \chi^2 \) values, contained the ambulatory systolic blood pressure parameters. Addition of the quadratic function of 24-hour ambulatory diastolic blood pressure \([24\text{-hour (diastolic blood pressure)}]^2\) to the baseline model also significantly enhanced the prediction of subsequent events, indicating a curvilinear relationship with subsequent cardiovascular risk. The equivalent function for systolic blood pressure did not exhibit any independent prognostic value. Neither the measures of blood pressure and heart rate variability (including hourly SDs of blood pressure and heart rate, degree of nocturnal decrease in blood pressure, and nondipper status) nor the white-coat effect of systolic and diastolic blood pressures was able to provide any incremental prognostic information for the prediction of future events.

In the regression model containing 24-hour ambulatory systolic blood pressure, age \((P<0.001)\), sex \((P<0.001)\), race (South Asians versus whites, \(P=0.008\)), diabetes \((P=0.05)\), previous history of cardiovascular disease \((P<0.001)\), and 24-hour ambulatory blood pressure \((P=0.001)\) were independent predictors of time to a first morbid event (Table 5).

Discussion

Since the introduction of ambulatory blood pressure monitoring >30 years ago, only 3 longitudinal studies have assessed the prognostic value of this test. Perloff et al\(^{11}\) measured daytime ambulatory blood pressure using a semiautomatic device in 1076 hypertensive subjects and showed that ambulatory blood pressures that were higher than predicted from a regression line between ambulatory blood pressure and office blood pressure were associated with an adverse outcome. Importantly, however, use of a patient-activated, semiautomatic, indirect blood pressure recorder did not allow measurement of nocturnal blood pressure. Verdecchia et al\(^{12}\) remedied this limitation by performing 24-hour, intermittent, noninvasive ambulatory blood pressure monitoring in 1187 subjects with essential hypertension and 205 normotensive

### Table 4. Predictive Value of Clinic and Ambulatory Blood Pressure Parameters When Added Individually to a Regression Model Containing Clinical Variables and Respective \( \chi^2 \) and Probability Values

<table>
<thead>
<tr>
<th>Regression Model</th>
<th>( \chi^2 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical variables + 24-h systolic BP</td>
<td>11.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinical variables + nighttime systolic BP</td>
<td>10.57</td>
<td>0.001</td>
</tr>
<tr>
<td>Clinical variables + daytime systolic BP</td>
<td>10.33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinical variables + nighttime diastolic BP</td>
<td>9.87</td>
<td>0.004</td>
</tr>
<tr>
<td>Clinical variables + 24-h diastolic BP</td>
<td>7.58</td>
<td>0.008</td>
</tr>
<tr>
<td>Clinical variables + 24-h pulse pressure</td>
<td>6.12</td>
<td>0.01</td>
</tr>
<tr>
<td>Clinical variables + daytime diastolic BP</td>
<td>5.88</td>
<td>0.02</td>
</tr>
<tr>
<td>Clinical variables + 24-h (diastolic BP)^2</td>
<td>12.59</td>
<td>0.002</td>
</tr>
<tr>
<td>Clinical variables + clinic systolic BP</td>
<td>3.94</td>
<td>NS</td>
</tr>
<tr>
<td>Clinical variables + clinic diastolic BP</td>
<td>0.22</td>
<td>NS</td>
</tr>
</tbody>
</table>

BP indicates blood pressure.
control subjects. They showed that the risk conferred by white-coat hypertension was similar to normotension, but in those with ambulatory hypertension, particularly in female nondippers, the event rate was significantly higher. Finally, Ohkubo et al. showed ambulatory blood pressure monitoring to be superior to clinic measurement for the prediction of all-cause mortality in a general Japanese population. However, these findings are not directly applicable to Western populations given that only 13% of deaths were attributable to heart disease. Moreover, clinic blood pressure was taken at only 1 sitting by an automated device.

The present study provides the longest follow-up data evaluating the prognostic value of ambulatory blood pressure monitoring and differs from previous reports in providing the only substantial data obtained with the intra-arterial technique. In our study, ambulatory blood pressure was evaluated as a continuous variable, thereby allowing assessment of the relationships between stratified levels of ambulatory blood pressure and subsequent cardiovascular risk. Linear and nonlinear relationships between ambulatory blood pressure and cardiovascular morbidity and mortality have not previously been evaluated in a hypertensive population but have important treatment implications. Our findings indicate that ambulatory blood pressure monitoring yields greater prognostic information than clinic blood pressure measurements. The addition of any 1 of the 24-hour, daytime, or nighttime mean ambulatory systolic or diastolic blood pressure parameters or ambulatory pulse pressure provided independent information for the prediction of all-cause events. This partly reflects the high degree of colinearity between systolic and diastolic blood pressures, making it difficult to determine the relative contribution of each of these components of blood pressure with disease risk. However, accumulating epidemiological data suggest that systolic blood pressure may confer greater prognostic information than diastolic blood pressure, particularly in the elderly. Our results lend toward this view, with the most predictive regression models containing the ambulatory systolic blood pressure parameters. These findings reaffirm the importance of systolic blood pressure in the pathogenesis of cardiovascular complications and counter the traditionally held assumption that diastolic blood pressure is the main determinant of cardiovascular disease. Previous studies have shown that a blunted decrease in nocturnal blood pressure is associated with left ventricular hypertrophy.

