

Superiority of Ambulatory Over Clinic Blood Pressure Measurement in Predicting Mortality

The Dublin Outcome Study

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Abstract—The purpose of this study was to determine if ambulatory blood pressure measurement predicted total and cardiovascular mortality over and beyond clinic blood pressure measurement and other cardiovascular risk factors; 5292 untreated hypertensive patients referred to a single blood pressure clinic who had clinic and ambulatory blood pressure measurement at baseline were followed up in a prospective study of mortality outcome. Multiple Cox regression was used to model time to total and cause-specific mortality for ambulatory blood pressure measurement while adjusting for clinic blood pressure measurement and other risk factors at baseline. There were 646 deaths (of which 389 were cardiovascular) during a median follow-up period of 8.4 years. With adjustment for gender, age, risk indices, and clinic blood pressure, higher mean values of ambulatory blood pressure were independent predictors for cardiovascular mortality. The relative hazard ratio for each 10-mm Hg increase in systolic blood pressure was 1.12 (1.06 to 1.18; $P<0.001$) for daytime and 1.21 (1.15 to 1.27; $P<0.001$) for nighttime systolic blood pressure. The hazard ratios for each 5-mm Hg increase in diastolic blood pressure were 1.02 (0.99 to 1.07; $P=NS$) for daytime and 1.09 (1.04 to 1.13; $P<0.01$) for nighttime diastolic pressures. The hazard ratios for nighttime ambulatory blood pressure remained significant after adjustment for daytime ambulatory blood pressure. These results have 2 important clinical messages: ambulatory measurement of blood pressure is superior to clinic measurement in predicting cardiovascular mortality, and nighttime blood pressure is the most potent predictor of outcome. (*Hypertension*. 2005;46:156-161.)

Key Words: blood pressure ■ blood pressure monitoring, ambulatory ■ cardiovascular diseases ■ hypertension ■ mortality

The most commonly used technique of blood pressure measurement in clinical practice is the auscultatory method with a mercury sphygmomanometer and stethoscope. A metaanalysis of clinic blood pressure measurement (CBPM) in 1 million adults participating in 61 prospective studies showed that a 10-mm Hg higher usual systolic blood pressure (SBP) or 5-mm Hg higher usual diastolic blood pressure (DBP) would be associated with $\approx 40\%$ higher risk of stroke death and $\approx 30\%$ higher risk of death from ischemic heart disease and other vascular causes.¹ There are, however, numerous criticisms of CBPM, which include interobserver and intraobserver variability, and terminal digit preferences,^{2,3} all of which may bias the accuracy of measurement. Moreover, CBPM cannot detect white-coat hypertension, the prevalence of which can be as high as 30%.⁴

There is growing evidence from a number of small studies that ambulatory blood pressure measurement (ABPM) is a

better predictor of outcome than CBPM,⁵⁻¹³ but only one large Japanese population study has shown ABPM to be better predictor of cardiovascular mortality than CBPM.⁸ Similarly, evidence is accumulating to demonstrate that nighttime pressure is superior to daytime pressure in predicting cardiovascular outcome.^{7,14-21} The objective of this study, therefore, was to determine the additional predictive value of ABPM over and above CBPM, and also to estimate the superiority of nighttime pressure over daytime pressure in a large Western population of untreated hypertensive patients from a single center followed-up for up to 20 years.

Methods

Study Population

The Blood Pressure Unit (formerly located at the Charitable Infirmary and now based at Beaumont Hospital in Dublin) has been in operation for 22 years. The majority of patients are referred to the

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TABLE 1. Characteristics of Study Population

