Journal of the American College of Cardiology Vol. 58, No. 11, 2011

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.04.043

Hypertension

Decreasing Sleep-Time Blood Pressure Determined by Ambulatory Monitoring Reduces Cardiovascular Risk

Ramón C. Hermida, PHD, Diana E. Ayala, MD, MPH, PHD, Artemio Mojón, PHD, José R. Fernández, PHD

Vigo, Spain

Objectives We investigated whether reduced cardiovascular risk is more related to the progressive decrease of asleep or awake blood pressure.

Background Independent studies have concluded that elevated sleep-time blood pressure is a better predictor of cardiovascular risk than awake or 24-h blood pressure means. However, the impact on cardiovascular risk of changes in these ambulatory blood pressure characteristics has not been properly investigated.

Methods We prospectively studied 3,344 subjects (1,718 men and 1,626 women), 52.6 ± 14.5 years of age, during a median follow-up of 5.6 years. Those with hypertension at baseline were randomized to ingest all their prescribed hypertension medications upon awakening or ≥1 of them at bedtime. Blood pressure was measured for 48 h at baseline and again annually or more frequently (quarterly) if treatment adjustment was required.

Results With data collected at baseline, when asleep blood pressure was adjusted by awake mean, only the former was a significant predictor of outcome in a Cox proportional hazards model also adjusted for sex, age, and diabetes. Analyses of changes in ambulatory blood pressure during follow-up revealed a 17% reduction in cardiovascular risk for each 5-mm Hg decrease in asleep systolic blood pressure mean ($p < 0.001$), independently of changes in any other ambulatory blood pressure parameter.

Conclusions The sleep-time blood pressure mean is the most significant prognostic marker of cardiovascular morbidity and mortality. Most importantly, the progressive decrease in asleep blood pressure, a novel therapeutic target that requires proper patient evaluation by ambulatory monitoring, was the most significant predictor of event-free survival. (Prognostic Value of Ambulatory Blood Pressure Monitoring in the Prediction of Cardiovascular Events and Effects of Chronotherapy in Relation to Risk [the MAPEC Study]; NCT00295542) (J Am Coll Cardiol 2011; 58:1165–73) © 2011 by the American College of Cardiology Foundation

During the past 2 decades, specific features of the 24-h blood pressure (BP) pattern determined by ambulatory blood pressure monitoring (ABPM) have been assessed as potential sources of injury to target tissues and triggers of cardiac and cerebrovascular events. For instance, the extent of the BP surge upon wakening has been associated with increased cardiovascular disease (CVD) morbidity and mortality in some but not all studies (1,2). A growing number of studies (3–6) have consistently shown an association between blunted asleep BP decline and increased incidence of fatal and nonfatal CVD events. Independent prospective studies have also concluded that the asleep BP mean is a better predictor of CVD risk than the awake or 24-h BP means (5–10).

See page 1174

A limitation of all the previous studies on the prognostic value of ABPM is their reliance on a single baseline profile from each participant at the time of inclusion, without accounting for possible changes in the level and pattern of ambulatory BP during the years of follow-up, mainly associated with hypertension therapy, aging, and developing target organ damage and/or concomitant diseases. Thus, the potential reduction in CVD risk associated with modifying prognostic ABPM parameters (i.e., specifically reducing asleep BP) (9) is still a matter of debate. The MAPEC (Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares [i.e.,

From the Bioengineering and Chronobiology Laboratories, University of Vigo, Vigo, Spain. This independent investigator-promoted research was supported by unrestricted grants from Ministerio de Ciencia e Innovación (SAF2006-6254-FEDER; SAF2009-7028-FEDER); Consellería de Presidencia, Relacións Institucionais e Administración Pública, Secretaría Xeral de Investigación e Desenvolvemento, Xunta de Galicia (PGIDIT03-PXIB-32201PR); Consellería de Economía e Industria, Dirección Xeral de Investigación e Desenvolvemento, Xunta de Galicia (INCITE07-PXI-322003ES; INCITE08-E1R-322063ES; INCITE09-E2R-322099ES; 09CSA018322PR); and Vicerrectorado de Investigación, University of Vigo. All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received January 14, 2011; revised manuscript received March 28, 2011, accepted April 21, 2011.

JACC Vol. 58, No. 11, 2011
September 6, 2011:1165–73

Abbreviations and Acronyms

ABPM = ambulatory blood pressure monitoring
BP = blood pressure
CI = confidence interval
CVD = cardiovascular disease
DBP = diastolic blood pressure
HR = hazard ratio
SBP = systolic blood pressure

Ambulatory Blood Pressure Monitoring for Prediction of Cardiovascular Events]) study was specifically designed to investigate prospectively whether specific changes in the circadian BP profile results in reduced CVD risk (11). In particular, we investigated whether changes of ambulatory BP characteristics during follow-up might be related to increased survival in subjects who were systematically evaluated by periodic—at least annually—ABPM.

Methods

Inclusion and exclusion criteria. An extended version of Methods is available in the Online Appendix. In summary, the sample represents a population of Spanish subjects of both sexes ≥18 years of age. Inclusion criteria required subjects to be normotensive, untreated hypertensive, or resistant to treatment (uncontrolled BP according to the ABPM threshold values outlined in the following text while compliant to 3 optimally dosed hypertension medications of different classes, including a diuretic unless contraindicated or intolerant or any subject treated with >3 hypertension medications [12]). Exclusion criteria were pregnancy, history of drug/alcohol abuse, night/shift-work employment, diagnosis of acquired immunodeficiency syndrome, type 1 diabetes, secondary hypertension, CVD disorders (unstable angina pectoris, heart failure, life-threatening arrhythmia, kidney failure, and grade III to IV retinopathy), intolerance to ABPM, and inability to communicate and comply with all of the study requirements. Participants represent a consecutive series of persons fulfilling these exclusion/inclusion criteria, recruited among those referred to the hospital for ABPM evaluation, mainly to confirm/discard the diagnosis of hypertension suspected by daytime clinic cuff BP measurement in untreated subjects, or to evaluate BP control in already treated patients. Additional reasons to request ABPM included, among several others, impaired fasting glucose, metabolic syndrome, diabetes, chronic kidney disease, previous complications in pregnancy, suspicion of sleep disorders, and age over 60 years. This prospective single-center study (registered online with identifier code NCT00295542) was approved by the state Ethics Committee of Clinical Research. All participants gave written informed consent.

