ESC European Society of Cardiology

European Heart Journal (2018) **0**, 1–14
doi:10.1093/eurheartj/ehy475

CLINICAL RESEARCH
Hypertension

Asleep blood pressure: significant prognostic marker of vascular risk and therapeutic target for prevention

Ramón C. Hermida[1]*, Juan J. Crespo[1,2], Alfonso Otero[3], Manuel Domínguez-Sardiña[2], Ana Moyá[4], María T. Ríos[1,2], María C. Castiñeira[1,5], Pedro A. Callejas[1,2], Lorenzo Pousa[1,2], Elvira Sineiro[1,4], José L. Salgado[1,2], Carmen Durán[2], Juan J. Sánchez[1,6], José R. Fernández[1], Artemio Mojón[1], and Diana E. Ayala[1]; for the Hygia Project Investigators[†]

[1]Bioengineering & Chronobiology Laboratories, Atlantic Research Center for Information and Communication Technologies (AtlantTIC), University of Vigo, Vigo, 36310 Spain; [2]Estructura de Gestión Integrada de Vigo, Servicio Galego de Saúde (SERGAS), Vigo, Spain; [3]Servicio de Nefrología, Complejo Hospitalario Universitario, Estructura de Gestión Integrada de Ourense, Verín y O Barco de Valdeorras, Servicio Galego de Saúde (SERGAS), Ourense, Spain; [4]Estructura de Xerencia Integrada Pontevedra e O Salnés, Servicio Galego de Saúde (SERGAS), Pontevedra, Spain; [5]Estructura de Gestión Integrada de Lugo, Cervo y Monforte de Lemos, Servicio Galego de Saúde (SERGAS), Lugo, Spain; and [6]Estructura de Gestión Integrada de Santiago de Compostela, Servicio Galego de Saúde (SERGAS), Santiago de Compostela, Spain

Received 1 March 2018; revised 18 April 2018; editorial decision 20 July 2018; accepted 20 July 2018

Aims Sleep-time blood pressure (BP) is a stronger risk factor for cardiovascular disease (CVD) events than awake and 24 h BP means, but the potential role of asleep BP as therapeutic target for diminishing CVD risk is uncertain. We investigated whether CVD risk reduction is most associated with progressive decrease of either office or ambulatory awake or asleep BP mean.

Methods and results We prospectively evaluated 18 078 individuals with baseline ambulatory BP ranging from normotension to hypertension. At inclusion and at scheduled visits (mainly annually) during follow-up, ambulatory BP was measured for 48 consecutive hours. During the 5.1-year median follow-up, 2311 individuals had events, including 1209 experiencing the primary outcome (composite of CVD death, myocardial infarction, coronary revascularization, heart failure, and stroke). The asleep systolic blood pressure (SBP) mean was the most significant BP-derived risk factor for the primary outcome [hazard ratio 1.29 (95% CI) 1.22–1.35 per SD elevation, $P < 0.001$], regardless of office [1.03 (0.97–1.09), $P = 0.32$], and awake SBP [1.02 (0.94–1.10), $P = 0.68$]. Most important, the progressive attenuation of asleep SBP was the most significant marker of event-free survival [0.75 (95% CI 0.69–0.82) per SD decrease, $P < 0.001$], regardless of changes in office [1.07 (0.97–1.17), $P = 0.18$], or awake SBP mean [0.96 (0.85–1.08), $P = 0.47$] during follow-up.

Conclusion Asleep SBP is the most significant BP-derived risk factor for CVD events. Furthermore, treatment-induced decrease of asleep, but not awake SBP, a novel hypertension therapeutic target requiring periodic patient evaluation by ambulatory monitoring, is associated with significantly lower risk for CVD morbidity and mortality.

Keywords Asleep blood pressure • Ambulatory blood pressure monitoring • Bedtime hypertension chronotherapy • Cardiovascular risk • Stroke

* Corresponding author. Tel: 34-986-812148, Fax: 34-986-812116, Email: rhermida@uvigo.es

† A complete list of the members of the Hygia Project is provided in the Supplementary material online.