Parameters	Alive	Dead	
		Cardiovascular	Noncardiovascular
n	4646	389	257
Age, years	51.5 (14.2)	67.5 (11.9)*	64.4 (13.7)
Female, %	54.8	43.5*	48.7
Body mass index, kg/m ²	27.5 (3.6)	27.7 (3.4)	25.6 (4.1)
Current smoking, %	22.9	30.6*	29.1
Diabetes, %	4.9	7.7*	5.8
Previous cardiovascular complications, %	9.3	23.1*	15.2
Clinic SBP	161.1 (26.8)	173.7 (31.1)*	167.2 (32.2)
Clinic DBP	93.2 (14.6)	92.3 (16.1)	91.7 (17.8)
Daytime SBP	145.4 (18.4)	153.1 (22.8)*	148.1 (20.4)
Daytime DBP	89.1 (12.5)	88.2 (14.7)	87.7 (13.2)
Nighttime SBP	127.2 (18.7)	142.4 (25.3)*	135.6 (24.1)
Nighttime DBP	74.8 (12.8)	78.8 (15.2)*	77.6 (14.7)
24-hour SBP	137.1 (20.3)	146.3 (25.1)*	143.0 (23.6)
24-hour DBP	82.1 (11.2)	84.6 (13.1)*	83.1 (12.1)

DBP indicates diastolic blood pressure; SBP, systolic blood pressure.

All pressures in mm Hg.

Values are means (\pm SD) or n of subjects (%).

Body mass index is the weight in kilograms divided by the square of height in meters.

*Statistical significance ($P < 0.05$) of difference between alive group and cardiovascular dead group.

Unit by their family doctors because of an elevated CBPM; 14 414 such patients were entered into a database during the study period (June 1, 1980 to September 30, 2002). To be eligible for inclusion in the present report, patients had to be either untreated at baseline or to have had all antihypertensive drugs discontinued for 1 week before their baseline visit to the unit; demographic details and cardiovascular risk factors (sex, age, body mass index, smoking status, presence of diabetes mellitus, and history of previous cardiovascular events) had to be recorded; and the ABPM record had to include at least 10 daytime and 5 nighttime readings. Because of insufficient ABPM measurements, 201 patients were excluded. The total number of participants fulfilling the entry criteria on September 30, 2002 was 5292. The Hospital Ethics Committee approved the study.

Clinic Blood Pressure Measurement

A nurse measured blood pressure in the nondominant arm after 5 minutes of quiet sitting in accordance with contemporary recommendations^{22,23} using either a standard mercury sphygmomanometer or a calibrated and validated automated sphygmomanometer—the Omron HEM-705CP.²⁴ CBPM was calculated as the mean of 3 measurements.

Ambulatory Blood Pressure Measurement

ABPM measurements were made every half-hour throughout the 24-hour period using SpaceLabs 90202 and 90207 monitors (SpaceLabs Inc, Wokingham, Berkshire, UK), both of which have been previously shown to be accurate.^{25,26} All data were transferred into a software package (dabl Cardiovascular; Dabl Limited),²⁷ which allows calculation of SBP and DBP for the daytime period (average of readings between 0900 and 2100 hours), the nighttime period (average of readings between 0100 and 0600 hours), and the 24-hour period without applying any editing criteria.^{28,29} ABPM measurements were time-weighted. Hypertension was defined as a mean daytime ABPM of ≥ 135 mm Hg systolic or 85 mm Hg diastolic.³⁰

Mortality Outcome

In the absence of a unique identifier to permit ready identification of subjects on the death register, mortality outcome was ascertained by

searching a national computerized register of deaths for each individual whose name appeared in the dabl blood pressure database. This process was completed in a number of stages, which have been described previously.³¹ Briefly, the register was first searched for patients having both similar names and approximate date of birth, so as to allow for different versions of first and surnames and/or misspelling in the death certificate, and also to overcome the omission of the actual date of birth by allowing a 2-year margin of error. If there was no match using these 2 criteria, the individual was considered to be alive. Where there was a positive match, the relevant death certificate was examined, and further confirmation of death was sought by checking addresses, hospital records, and family doctors records. This process provided definite evidence that 646 people from the 5292 individuals in the study cohort had died by September 30, 2002. Because Irish death certificates state the cause of death but are not coded, the death certificate of each individual was examined and the cause of death was coded according to the World Health Organization's International Classification of Diseases, 9th Revision (ICD-9).³² Cardiac mortality included myocardial infarction (ICD-9, 4100 to 4109), heart failure (4280 to 4289), sudden death (7980 to 7989), and chronic coronary heart disease (4140 to 4149). Cardiovascular mortality consisted of cardiac mortality, stroke (4300 to 4389), and other vascular deaths.