Subjects and diagnostic criteria. Between 2000 and 2007, we recruited 3,612 subjects fulfilling the inclusion/exclusion criteria. Among these, 3,344 (1,718 men/1,626 women, age 52.6 ± 14.5 years) provided all required information for the study. The remaining 268 subjects were eliminated due to inadequate ABPM sampling at baseline and their lack of consent for additional ABPM evaluations. We established a priori a minimum time of follow-up of 6 months for each subject and a minimum median follow-up of 5 years (11). Diagnosis of hypertension (in untreated subjects) was based on accepted ABPM criteria—an awake BP mean of ≥135/85 mm Hg for systolic blood pressure (SBP)/diastolic blood pressure (DBP) and/or an asleep BP mean ≥120/70 mm Hg (13). At the time of recruitment, 734 subjects were normotensive and 2,610 were hypertensive (776 with resistant hypertension) according to these ABPM criteria.

Study design. Patients with untreated hypertension were randomly assigned to 1 of 2 monotherapy treatment-time groups, either upon awakening in the morning or at bedtime at night, as extensively described elsewhere (14). Randomization of subjects to treatment-time (awakening or bedtime) was done separately for each allowed individual hypertension medication (valsartan, telmisartan, olmesartan, ramipril, spirapril, amlodipine, nifedipine GITS, nebivolol, torasemide). This ensured that the proportion of subjects treated with each medication was similar across the 2 treatment times. If subjects were uncontrolled based on ABPM criteria after 3 months of monotherapy, additional medications could be added in keeping with current clinical practice.

Participants with resistant hypertension were randomized to either: 1) modify the nature of their treatment, exchanging 1 of their medications with a new 1, thus without modifying the total number of medications but retaining the upon-waking ingestion time for all medications; or 2) shift the ingestion-time of 1 BP-lowering medication to bedtime (14). After this first randomization, investigators were allowed to exchange additional medications for others of different classes (keeping always the upon-waking ingestion time of all medications) in the first randomized group; progressively shift additional medications to bedtime in the second randomized group; or prescribe additional medications in either group. Changes in therapeutic scheme during follow-up in uncontrolled subjects (those with ambulatory BP above the thresholds provided in the preceding text) were always based on the results from periodic evaluation by ABPM (see the following text). The protocol did not allow dividing any prescribed medication in 2 or more doses. Thus, patients randomized to the bedtime-treatment group were never ingesting in the morning any of the medications ingested at bedtime.

Blood samples were obtained the same week each 48-h ABPM session was initiated. Participants reported to the hospital between 8:00 AM and 9:00 AM, after overnight fasting, for blood withdrawal from an antecubital vein. Samples were analyzed with routine automatic techniques in the hospital laboratory. Just before commencing ABPM, 6 clinic BP measurements were always obtained by the same investigator with a validated automatic oscillometric device (HEM-705IT, Omron Health Care, Inc., Vernon Hills, Illinois) after the subject had rested in a seated position for ≥10 min.

ABPM assessment. At inclusion as well as at each scheduled visit for ABPM during follow-up (see the following text), the SBP and DBP of each subject were automatically measured every 20 min between 7:00 AM and 11:00 PM and every 30 min during the night for 48 consecutive hours with a calibrated SpaceLabs 90207 ABPM monitor (SpaceLabs Inc., Issaquah, Washington). Participants were instructed to do their usual activities with minimal restrictions but to adhere to a similar schedule during the 2 days of ABPM and avoid daytime napping. During monitoring, subjects maintained a diary listing the times of retiring to bed at night and awakening in the morning. The BP series were considered invalid for analysis if ≥30% of the measurements were missing, if data were lacking for an interval of >2 h, or if the nighttime sleep period was <6 or >12 h during ABPM.

Actigraphy. All subjects wore an actigraph (Mini-Motion-Logger, Ambulatory Monitoring, Inc., Ardsley, New York) on the dominant wrist to monitor physical activity every min during 48-h ABPM. The actigraphy data, combined with patient diaries, were used to corroborate the absence of daytime napping and define the commencement and termination of the daytime awake and nocturnal asleep spans so the respective BP means for each subject could be accurately determined.

Follow-up. The same evaluation procedure described in the preceding text—including conventional clinic BP measurement, 48-h ABPM and wrist activity monitoring, and blood sampling—was scheduled annually in all participants or more frequently (after 3 months of any change in therapy in treated subjects) if the therapeutic scheme was modified to improve ambulatory BP control. Investigators blinded to the timed-treatment scheme of each participant (thus excluding those performing clinic evaluation at each visit to the hospital, clinic and ambulatory BP measurement, and/or statistical analyses) reviewed at least annually the complete clinical records of all enrolled subjects to assess CVD morbidity and mortality. Registered events included: death from all causes, myocardial infarction, angina pectoris, coronary revascularization, heart failure, acute arterial occlusion of lower extremities, thrombotic occlusion of the retinal artery, hemorrhagic stroke, ischemic stroke, and transient ischemic attack.

Statistical methods. To correct for measurement errors and outliers, ABPM profiles were edited according to conventional criteria. Thus, SBP readings >250 or <70 mm Hg, DBP >150 or <40 mm Hg, and pulse pressure (difference between SBP and DBP) >150 or <20 mm Hg were automatically discarded. The sleep-time relative BP decline (an index of BP dipping), defined as the percentage decrease in mean BP during nocturnal sleep relative to the mean BP during daytime activity, was calculated as: ([awake BP mean − asleep BP mean]/awake BP mean) × 100, with all the data sampled by 48-h ABPM. For comparative purposes, a subject was defined as dipper if the sleep-time relative SBP decline was ≥10% and as nondipper otherwise. The morning BP surge was calculated as the difference between the average BP during the first 2 h after wake-up time and the hourly average centered on the lowest nocturnal sleep-time BP reading (1). The ambulatory arterial stiffness index was calculated as 1 minus the regression slope of DBP on SBP from ABPM (15).