Introduction

Specific features of the 24 h blood pressure (BP) pattern determined by ambulatory blood pressure (ABP) monitoring (ABPM) have been explored as biomarkers or mediators of target tissue injury and triggers of and risk factors for cardiovascular disease (CVD) events.[1] Various independent prospective investigations and meta-analyses demonstrate the ABPM-derived asleep BP mean is a stronger risk factor for CVD events than the awake and 24 h BP means or daytime office blood pressure measurements (OBPM).[2–7] On the basis of the substantial evidence documenting ABP is a marker of long-term CVD outcomes independently of OBPM,[2,5–8] several international guidelines and recommendations now propose ABPM as requirement to confirm the diagnosis of adult hypertension.[9,10]

All previous studies addressing the merit of ABPM vs. OBPM as risk factor or even predictor for CVD events, except the Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares Study (MAPEC, Ambulatory Blood Pressure Monitoring for Prediction of Cardiovascular Events),[5,11] relied solely upon a single, low-reproducible[12] 24 h ABPM evaluation per participant. This approach is unsound because it presumes all features of the baseline-determined ABP pattern are maintained without alteration throughout the many years of follow-up despite institution or modification of BP-lowering therapy, aging, and development of target organ damage and concomitant morbidity. Additionally, lack of systematic and multiple ABPM evaluations of participants over time in all previously reported long-term follow-up studies, except MAPEC, precluded exploration of the potential relationship between modification of specific ABP parameters by hypertension therapy and reduction of CVD risk. Incorporation of periodic, at least annual, ABPM patient assessment during follow-up in the single-centre MAPEC Study first established therapeutic reduction of the asleep BP mean and enhancement of the sleep-time relative BP decline towards the normal dipper BP pattern lessen CVD risk,[5] results yet awaiting validation particularly in the routine primary care clinical setting.

The Hygia Project is a research network established to extend the use of ABPM in primary care to diagnose hypertension, evaluate response to treatment, and assess patient CVD and other risks.[13] Among the multiple ongoing ABPM-based studies within the network, we here report the findings on two of the main objectives of the Hygia Project, namely to: (i) compare the potential incremental value of multiple ABPM-derived parameters with OBPM as risk markers of CVD morbidity and mortality and (ii) most important from the therapeutic point of view, prospectively investigate whether specific treatment-induced changes in ABPM-derived parameters, primarily the progressive decrease in asleep BP mean, reduce CVD risk.

Methods

Inclusion and exclusion criteria

The prospective multicentre Hygia Project was approved by the state Ethics Committee of Clinical Research. Details of the study design, management, investigators' training, quality control, safety and compliance assessment, clinical and ABPM procedures, sample size calculations, follow-up, and all other relevant methodological aspects of the Hygia Project are extensively described elsewhere.[13] Presently, the Hygia Project is composed of 40 clinical sites (primary care centres) within the Galician Social Security Health Service [Servicio Galego de Saúde (SERGAS), Northern Spain] involving 292 investigators properly trained to ABPM and all study procedures. The sample for testing the two specific hypotheses stated above represents a population of Spanish men and women ≥18 years of age, adhering to a routine of daytime activity and night-time sleep, referred for ABPM mainly to confirm/refute the diagnosis of hypertension inferred by daytime OBPM of untreated individuals or to evaluate BP control in treated hypertensive persons, and who provided written informed consent for inclusion. Exclusion criteria were pregnancy, history of drug/alcohol abuse, night/shift-work employment, acquired immunodeficiency syndrome, secondary hypertension, CVD disorders (unstable angina pectoris, heart failure, life-threatening arrhythmia, atrial fibrillation, kidney failure, and Grade III–IV retinopathy), intolerance to ABPM, and inability to communicate and comply with all study requirements. For the present study, the targeted median follow-up was 5 years, with an a priori required ≥1-year minimal follow-up per participant.[13]

Participants, treatment, and diagnostic criteria

Between 2008 and 2015, we recruited 18 731 persons who fulfilled the inclusion/exclusion criteria, with 18 158 providing all required information for study. The other 573 individuals were excluded due to inadequate ABPM sampling at baseline and non-consent for follow-up ABPM evaluations. Additionally, 80 participants were excluded due to lack of the required 1-year minimum follow-up. Thus, the final evaluated population for the hypotheses tested herein is 18 078 persons [9769 men/8309 women; 59.1 ± 14.3 (mean ± standard deviation (SD)) years of age]. Hypertension was defined according to current ABPM criteria: awake systolic blood pressure (SBP)/diastolic blood pressure (DBP) mean ≥135/85 mmHg, or asleep SBP/DBP mean ≥120/70 mmHg, or BP-lowering treatment.[14,15] According to these ABPM criteria, 15 674 participants were hypertensive at the time of recruitment (9709 untreated) and assigned, as previously described,[13] either to ingest the entire dose of at least one BP-lowering medication (ARB, ACEI, CCB, ß-blocker, and/or diuretic) at bedtime (and the remaining ones, if any, upon awakening) or all of them upon awakening (Supplementary material online, *Table S1*). Participating physicians were given the choice of prescribing any medication of their choice from any of the five listed recommended therapeutic classes as first-line therapy in untreated participants and combination therapy for uncontrolled individuals. If, based on the ABPM threshold criteria provided above, the ABP of a given patient remained uncontrolled at any time during follow-up when treated with medication(s) at the maximum recommended dose(s), additional therapy could be added in keeping with current clinical practice guidelines.[15]