Statistical Analysis

The analyses were performed using SAS software, version 9 (SAS Institute Inc, Cary, NC). We compared means and proportions by the large sample z-test and the χ^2 statistic, respectively. We divided the distributions of the baseline blood pressure into quintiles. From one overall logistic regression model adjusted for gender and age, we computed the risk of an adverse outcome in each blood-pressure quintile relative to the common risk in all patients. We plotted these 5 risk estimates with 95% confidence intervals (CIs) against the average blood pressure in each quintile.³³ This analysis was performed on ambulatory SBP and DBP to test the hypothesis that ABPM predicts cardiovascular mortality. We then introduced CBPM and ABPM, or daytime and nighttime ABPM, as continuous variables in Cox proportional hazards regression. Relative hazard ratios

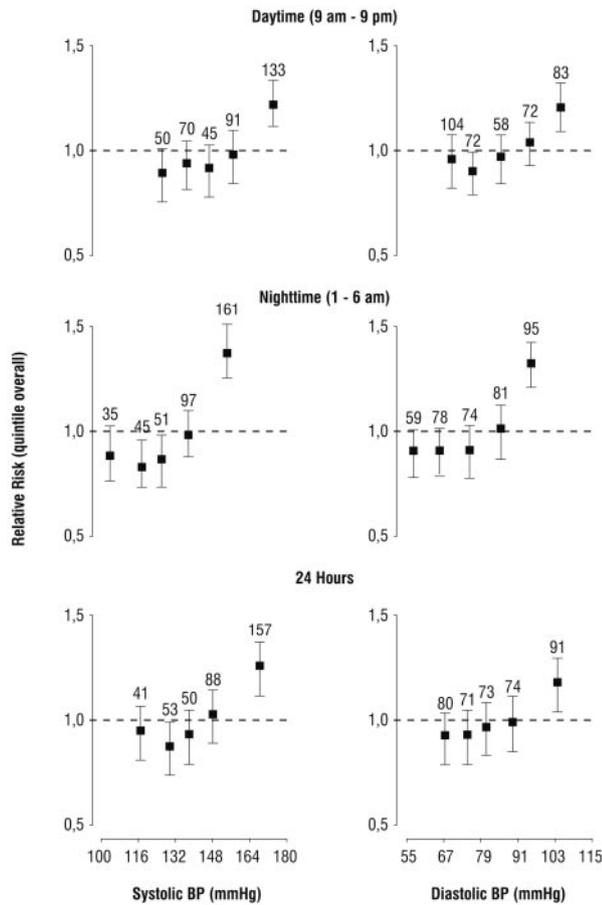


Figure 1. Associations between cardiovascular mortality and ambulatory blood pressure in 5292 patients. Solid diamonds represent risks in quintiles of the blood pressure distributions relative to common risk in all patients with adjustment applied to gender and age. Vertical lines denote 95% CIs. Numbers represent the number of cardiovascular deaths in each quintile.

and 95% CIs were calculated for each 10-mm Hg and 5-mm Hg increase in SBP and DBP, respectively. Adjustments were made for gender, age, body mass index, presence of diabetes mellitus, history of cardiovascular events, and current smoking status, along with further adjustment for CBPM.

Results

Baseline Characteristics

The characteristics of the patient populations are shown in Table 1. Mean follow-up was 7.9 years (interquartile range, 5.6 years to 10.6 years). Ages at baseline ranged from 16.2 years to 92.4 years. There were 646 deaths, of which 389 were cardiovascular. The prevalence of known cardiovascular risk factors was higher among patients who died of cardiovascular causes.

Clinic and Ambulatory Blood Pressures as Predictors of Mortality Risk

Using a nonparametric approach with adjustment for gender and age, patients in the highest quintile for nighttime pressures were at higher relative risk compared with the overall group (Figure 1). Patients in the highest quintile for nighttime SBP had a relative risk of a cardiovascular death of 1.30 (95% CI, 1.17 to 1.45; $P < 0.001$).