The CVD risk was evaluated based on the: 1) baseline ABPM evaluation from every participant; and 2) changes in any tested parameter/participant during follow-up. The primary outcomes study endpoint was total CVD morbidity and mortality, which included all the events listed in the preceding text. We also used, as an additional primary endpoint, major CVD events (i.e., a composite of CVD deaths, myocardial infarction, and stroke). Demographic and clinical characteristics were compared among groups of subjects experiencing or not experiencing an event by *t* test (continuous variables) or nonparametric chi-square test (proportions). The Cox proportional hazards model, with adjustment for significant confounding variables, was used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for events associated with each tested potential prognostic BP parameter at baseline; these HRs were standardized by calculating them for 1-SD increments for each BP parameter. By contrast, the prognostic value of BP reduction during follow-up was evaluated by entering the change in the tested ABPM parameter as a time-dependent covariate in the Cox regression analysis. For survival analysis, follow-up was established as either the time to the first documented event or the time to the last evaluation in event-free subjects. Statistical analyses were performed with SPSS software (version 13.0 for Macintosh, SPSS, Inc., Chicago, Illinois) and KaleidaGraph (version 3.6.4, Synergy Software, Reading, Pennsylvania).

Results

Demographic characteristics and laboratory variables in event and nonevent subjects. During the median follow-up period of 5.6 years (range 0.5 to 8.6 years), we documented 331 first events (58 deaths, 45 myocardial infarctions, 51 angina pectoris, 35 coronary revascularizations, 44 cerebrovascular events, 46 heart failures, 21 cases of aortoiliac occlusive disease, and 31 thrombotic occlusions of the retinal artery). Event-subjects were: predominantly men; of older age; and who at baseline were likely to have type 2 diabetes, obstructive sleep apnea, metabolic syndrome, and/or abdominal obesity (Table 1). In addition, at baseline they had higher clinic BP (including pulse pressure, even after correcting for age), glucose, creatinine, uric acid, triglycerides, plasma fibrinogen, and erythrocyte sedimentation rate but lower estimated glomerular filtration rate (Table 1). All differences between groups reported in Table 1 with a p value <0.002 stand as significant after correcting for multiple testing.

JACC Vol. 58, No. 11, 2011
September 6, 2011:1165–73

Table 1 Baseline Characteristics of Subjects Investigated

Variable*	No Event	Event	p Value Between Groups
Demographic characteristics			
Patients	3,013	331	
Male	49.6%	70.0%	<0.001
Diabetes	16.6%	32.3%	<0.001
Obstructive sleep apnea	8.6%	16.3%	<0.001
Metabolic syndrome	50.4%	70.7%	<0.001
Cigarette smoking	14.8%	12.1%	0.177
Obesity	41.6%	48.3%	0.019
Anthropometric variables and office BP			
Age, yrs	51.4 ± 14.2	63.5 ± 11.7	<0.001
Height, cm	162.6 ± 10.0	160.9 ± 9.2	0.002
Weight, kg	78.5 ± 15.6	78.6 ± 15.8	0.904
BMI, kg/m^2	29.7 ± 5.1	30.3 ± 5.1	0.033
Waist, cm	95.4 ± 12.5	99.3 ± 13.3	<0.001
Clinic SBP, mm Hg†	149.7 ± 18.9	161.3 ± 25.2	<0.001
Clinic DBP, mm Hg†	85.8 ± 11.1	86.8 ± 13.6	0.152
Clinic PP, mm Hg†	63.9 ± 13.3	74.5 ± 18.4	<0.001
Clinic HR, beats/min†	74.8 ± 12.2	72.7 ± 13.1	0.002
Clinical laboratory test values			
Glucose, mg/dl	106.0 ± 31.9	120.4 ± 44.9	<0.001
Creatinine, mg/dl	0.95 ± 0.23	1.07 ± 0.32	<0.001
Uric acid, mg/dl	5.7 ± 1.6	6.3 ± 1.9	<0.001
Total cholesterol, mg/dl	210.0 ± 40.1	211.2 ± 43.2	0.635
Triglycerides, mg/dl	115.1 ± 79.1	126.5 ± 65.6	0.015
HDL cholesterol, mg/dl	48.2 ± 15.6	46.3 ± 14.2	0.046
LDL cholesterol, mg/dl	138.3 ± 34.4	141.2 ± 34.8	0.169
Fibrinogen, mg/dl	319.7 ± 78.7	348.0 ± 86.6	<0.001
Erythrocyte sedimentation rate, mm	13.7 ± 11.4	20.0 ± 20.8	<0.001
Glomerular filtration rate, ml/min/1.73 m^2‡	80.1 ± 17.9	71.7 ± 18.5	<0.001
Ambulatory BP			
Awake SBP mean, mm Hg	130.5 ± 14.0	139.2 ± 18.2	<0.001
Asleep SBP mean, mm Hg	117.3 ± 14.9	133.5 ± 22.3	<0.001
48-h SBP mean, mm Hg	126.4 ± 13.7	137.2 ± 18.5	<0.001
Sleep-time relative SBP decline, %	10.1 ± 6.9	4.2 ± 10.0	<0.001
Awake DBP mean, mm Hg	81.1 ± 10.6	79.5 ± 12.5	0.012
Asleep DBP mean, mm Hg	68.5 ± 10.2	71.7 ± 11.8	<0.001
48-h DBP mean, mm Hg	77.1 ± 10.2	76.9 ± 11.7	0.680
Sleep-time relative DBP decline, %	15.3 ± 7.7	9.4 ± 10.4	<0.001
Awake PP mean, mm Hg	49.4 ± 10.1	59.7 ± 14.7	<0.001
Asleep PP mean, mm Hg	48.8 ± 10.3	61.8 ± 17.6	<0.001
48-h PP mean, mm Hg	49.3 ± 10.0	60.3 ± 15.3	<0.001
Sleep-time relative PP decline, %	0.8 ± 9.1	−3.5 ± 12.8	<0.001
Nondipper	46.0%	72.5%	<0.001