Diabetes was defined as fasting glucose ≥126 mg/dL on at least two clinical assessments ≥3 months apart in participants without prior history of diabetes, or glucose-lowering treatment.[16] Diagnosis of metabolic syndrome was established by the National Cholesterol Education Program Adult Treatment Panel III (ATP-III) revised definition.[17] Chronic kidney disease (CKD) was defined as either estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, albuminuria (albumin/creatinine ratio ≥30 mg/gCr), or both, on at least two occasions ≥3 months apart.[18] eGFR (mL/min/1.73 m^2) was estimated by the CKD-EPI equation.[19] Diagnosis of obstructive sleep apnoea (apnoea/hypopnoea index ≥10) was corroborated by overnight in-hospital polysomnography when the participant reported significant daytime hypersomnia or he/she or bedmate reported loud snoring, choking, interrupted breathing, and/or multiple awakenings during night-time sleep.

Ambulatory blood pressure and other assessments

At inclusion and thereafter at every scheduled clinic visit throughout follow-up, trained investigators obtained at least three consecutive OBPM from participants using a validated automatic oscillometric device (HEM-705IT, Omron Health Care Inc., Vernon Hills, IL, USA) after resting in a seated position for ≥10 min. Immediately thereafter, ABPM was instituted with a properly calibrated and validated SpaceLabs 90207 device (SpaceLabs Inc., Issaquah, WA, USA) to measure SBP, DBP, and heart rate every 20 min between 07:00 and 23:00 h and every 30 min during the night for 48 consecutive hours. The BP cuff was always worn on the non-dominant arm. Upper arm circumference was measured at each study visit to ensure proper cuff size for OBPM and ABP assessment. The monitoring period was 48 h, instead of the most usual 24 h, to optimize reproducibility of results, as accurate calculation of ABP characteristics (including mean BP values), and dipping classification depends markedly on ABPM duration.[12] Individuals were instructed to adhere to their usual activities with minimal restrictions, but to avoid daytime napping and maintain a similar activity-rest schedule during the two consecutive days of monitoring. Participants kept a diary to list, among other information, time of retiring to bed at night, awakening in the morning, consumption of meals, and ingestion of medications. Such individualized information was used to derive the awake and asleep BP means of each person. In keeping with current recommendations,[14] BP series were considered invalid for analysis, and thus requiring repeated ABPM, if ≥30% of the measurements were missing, data were lacking for an interval of >2 h, data were obtained when the rest-activity schedule was irregular or inconsistent during the 2 days of monitoring, or the sleep span was <6 h or >12 h.

Blood and urine samples were obtained at every clinic visit for ABPM evaluation. Participants arrived to the clinical centre between 08:00 and 09:00 h, after overnight fasting, for blood withdrawal from an antecubital vein. Blood and urine samples were analysed using routine automatic techniques at the corresponding laboratory facility of the SERGAS, all complying with the same quality standards.

Follow-up

Identical above-described evaluation procedures were scheduled annually, or more frequently in uncontrolled hypertensive participants and those affected by compelling clinical conditions associated with increased CVD risk—including diabetes, CKD, and past CVD events.[13] Investigators, mainly those of the Hygia Project Scientific Committee, reviewed the complete electronic clinical records of every enrolled participant at least annually and at least 1 year following each person's last ABPM evaluation. Categorization of CVD and other events listed in the electronic clinical records was accomplished by previously defined diagnostic criteria at the corresponding referring tertiary hospital services and by external non-investigator medical specialists.[13] The Hygia Project Events Committee, composed of independent clinicians blinded to medical records, ABPM findings, and treatment scheme of those with hypertension, periodically and collegiately evaluated such clinical reports, dissociated from the participant's identification, to ascertain and certify every documented event. Registered events include: death from all causes, myocardial infarction, angina pectoris, coronary revascularization, heart failure, lower extremities acute arterial occlusion, retinal artery thrombotic occlusion, haemorrhagic stroke, ischaemic stroke, and transient ischaemic attack. The a priori defined primary vascular study endpoint is CVD outcome (composite of CVD death, myocardial infarction, coronary revascularization, heart failure, ischaemic stroke, and haemorrhagic stroke).[13]