coronary heart disease, and cerebrovascular manifestations. In the present study, although the proportion of nondippers was greater and the levels of nocturnal decrease in systolic and diastolic blood pressures were lower in the group of patients with compared with those without events, these parameters failed to provide independent prognostic information after adjustment for clinical variables.

Analysis of the relationships between 24-hour ambulatory systolic blood pressure and all-cause, coronary, and cerebrovascular events revealed a positive linear relationship with each category of event. Previous studies have also reported a positive linear relationship between systolic pressure and the incidence of stroke and found the lowest risk of a coronary event to be associated with the lowest systolic blood pressure. In contrast, 24-hour ambulatory diastolic blood pressure demonstrated a curvilinear relationship with all-cause and coronary events, indicating no reduction in risk below a threshold level of diastolic blood pressure. Much controversy surrounds the notion that lowering diastolic blood pressure too far in certain patients with hypertension may provoke a coronary event. Proponents of this J-curve phenomenon have emphasized the consistency of this finding across a variety of populations with hypertension and formed the hypothesis that an inappropriately low, treated diastolic blood pressure may lead to myocardial ischemia in predisposed subjects because of a failure of autoregulation in the coronary circulation. Others argue that the effect occurs as a result of an irregularity in small sets of data compounded by biased methods of analysis and suggest that the association between low blood pressure and mortality merely reflects a deterioration in general health rather than a treatment-induced causal relationship. Our finding of a nonlinear relationship between baseline pretreatment 24-hour ambulatory intra-arterial diastolic blood pressure and subsequent coronary events adds to the body of evidence in favor of a curved relationship, which has been observed in untreated populations. For cerebrovascular events, most studies have found the lowest diastolic pressures to be associated with the lowest event rates. The positive linear relationship between 24-hour ambulatory diastolic blood pressure and cerebrovascular events in the present study concurs with these findings.

In addition to the ambulatory blood pressure parameters, age, male sex, South Asian origin, diabetes mellitus, and previous history of cardiovascular disease were independent predictors of events. The increased risk of subsequent morbidity and mortality in South Asians compared with their white counterparts is consistent with epidemiological data from the United Kingdom and elsewhere, showing that South Asians are particularly prone to coronary heart disease and have a higher mortality from cerebrovascular disease than white subjects.

Most of the prognostically important baseline demographic parameters were assessed in this study, but family history of cardiovascular disease was inadequately documented and hence not taken into account. Although the much-quoted New Zealand chart for assessment of cardiovascular risk does not include an evaluation of family history, data from the Framingham study suggest that this variable is an independent risk factor for coronary heart disease. It is therefore possible
that an evaluation of family history of cardiovascular disease in our study may have altered the findings of multivariate analysis, but the inclusion of noncardiovascular death as an end point may have dampened its effects. A second limitation of this study was the lack of a formalized protocol for the assessment of blood pressure control and administration of antihypertensive drug therapy. Both of these aspects of hypertension management were left entirely to the discretion of the attending physician of the hypertension clinic or to the family practitioner. Blood pressure control was based on clinic blood pressure measurements as part of standard clinical practice; it was not considered justifiable on ethical grounds to repeat intra-arterial blood pressure monitoring, particularly in the face of developing noninvasive technologies for ambulatory blood pressure measurement in subsequent years. The vast majority of patients in this study were subjected to many switches in drug therapy, having been treated with a variety of regimens over the years, as is inevitably the case in large, longitudinal, cohort studies of this nature. Consequently, it was not possible to reliably evaluate the effect of specific classes of antihypertensive drug therapy on prognosis. Despite the importance of such treatment on events, highly significant relationships between baseline ambulatory blood pressure and subsequent risk remained, indicating only partial modification of risk by treatment in these patients. Similar independent relationships were not observed with clinic blood pressure. This study therefore shows that assessment of the 24-hour blood pressure load, particularly systolic blood pressure, provides a superior method of identifying high-risk patients.

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References
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