Values are shown as n, %, or mean ± SD. *Metabolic syndrome: National Cholesterol Education Program Adult Treatment Panel III revised definition (16). Obesity: body mass index (BMI) ≥30 kg/m^2. The sleep-time relative blood pressure (BP) decline, an index of BP dipping, is defined as the percentage decline in mean BP during nocturnal sleep relative to the mean BP during daytime activity and calculated as: ([awake BP mean − asleep BP mean]/awake BP mean) × 100. Nondipper: patients with sleep-time relative systolic blood pressure (SBP) decline <10%, with data sampled by ambulatory blood pressure monitoring (ABPM) for 48 consecutive hours. †Values correspond to the average of 6 conventional BP measurements obtained for each subject at the clinic before starting 48-h ABPM. ‡Glomerular filtration rate was estimated with the Chronic Kidney Disease Epidemiology Collaboration equation (17).

DBP = diastolic blood pressure; HDL = high-density lipoprotein; HR = heart rate; LDL = low-density lipoprotein; PP = pulse pressure.

Baseline clinic and ambulatory BP as predictors of CVD risk. At baseline, the 48-h mean of SBP but not of DBP was significantly higher among event-subjects (Table 1). The largest difference between groups was in asleep SBP mean. The sleep-time relative BP decline was significantly lower ($p < 0.001$), and the prevalence of nondipping was significantly higher (73% vs. 46%) among event-subjects ($p < 0.001$) (Table 1).

Table 2 shows the HR of CVD events estimated by the Cox proportional hazards model, calculated on the basis of the first ABPM profile from each subject. Adjustments were applied for sex, age, and diabetes (left column), because

Table 2 HRs of Total and Major CVD Events Associated With Baseline Clinic and Ambulatory BP

Parameters	Total CVD Events		Major CVD Events	
	Adjusted HR	Further Adjustment by Clinic BP	Adjusted HR	Further Adjustment by Clinic BP
SBP				
Clinic	1.35 (1.22–1.49)*	—	1.68 (1.41–2.00)*	—
Awake mean	1.35 (1.23–1.49)*	1.23 (1.09–1.38)†	1.61 (1.39–1.88)*	1.36 (1.12–1.65)†
Asleep mean	1.52 (1.40–1.66)*	1.48 (1.33–1.64)*	1.84 (1.60–2.11)*	1.69 (1.43–2.01)*
48-h mean	1.43 (1.31–1.57)*	1.35 (1.20–1.51)*	1.72 (1.49–1.99)*	1.52 (1.26–1.84)*
Sleep-time relative decline	0.72 (0.66–0.79)*	0.74 (0.68–0.81)*	0.65 (0.56–0.75)*	0.65 (0.56–0.77)*
SD, awake	1.29 (1.18–1.42)*	1.21 (1.09–1.33)*	1.51 (1.30–1.75)*	1.36 (1.15–1.61)*
SD, asleep	1.22 (1.11–1.34)*	1.12 (1.02–1.25)‡	1.43 (1.22–1.67)*	1.26 (1.06–1.49)†
SD, 48 h	1.24 (1.13–1.36)*	1.14 (1.03–1.27)‡	1.41 (1.22–1.64)*	1.27 (1.06–1.51)†
Morning surge	0.79 (0.72–0.86)*	0.79 (0.73–0.87)*	0.75 (0.63–0.89)†	0.76 (0.65–0.89)†
DBP				
Clinic	1.12 (1.01–1.25)‡	—	1.35 (1.12–1.64)†	—
Awake mean	1.07 (0.95–1.20)	0.98 (0.84–1.14)	1.37 (1.11–1.69)†	1.19 (0.91–1.56)
Asleep mean	1.30 (1.17–1.44)*	1.31 (1.16–1.48)*	1.65 (1.38–1.98)*	1.61 (1.31–1.99)*
48-h mean	1.15 (1.02–1.29)‡	1.10 (0.95–1.28)	1.50 (1.23–1.84)*	1.40 (1.08–1.81)†
Sleep-time relative decline	0.73 (0.66–0.80)*	0.72 (0.65–0.79)*	0.65 (0.54–0.77)*	0.63 (0.53–0.76)*
SD, awake	1.17 (1.06–1.30)†	1.15 (1.04–1.28)†	1.44 (1.23–1.69)*	1.37 (1.16–1.63)*
SD, asleep	1.08 (0.98–1.19)	1.06 (0.96–1.17)	1.19 (1.01–1.41)‡	1.14 (0.96–1.35)
SD, 48 h	1.05 (0.95–1.17)	1.02 (0.91–1.14)	1.20 (0.99–1.44)	1.11 (0.92–1.35)
Morning surge	0.75 (0.68–0.83)*	0.74 (0.67–0.82)*	0.78 (0.64–0.04)†	0.76 (0.63–0.91)†
PP				
Clinic	1.35 (1.23–1.48)*	—	1.61 (1.37–1.89)*	—
Awake mean	1.38 (1.26–1.51)*	1.26 (1.11–1.44)*	1.50 (1.29–1.73)*	1.21 (0.98–1.50)
Asleep mean	1.44 (1.34–1.56)*	1.43 (1.27–1.61)*	1.67 (1.47–1.91)*	1.56 (1.28–1.90)*
48-h mean	1.42 (1.31–1.55)*	1.36 (1.19–1.54)*	1.58 (1.37–1.82)*	1.36 (1.10–1.68)†
Sleep-time relative decline	0.79 (0.72–0.86)*	0.80 (0.73–0.88)*	0.70 (0.61–0.81)*	0.69 (0.60–0.80)*
SD, awake	1.31 (1.19–1.45)*	1.18 (1.05–1.32)†	1.50 (1.27–1.77)*	1.28 (1.05–1.56)‡
SD, asleep	1.26 (1.15–1.38)*	1.16 (1.05–1.28)†	1.46 (1.26–1.69)*	1.29 (1.10–1.52)†
SD, 48 h	1.37 (1.26–1.50)*	1.26 (1.13–1.40)*	1.65 (1.42–1.91)*	1.47 (1.23–1.76)*
Morning surge	0.89 (0.81–0.98)‡	0.89 (0.81–0.97)†	0.82 (0.70–0.97)‡	0.81 (0.69–0.94)†
AASI	1.38 (1.22–1.57)*	1.31 (1.16–1.49)*	1.45 (1.20–1.87)*	1.36 (1.07–1.71)‡