Table 2 shows the relative hazard ratios for 10- and 5-mm Hg increases in SBP and DBP, respectively, before and after adjustment for CBPM. With adjustments applied for baseline characteristics, the systolic ABPM predicted all mortality outcomes over and beyond systolic CBPM ($P < 0.001$). Table 3 provides the fully adjusted Cox regression models for cardiovascular mortality and shows that the significance levels were considerably higher for the ambulatory than for the conventional blood pressure. ABPM was not forced into the models for any of the fatal outcome analyses. The hazard ratios associated with a 10-mm Hg increase in SBP were 1.12 (95% CI, 1.06 to 1.19; $P < 0.001$), 1.21 (95% CI, 1.13 to 1.28; $P < 0.001$), and 1.19 (95% CI, 1.13 to 1.27; $P < 0.001$) for daytime, nighttime, and 24-hour ABPM, respectively. The corresponding adjusted relative hazard ratios associated with a 5-mm Hg increase in DBP were 1.03 (95% CI, 0.99 to 1.07; $P = \text{NS}$), 1.07 (95% CI, 1.04 to 1.13; $P < 0.05$), and 1.09 (95% CI, 1.02 to 1.11; $P < 0.01$). Nighttime ABPM provides additional predictive information over daytime ABPM, as does ABPM SBP over ABPM DBP, for total, cardiovascular, stroke, and cardiac mortality (Table 4).

TABLE 2. Relative Hazard Ratios Associated With Clinic and Ambulatory Blood Pressures

Parameters	Unadjusted for Clinic Blood Pressure				Adjusted for Clinic Blood Pressure			
	All-Cause Mortality	Cardiovascular	Stroke	Cardiac	All-Cause Mortality	Cardiovascular	Stroke	Cardiac
No. of events	646	389	103	254	646	389	103	254
Clinic SBP	1.02 (0.99–1.05)	1.06 (1.02–1.10)†	1.07 (1.00–1.15)*	1.06 (1.01–1.10)*				
Daytime SBP	1.09 (1.04–1.13)†	1.15 (1.10–1.21)‡	1.18 (1.08–1.30)†	1.12 (1.06–1.19)†	1.07 (1.03–1.12)†	1.12 (1.06–1.18)‡	1.17 (1.05–1.30)†	1.11 (1.04–1.19)†
Nighttime SBP	1.14 (1.10–1.18)‡	1.21 (1.16–1.27)‡	1.30 (1.19–1.40)‡	1.16 (1.10–1.23)‡	1.15 (1.11–1.20)‡	1.21 (1.15–1.27)‡	1.30 (1.19–1.42)‡	1.15 (1.04–1.23)†
24-hour SBP	1.11 (1.07–1.16)‡	1.19 (1.14–1.26)‡	1.27 (1.15–1.40)‡	1.17 (1.09–1.24)‡	1.13 (1.08–1.19)‡	1.19 (1.13–1.27)‡	1.28 (1.15–1.43)‡	1.16 (1.07–1.25)‡
Clinic DBP	1.01 (0.99–1.04)	1.03 (1.00–1.07)*	1.06 (0.99–1.12)	1.02 (0.98–1.06)				
Daytime DBP	1.02 (0.99–1.06)	1.04 (1.00–1.08)*	1.09 (1.01–1.17)*	1.03 (0.98–1.07)	1.02 (0.99–1.05)	1.03 (0.99–1.07)	1.07 (0.99–1.16)	1.02 (0.97–1.07)
Nighttime DBP	1.07 (1.04–1.10)†	1.09 (1.05–1.13)†	1.14 (1.07–1.22)†	1.06 (1.01–1.11)*	1.08 (1.04–1.11)‡	1.09 (1.04–1.13)‡	1.14 (1.06–1.22)‡	1.06 (1.01–1.11)*
24-hour DBP	1.06 (1.02–1.09)*	1.07 (1.03–1.12)†	1.13 (1.05–1.22)†	1.05 (1.00–1.10)	1.05 (1.02–1.09)*	1.09 (1.02–1.11)†	1.12 (1.03–1.22)*	1.05 (0.99–1.11)

Relative hazard ratios (95% confidence intervals) for each 10-mm Hg increase in systolic pressure and 5-mm Hg increase in diastolic pressure with adjustments applied for baseline characteristics including gender, age, body mass index, presence of diabetes mellitus, history of cardiovascular events, and smoking status, along with further adjustment for clinic blood pressure measurement.