Hazard ratio (HR) (95% confidence interval [CI]) was standardized by calculating for 1-SD increments. Adjustments were applied for the only consistently significant influential characteristics (sex, age, and diabetes). The sleep-time relative BP decline, an index of BP dipping, is defined as the percentage decline in BP during nocturnal sleep relative to the mean BP during daytime activity and calculated as: ([awake BP mean − asleep BP mean]/awake BP mean) × 100. The morning BP surge was calculated as the difference between the average BP during the first 2 h after wake-up time and the hourly average centered on the lowest BP reading recorded during nocturnal sleep. The ambulatory arterial stiffness index (AASI) was calculated as 1 minus the regression slope of DBP on SBP from ABPM. *$p < 0.001$; †$p < 0.01$; ‡$p < 0.05$.

CVD = cardiovascular disease; other abbreviations as in Table 1.

these influential factors were the only ones—among all the demographic and laboratory variables shown in Table 1—that were consistently significant in all tested models. Results documented increased CVD risk associated with older age (HR: 1.07, 95% CI: 1.06 to 1.08, $p < 0.001$, for each additional year of age), male sex (HR: 2.44, 95% CI: 1.93 to 3.08, $p < 0.001$, compared with women), and presence of diabetes (HR: 1.53, 95% CI: 1.21 to 1.94, $p < 0.001$, compared with no diabetes). Results remained mainly unchanged when the Cox proportional hazards models were further adjusted by baseline clinic BP (Table 2, right column); clinic BP was not a significant predictor of outcome in the models including asleep or 48-h BP mean. Moreover, a greater morning BP surge, calculated as defined (1), was significantly associated with lower CVD risk (Table 2). Finally, when asleep and awake SBP mean were used jointly in the same Cox regression model, only the former was a significant predictor of outcome. Most important, the asleep BP mean was also a most significant predictor of major CVD events (HR: 1.84, 95% CI: 1.60 to 2.11 for 1-SD elevation in asleep SBP mean, $p < 0.001$) (Table 2, right columns).

Changes in clinic and ambulatory BP during follow-up as predictors of CVD risk. Table 3 (left column) shows the results from time-dependent Cox regression analysis (adjusted by age, sex, diabetes, baseline BP, and number of hypertension medications used for treatment) for total CVD events. The progressive decrease in awake, asleep, and 48-h BP mean was associated with significantly increased survival. Changes in SD, morning BP surge, and ambulatory arterial stiffness index during follow-up were mainly not significantly associated with reduced/increased risk. The decrease in asleep BP mean during follow-up was also a significant predictor of survival from major events (HR: 0.81, 95% CI: 0.73 to 0.91 for SBP; HR: 0.68, 95% CI: 0.56 to 0.82 for DBP; $p < 0.001$) (Table 3, right column). When

Table 3 Adjusted HR of Total and Major CVD Events Associated With Reduction in Clinic and Ambulatory BP During Follow-Up

Parameters	Total Events	Major Events	Total Events	Major Events
SBP				
Clinic BP	0.93 (0.89–0.97)*	0.93 (0.85–1.02)	0.73 (0.63–0.86)†	0.78 (0.57–1.06)
Awake mean	0.86 (0.81–0.91)†	0.85 (0.75–0.95)*	0.66 (0.58–0.78)†	0.65 (0.49–0.88)*
Asleep mean	0.83 (0.78–0.87)†	0.81 (0.73–0.91)†	0.61 (0.53–0.71)†	0.60 (0.45–0.80)†
48-h mean	0.84 (0.79–0.90)†	0.83 (0.74–0.92)*	0.63 (0.54–0.73)†	0.62 (0.46–0.82)*
Sleep-time relative decline	0.75 (0.67–0.84)†	0.71 (0.57–0.88)†	0.67 (0.57–0.79)†	0.62 (0.46–0.83)†
SD, awake	0.98 (0.94–1.03)	1.00 (0.93–1.09)	0.94 (0.80–1.09)	1.03 (0.78–1.35)
SD, asleep	0.96 (0.92–1.00)‡	0.97 (0.89–1.05)	0.84 (0.72–0.98)‡	0.87 (0.64–1.18)
SD, 48 h	0.99 (0.94–1.04)	1.03 (0.95–1.13)	0.97 (0.82–1.14)	1.12 (0.82–1.52)
Morning surge	0.99 (0.98–1.01)	1.00 (0.98–1.03)	0.98 (0.83–1.17)	1.13 (0.80–1.60)
DBP				
Clinic BP	0.85 (0.78–0.92)†	0.86 (0.73–1.02)	0.69 (0.58–0.82)†	0.73 (0.52–1.03)
Awake mean	0.79 (0.72–0.87)†	0.76 (0.63–0.93)*	0.65 (0.54–0.77)†	0.64 (0.46–0.89)*
Asleep mean	0.71 (0.65–0.77)†	0.68 (0.56–0.82)†	0.54 (0.46–0.63)†	0.51 (0.37–0.72)†
48-h mean	0.73 (0.67–0.80)†	0.70 (0.57–0.87)*	0.58 (0.49–0.68)†	0.58 (0.42–0.80)*
Sleep-time relative decline	0.76 (0.69–0.84)†	0.77 (0.63–0.93)*	0.64 (0.54–0.75)†	0.65 (0.48–0.89)*
SD, awake	0.97 (0.91–1.04)	0.95 (0.84–1.08)	0.92 (0.78–1.09)	0.89 (0.66–1.19)
SD, asleep	0.96 (0.91–1.02)	0.98 (0.87–1.09)	0.90 (0.75–1.07)	0.93 (0.67–1.30)
SD, 48 h	1.06 (0.98–1.14)	1.06 (0.92–1.21)	1.16 (0.97–1.39)	1.14 (0.82–1.60)
Morning surge	1.00 (0.97–1.02)	1.01 (0.97–1.05)	1.17 (0.98–1.41)	1.18 (0.83–1.67)
PP				
Clinic BP	0.94 (0.88–1.00)‡	0.95 (0.83–1.09)	0.85 (0.72–0.99)‡	0.89 (0.66–1.21)
Awake mean	0.86 (0.77–0.97)‡	0.88 (0.71–1.10)	0.83 (0.72–0.96)‡	0.84 (0.64–1.11)
Asleep mean	0.84 (0.75–0.94)*	0.80 (0.65–0.98)‡	0.80 (0.69–0.92)*	0.75 (0.57–0.98)‡
48-h mean	0.85 (0.76–0.96)*	0.84 (0.67–1.05)	0.83 (0.72–0.95)*	0.81 (0.62–1.06)
Sleep-time relative decline	0.92 (0.84–0.99)‡	0.83 (0.70–0.98)‡	0.84 (0.71–0.99)‡	0.69 (0.50–0.96)‡
SD, awake	0.96 (0.89–1.04)	0.97 (0.84–1.12)	0.92 (0.78–1.08)	0.94 (0.70–1.27)
SD, asleep	0.93 (0.87–0.99)‡	0.97 (0.86–1.11)	0.84 (0.72–0.98)‡	0.94 (0.70–1.26)
SD, 48 h	0.93 (0.86–1.01)	0.97 (0.83–1.13)	0.87 (0.75–1.02)	0.94 (0.70–1.26)
Morning surge	0.99 (0.97–1.01)	1.00 (0.96–1.04)	0.91 (0.76–1.08)	1.00 (0.71–1.41)
AASI	0.87 (0.76–1.00)	0.94 (0.72–1.22)	0.84 (0.69–1.00)	0.91 (0.64–1.31)

Left columns: Hazard ratio (95% CI) for each 5-mm Hg decrease in BP, 5% increase in sleep-time relative BP decline, 1-mm Hg decrease in morning surge, and 0.1 decrease in AASI during follow-up. Right columns provide HR standardized by calculating for 1-SD change in each ABPM parameter during follow-up. Adjustments were applied for the only significant influential characteristics (sex, age, diabetes, baseline BP, and number of hypertension medications used for treatment). Change in BP was entered as a time-dependent covariate in the Cox regression models. The sleep-time relative BP decline, an index of BP dipping, is defined as the percentage decline in BP during nocturnal sleep relative to the mean BP during daytime activity and calculated as: ([awake BP mean − asleep BP mean]/awake BP mean) × 100. The morning BP surge was calculated as the difference between the average BP during the first 2 h after wake-up time and the hourly average centered on the lowest BP reading recorded during nocturnal sleep. The AASI was calculated as 1 minus the regression slope of DBP on SBP from ABPM. *$p < 0.01$; †$p < 0.001$; ‡$p < 0.05$.
Abbreviations as in Tables 1 and 2.

the changes in asleep and awake BP mean were used jointly in the same Cox regression model, only the decrease in asleep BP mean was significant associated with increased survival.

When subjects were categorized according to their baseline assessment with the ABPM threshold values previously outlined, the reduced HR associated with each 5-mm Hg decrease in asleep SBP mean during follow-up was significant for both subjects with either normal (HR: 0.81, 95% CI: 0.68 to 0.95, $p = 0.005$) or elevated BP (HR: 0.84, 95% CI: 0.79 to 0.89, $p < 0.001$). For this latter group, the increased survival associated with reducing asleep SBP mean was statistically significant independently of treatment time (HR: 0.88, 95% CI: 0.82 to 0.95, $p < 0.001$, for patients treated with all medications on awakening; HR: 0.76, 95% CI: 0.67 to 0.86, $p < 0.001$, for those treated with ≥1 medication at bedtime).

Figure 1 shows, for the studied population divided in quintiles, the relationship between the decrease in asleep SBP mean from baseline and CVD risk. Adjusted HR was significantly higher ($p < 0.001$) in the last 3 quintiles, compared with the first 2 classes. There was a progressive reduction from 67% to 36% in the percentage of hypertensive subjects treated at bedtime across the quintiles, somehow indicating the association between bedtime-treatment, increased asleep BP reduction, and decreased CVD risk. Figure 2 shows a J-shaped relationship between changes in clinic SBP during follow-up and CVD risk; the adjusted HR was significantly higher ($p = 0.008$) in the first than in the second quintile, and then it significantly increased again in the other 3 classes ($p < 0.001$,

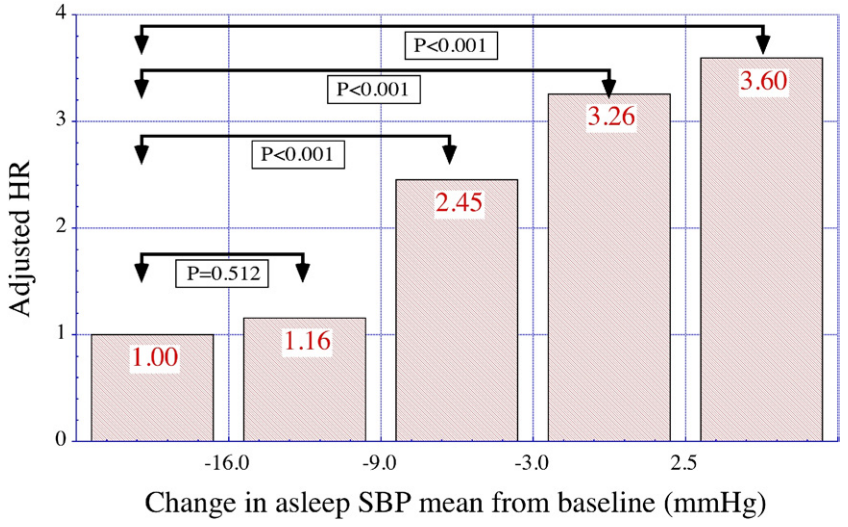

Figure 1 HR as a Function of the Change in Asleep SBP Mean During Follow-Up

Hazard ratio (HR) was adjusted by age, sex, diabetes, baseline blood pressure (BP), and number of hypertension medications used for treatment. Studied population was divided into 5 classes of equal size (quintiles). Negative change indicates a BP reduction during follow-up. SBP = systolic blood pressure.