Cardiac fatal endpoint includes heart failure, myocardial infarction, and sudden death.

Significance of the hazard ratios: * $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$.

TABLE 3. Relative Hazard Ratios Independently Associated With Daytime and Nighttime Systolic and Diastolic Ambulatory Blood Pressure

Model		All-Cause Mortality	Cardiovascular	Stroke	Cardiac
n of events		646	389	103	254
Model 1	Daytime SBP	0.95 (0.90–1.00)	0.96 (0.90–1.04)	0.95 (0.83–1.08)	1.01 (0.93–1.10)
	Nighttime SBP	1.18 (1.12–1.24)‡	1.23 (1.15–1.31)‡	1.34 (1.19–1.50)‡	1.15 (1.06–1.25)‡
Model 2	Daytime DBP	0.95 (0.92–0.99)*	0.96 (0.91–1.01)	0.98 (0.89–1.08)	0.97 (0.91–1.04)
	Nighttime DBP	1.11 (1.06–1.15)‡	1.12 (1.06–1.17)†	1.16 (1.06–1.27)†	1.08 (1.01–1.15)*
Model 3	Daytime SBP	1.10 (1.04–1.16)‡	1.19 (1.11–1.27)‡	1.20 (1.06–1.36)†	1.18 (1.10–1.28)‡
	Daytime DBP	0.97 (0.94–1.02)	0.95 (0.90–1.00)*	0.98 (0.89–1.09)	0.94 (0.89–1.00)
Model 4	Nighttime SBP	1.16 (1.10–1.22)‡	1.29 (1.21–1.38)‡	1.37 (1.21–1.55)‡	1.24 (1.14–1.35)‡
	Nighttime DBP	0.98 (0.94–1.03)	0.93 (0.88–0.99)*	0.94 (0.85–1.04)	0.93 (0.87–1.00)*

Model 1=daytime SBP, nighttime SBP, gender, age, body mass index, presence of diabetes mellitus, history of cardiovascular events, and current smoking status.

Model 2=daytime DBP, nighttime DBP, gender, age, body mass index, presence of diabetes mellitus, history of cardiovascular events, and current smoking status.

Model 3=daytime SBP, daytime DBP, gender, age, body mass index, presence of diabetes mellitus, history of cardiovascular events, and current smoking status.

Model 4=nighttime SBP, nighttime DBP, gender, age, body mass index, presence of diabetes mellitus, history of cardiovascular events, and current smoking status.

Relative hazard ratios (95% confidence intervals) for each 10-mm Hg increase in systolic pressure and 5-mm Hg increase in diastolic pressure. Hazard ratios were also adjusted for baseline characteristics including gender, age, body mass index, presence of diabetes mellitus, history of cardiovascular events, and current smoking status.

Significance of the hazard ratios: * $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$.

Figure 2 demonstrates the absolute 5-year cardiovascular risk, after adjustment for other covariates, in relation to baseline ABPM and CBPM.

Discussion

To our knowledge, this single-center study is the largest to date to demonstrate that ABPM is a stronger predictor of cardiovascular mortality than CBPM, and that nighttime is superior to daytime ABPM in predicting cardiovascular mortality in a Western hypertensive population who were not using antihypertensive medication at the time of blood

pressure measurement. A possible limitation to our study might have been the omission of deaths because of patients leaving the jurisdiction or changing names as a consequence of marriage. However, given the mean age of the patients, these occurrences are not likely to have been significant. We did not have sufficient data on antihypertensive medication during follow-up to adjust for the potential effect of treatment on outcome.

The classic study by Perloff et al in 1983 was the first to demonstrate that ABPM was a better predictor of morbidity than CBPM in hypertensive patients.⁵ Since then, a number of

TABLE 4. Description of Fully Adjusted Models With All Relative Hazard Ratios Included for Cardiovascular Mortality

Parameter	SBP Daytime	SBP Nighttime	SBP 24-Hour	DBP Daytime	DBP Nighttime	DBP 24-Hour
ABPM	1.12 (1.06–1.18)‡	1.21 (1.15–1.27)‡	1.19 (1.13–1.27)‡	1.03 (0.99–1.07)	1.09 (1.04–1.13)‡	1.09 (1.02–1.11)†
Clinic SBP	1.02 (0.98–1.06)	1.01 (0.97–1.04)	1.00 (0.96–1.04)			
Clinic DBP				1.02 (0.99–1.06)	1.01 (0.97–1.04)	1.01 (0.98–1.05)
Gender	1.99 (1.62–2.44)‡	2.01 (1.64–2.47)‡	1.99 (1.62–2.45)‡	1.93 (1.57–2.37)‡	1.83 (1.49–2.25)‡	1.87 (1.52–2.30)‡
Age	1.10 (1.09–1.11)‡	1.09 (1.08–1.10)‡	1.09 (1.08–1.10)‡	1.10 (1.09–1.11)‡	1.10 (1.09–1.11)‡	1.10 (1.09–1.11)‡
Body mass index	0.97 (0.95–1.00)	0.98 (0.95–1.00)	0.97 (0.95–1.00)	0.97 (0.95–1.00)	0.98 (0.95–1.00)	0.98 (0.95–1.00)
Diabetes mellitus	1.33 (0.91–1.94)	1.30 (0.89–1.89)	1.31 (0.90–1.91)	1.37 (0.94–1.99)	1.38 (0.95–2.02)	1.37 (0.94–2.00)
History of cardiovascular disease	1.67 (1.31–2.13)‡	1.63 (1.28–2.07)‡	1.66 (1.31–2.12)‡	1.60 (1.26–2.04)‡	1.60 (1.25–2.03)‡	1.61 (1.26–2.05)‡
Smoking status	1.87 (1.48–2.37)‡	1.84 (1.46–2.32)‡	1.81 (1.43–2.29)‡	1.95 (1.54–2.46)‡	1.93 (1.53–2.43)‡	1.92 (1.52–2.42)‡

ABPM indicates ambulatory blood pressure measurement.

All models include ABPM, CBPM, gender, age, body mass index, presence of diabetes mellitus, history of cardiovascular events, and smoking status.

Relative hazard ratios (95 % confidence intervals) for each 10-mm Hg increase in SBP and 5-mm Hg increase in DBP, male gender, 1 year increase in age, 1 kg/m² increase in body mass index, the presence of diabetes mellitus, a positive history of cardiovascular events, and positive smoking status.

Significance of the hazard ratios: * $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$.

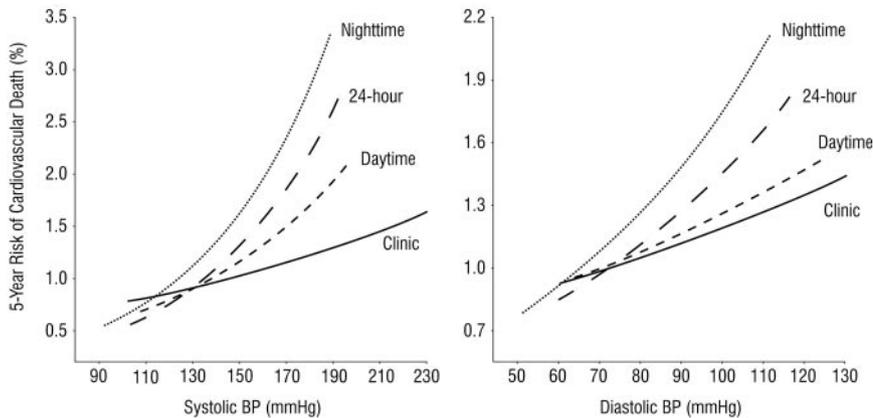


Figure 2. Adjusted 5-year risk of cardiovascular death in the study cohort of 5292 patients for CBPM and ABPM. Using multiple Cox regression, the relative risk was calculated with adjustment for baseline characteristics including gender, age, presence of diabetes mellitus, history of cardiovascular events, and smoking status. The 5-year risks are expressed as number of deaths per 100 subjects.