compared with the second quintile). The percentage of patients treated at bedtime was lower (45%) in the first as compared with the second quintile (56%).

Discussion

The MAPEC study is the first to prospectively assess the prognostic value of changes in ABPM parameters during a follow-up time of sufficient duration by systematic periodic evaluation, with highly reproducible 48-h ABPM and wrist actigraphy, in a relatively large cohort of subjects with baseline BP ranging from normotension to hypertension. The results corroborate a higher prognostic value of ABPM over clinic BP measurements as documented in previous studies (3,5). Analyses based on a single ABPM profile from each subject obtained at baseline (as customary in all previous studies on this topic) indicate that the asleep SBP mean was a most significant predictor of CVD events (Table 2). Moreover, when asleep SBP mean was adjusted

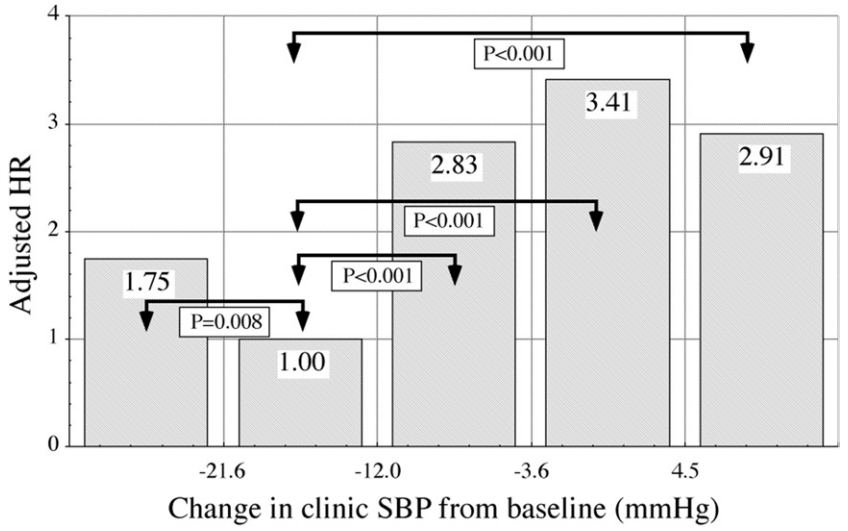

Figure 2 HR as a Function of the Change in Clinic SBP During Follow-Up

The HR was adjusted by age, sex, diabetes, baseline BP, and number of hypertension medications used for treatment. Studied population was divided into 5 classes of equal size (quintiles). Negative change indicates a BP reduction during follow-up. Abbreviations as in Figure 1.

by awake SBP mean, only the former was a significant predictor of outcome.

Most important from the therapeutic point of view, the evaluation of changes in ABPM during follow-up documented that the progressive decrease in asleep BP mean was significantly associated with event-free survival. The relationship between decreasing asleep BP and reduced CVD risk was significant for subjects with either normal or elevated ambulatory BP analyzed separately, suggesting risk-reduction benefits even below the current diagnostic threshold of 120 mm Hg for asleep SBP mean. All together, these results not only corroborate that the asleep BP mean is the most significant prognostic marker of CVD morbidity and mortality, as previously suggested (5–10), but also document for the first time that decreasing asleep BP mean significantly reduces CVD risk.

The findings summarized in Table 3 from this prospective study suggest the asleep BP mean should be considered a novel therapeutic target for reduction of CVD risk. Along these lines, a number of previous prospective trials reviewed elsewhere (18) have detected meaningful morning/evening treatment-time differences in BP-lowering efficacy, duration of action, safety profile, and/or effects on the circadian BP pattern of different classes of hypertension medications. For instance, a once-daily evening, in comparison with morning, ingestion schedule of angiotensin receptor blockers and angiotensin-converting enzyme inhibitors results in greater therapeutic effect on asleep BP independently of the terminal half-life of each individual medication (18). Thus, the impact of hypertension treatment-time on sleep-time BP regulation might be clinically relevant. The previously reported results of the randomized part of the MAPEC study indicate that treatment with ≥1 medication at bedtime was significantly associated with greater asleep BP reduction and significantly lower CVD risk than treatment with all hypertension medications upon awakening (14).

Therapeutic intervention in hypertension consists of adequate control of BP, the goal being to reduce/avert CVD morbidity and mortality. Some studies found that too high a reduction in clinic BP might be associated with increased CVD risk, whereas moderate reduction in clinic BP would decrease it. Thus, it has been suggested that CVD outcomes have a J-shaped relationship to BP, decreasing as BP was lowered and rising again as BP decreased further (19–21). We also found a J-shaped association in the relation between CVD risk and changes in clinic BP (Fig. 2) but not with changes in asleep BP mean (Fig. 1). The CVD risk decreased with progressive reduction in asleep BP mean. Moreover, the amount of the asleep BP reduction during follow-up was significantly correlated with increased number of patients treated at bedtime. It has been previously shown that increasing number of hypertension medications administered in the morning might lead to more intensive clinic BP reduction but also to an increased prevalence of nondipping as a consequence of the greater reduction in awake than asleep BP (22). We thus conclude that the actual controversy on the possible J-shaped relation with CVD risk, described so far only for clinic BP determined in patients presumably treated in the morning (19–21), might not apply (when avoiding nocturnal hypotension) to asleep BP, a more significant predictor of CVD morbidity and mortality.