studies have confirmed that ABPM is a stronger predictor of outcome than CBPM.⁵⁻¹³ A study in Spanish patients with refractory hypertension showed that patients with daytime ABPM in the lowest tertile (DBP <88 mm Hg) had a significantly lower rate of cardiovascular events over 4-year follow-up, irrespective of clinic pressures.⁶ In 808 patients followed-up for 4.4 years in the placebo-controlled Syst-Eur trial, cardiovascular risk was <10% between the lowest and highest CBPMs, whereas the difference was ≈50% between the lowest and highest ABPM recordings.⁷ A prospective Japanese study in 1542 patients showed that ABPM was a better predictor of mortality than screening blood pressure,⁸ and a further analysis has shown that ABPM is also a stronger predictor of stroke.⁹ In the Office versus Ambulatory blood pressure (OvA) study, both DBP and SBP ABPM predicted cardiovascular death in treated hypertensive patients after adjustment for CBPM.¹⁰ The results of our single-center study in a large population confirm the superiority of ABPM over CBPM in predicting cardiovascular mortality.

The dipper/nondipper classification of nocturnal blood pressure was first introduced in 1988 when a retrospective analysis suggested that nondipping hypertensive patients had a higher risk of stroke than the majority of patients with a dipping pattern.¹⁴ Since then, there have been many studies evaluating morbidity and dipping status, and although there has been some disagreement in the literature, on balance, most large-scale prospective studies support the concept that a diminished nocturnal blood pressure decline is associated with a worse prognosis.^{17,18} Moreover, 3 longitudinal studies conducted in patients with hypertension have shown that a diminished nocturnal decline in blood pressure predicts cardiovascular events.^{7,19,20} The first prospective study to demonstrate that a diminished nocturnal decline in blood pressure is a risk factor for cardiovascular mortality, independent of the overall blood pressure load during a 24-hour period, was the Ohasama study in a Japanese population, which showed that, on average, each 5% decrease in the decline in nocturnal blood pressure was associated with ≈20% greater risk of cardiovascular mortality. Importantly, this association was observed not only in hypertensive individuals but also in normotensive individuals.²¹ The results of our study confirm that the important Japanese finding of a higher nocturnal blood pressure being a predictor of mortality is also true for a Western population. In our study, for each 10-mm Hg

increase in mean nighttime SBP, the mortality risk increased by 21%.

The findings of our study have clinical relevance. Despite the abundance of evidence that ABPM is superior to CBPM, current guidelines generally recommend ABPM only for selected circumstances, such as the exclusion of white-coat hypertension. Our findings support the recommendation that ABPM is indispensable to the management of hypertension and that all patients with elevated CBPM should have an ABPM.³ Moreover, the emerging importance of nocturnal blood pressure as an independent risk for cardiovascular outcome strengthens the call for 24-hour measurement of blood pressure. Future guidelines will have to address these issues.

Perspectives

This study has important clinical implications. First, we have shown in a large cohort of untreated hypertensive patients that increasing levels of CBPM provide only a modest increase in cardiovascular risk compared with nighttime or 24-hour ABPM. Second, because patients with elevated ABPM are at greater risk, irrespective of CBPM, the ready availability of ABPM in clinical practice would permit treatment to be targeted at the patients likely to benefit most. Third, the strong predictive value of nighttime blood pressure makes it important in clinical practice to direct more attention to nocturnal blood pressure, and this observation raises an interesting hypothesis for a prospective randomized clinical trial to show if treatment based on nighttime pressure will improve outcome.

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