Study limitations. First, compared with other larger multicenter clinical trials on hypertensive patients entailing only clinic BP during follow-up, the sample size of the single-center MAPEC study might seem a limitation. However, the number of subjects participating in our study was considerably greater than that of most other published trials on the prognostic value of ABPM (3,4). Second, like most other studies in this field, inclusion criteria restricted the study to subjects with suspected or previously diagnosed hypertension. Nonetheless, the design of the MAPEC study also incorporates several strengths. Although all previous trials on the prognostic value of ABPM had relied on a single baseline profile from each subject, the MAPEC study is the first to provide results that are based on systematic periodic multiple evaluations by ABPM throughout the median 5.6 years of follow-up. This so-far unique approach allowed determination of the influence on CVD risk of specific changes during follow-up in relevant ABPM parameters. Further strengths of the MAPEC study are the use of: 1) 48-h instead of the most common 24-h ABPM sampling, to increase the reproducibility of the BP findings (23); and 2) wrist actigraphy to precisely and individually determine the beginning and end of the activity and sleep spans for each subject to enable the accurate calculation of the awake and asleep BP means.

Conclusions

Current international guidelines have already recognized the prognostic value of ABPM and suggest limited clinical situations in which the technique is recommended. These situations include: suspected white-coat hypertension, resistant hypertension, hypotensive symptoms after treatment, episodic hypertension, and autonomic dysfunction (13). Our findings further support ABPM for proper CVD risk assessment, taking into account the prognostic value of asleep BP, a novel therapeutic target requiring patient evaluation by ABPM. Moreover, the decreased CVD risk associated with progressively reducing the asleep BP mean suggests the need to use ABPM for the routine evaluation of treatment efficacy and proper definition of BP control.

Reprint requests and correspondence: Dr. Ramón C. Hermida, Bioengineering and Chronobiology Laboratories, E.I. Telecomunicación, Campus Universitario, Vigo (Pontevedra) 36310, Spain. E-mail: rhermida@uvigo.es.

REFERENCES

1. Kario K, Pickering TG, Umeda Y, et al. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in

elderly hypertensives: a prospective study. Circulation 2003;107:1401–6.
2. Gosse P, Lasserre R, Minifié C, Lemetayer P, Clementy J. Blood pressure on rising. J Hypertens 2004;22:1113–8.
3. Verdecchia P, Porcellati C, Schillaci G, et al. Ambulatory blood pressure: an independent predictor of prognosis in essential hypertension. Hypertension 1994;24:793–801.
4. 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.
5. Dolan E, Stanton A, Thijs L, et al. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. Hypertension 2005;46:156–61.
6. Boggia J, Li Y, Thijs L, et al. Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study. Lancet 2007;370:1219–29.
7. Ben-Dov IZ, Kark JD, Ben-Ishay D, Mekler J, Ben-Arie L, Bursztyn M. Predictors of all-cause mortality in clinical ambulatory monitoring. Unique aspects of blood pressure during sleep. Hypertension 2007;49:1235–41.
8. Fagard RH, Celis H, Thijs L, et al. Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. Hypertension 2008;51:55–61.
9. Fan HQ, Li Y, Thijs L, et al. Prognostic value of isolated nocturnal hypertension on ambulatory measurement in 8711 individuals from 10 populations. J Hypertens 2010;28:2036–45.
10. Hansen TW, Li Y, Boggia J, Thijs L, Richart T, Staessen JA. Predictive role of the nighttime blood pressure. Hypertension 2011;57:3–10.
11. Hermida RC. Ambulatory blood pressure monitoring in the prediction of cardiovascular events and effects of chronotherapy: rationale and design of the MAPEC study. Chronobiol Int 2007;24:749–75.
12. Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Hypertension 2008;51:1403–19.
13. Mancia G, De Backer G, Dominiczak A, et al., The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). 2007 guidelines for the management of arterial hypertension. J Hypertens 2007;25:1105–87.
14. Hermida RC, Ayala DE, Mojón A, Fernández JR. Influence of circadian time of hypertension treatment on cardiovascular risk: results of the MAPEC study. Chronobiol Int 2010;27:1629–51.
15. Dolan E, Thijs L, Li Y, et al. Ambulatory arterial stiffness index as a predictor of cardiovascular mortality in the Dublin Outcome Study. Hypertension 2006;47:365–70.
16. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome. An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735–52.
17. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.
18. Smolensky MH, Hermida RC, Ayala DE, Tiseo R, Portaluppi F. Administration-time-dependent effect of blood pressure-lowering medications: basis for the chronotherapy of hypertension. Blood Press Monit 2010;15:173–80.
19. Voko Z, Bots ML, Hofman A, Koudstaal PJ, Witteman JCM, Breteler MMB. J-shaped relation between blood pressure and stroke in treated hypertensives. Hypertension 1999;34:1181–5.
20. Okumura K, Ohya Y, Maehara A, Wakugami K, Iseki K, Takishita S. Effects of blood pressure levels on case fatality after acute stroke. J Hypertens 2005;23:1217–23.
21. ACCORD Study Group, Cushman WC, Evans GW, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575–85.
22. Hermida RC, Ayala DE, Fernández JR, Calvo C. Chronotherapy improves blood pressure control and reverts the nondipper pattern in patients with resistant hypertension. Hypertension 2008;51:69–76.
23. Hermida RC, Calvo C, Ayala DE, Fernández JR, Ruilope LM, López JE. Evaluation of the extent and duration of the "ABPM effect" in hypertensive patients. J Am Coll Cardiol 2002;40:710–7.

Key Words: ambulatory blood pressure monitoring ■ cardiovascular risk ■ chronotherapy ■ hypertension ■ sleep-time relative blood pressure decline.

APPENDIX

For the extended version of the Methods, please see the online version of this paper.