Statistical methods

Ambulatory blood pressure monitoring profiles were automatically edited according to conventional criteria to remove measurement errors and outliers: SBP readings >250 or <70 mmHg, DBP >150 or <40 mmHg, and pulse pressure (PP, SBP - DBP) >150 or <20 mmHg. The '48 h ABP mean' was calculated using all valid readings of the 48 h assessment span. Awake and asleep ABP means were calculated using all valid readings of the actual hours, respectively, of daytime activity and night-time sleep as differentiated by participant diary entries. To avoid confounding by non-equidistant BP sampling on mean values,[14] the 48 h, awake, and asleep spans were each divided into an integer number of classes of identical time length. The respective 48 h, awake, and asleep BP means were then determined as the average of the corresponding BP means obtained for each time-class. Sleep-time relative BP decline (index of BP dipping), percent decrease in mean BP during night-time sleep relative to mean BP during daytime activity, was calculated as: [(awake ABP mean - asleep ABP mean)/awake ABP mean] × 100, utilizing all valid data of 48 h ABPM. Participants were designated as dipper if the sleep-time relative SBP decline was ≥10%, and as non-dipper otherwise.[14,15]

Cardiovascular disease risk was evaluated on the basis of the: (i) baseline ABPM evaluation per participant, as customary in all previous ABPM reports[2–7]; (ii) final ABPM evaluation, i.e. that just before (usually <1 year) each documented event or last ABPM evaluation in non-event cases; and (iii) decrease from baseline during follow-up in OBPM and all potentially relevant ABPM-derived parameters.

Demographic and clinical characteristics were compared among groups of participants who did and did not experience an event by *t*-test (quantitative variables) or non-parametric χ^2 test (proportions). The Cox proportional-hazard model, adjusted for significant confounding variables, served to estimate hazard ratios (HR) and 95% CI for events per tested potential prognostic BP parameter as well as their combinations. We standardized these HR by expressing them in terms of 1-SD increments of the BP parameter. All demographic, anthropometric, and clinical laboratory variables of *Table 1* were tested as potential confounding variables by non-automatic (forward and backward) stepwise Cox survival analysis. Adjustments were finally applied for the jointly significant influential characteristics of age, sex, type 2 diabetes, CKD, cigarette smoking, high-density lipoprotein (HDL)-cholesterol, hypertension treatment-time (either all BP-lowering medications upon awakening vs. the daily dosing of at least one medication at bedtime), and history of previous CVD event, as they were the only ones consistently significant in the tested Cox regression models. On the other hand, the impact of BP reduction during follow-up on CVD risk was evaluated by entering the decrease from baseline in the analysed BP parameter at each subsequent ABPM evaluation as a time-dependent covariate in the Cox regression analysis, thus allowing also proper confirmation of the underlying hypotheses for the analysis. For survival analysis, follow-up was established as the time-interval from the date of the analysed ABPM assessment to either the date of the confirmed event or that of the last clinical evaluation in non-event participants.

We additionally compared the discriminative and predictive added value of the different tested ABPM parameters to OBPM by the C statistic (area under the receiver operating characteristic curve)[20] and Akaike Information Criterion (AIC).[21] Model selection was performed by evaluating differences in AIC between tested ABPM parameters according to the rules proposed by Burnham & Anderson.[22] Lack of significant collinearity between the asleep BP mean and all other tested OBPM and ABP parameters was ascertained by calculating tolerance coefficients and corresponding variance inflation factors. Statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) and R version 3.3.3 (R Foundation for Statistical Computing).

Table 1 Baseline characteristics of investigated participants

Variables	All participants	Participants with no event	Participants with event	P between groups	Standardized unadjusted HR of total events (95% CI); *P*-value	Standardized unadjusted HR of CVD outcome (95% CI); *P*-value
Demographic, anthropometric, and clinical characteristics						
Participants (*n*)	18 078	15 767	2311			
Age (years)	59.1 ± 14.3	57.8 ± 14.2	68.4 ± 11.4	<0.001	2.38 (2.26–2.50); <0.001	2.25 (2.33–2.69); <0.001
Sex (% men)	54.0	52.2	66.8	<0.001	1.79 (1.64–1.95); <0.001	1.79 (1.59–2.02); <0.001
Height (cm)	162.9 ± 9.7	163.0 ± 9.7	162.1 ± 9.2	<0.001	0.99 (0.98–0.99); <0.001	0.99 (0.98–0.99); <0.001
Weight (kg)	78.7 ± 15.2	78.8 ± 15.3	78.0 ± 14.8	0.019	0.96 (0.92–1.00); 0.06	0.96 (0.91–1.02); 0.21
BMI (kg/m^2)	29.6 ± 4.8	29.6 ± 4.8	29.6 ± 4.9	0.78	1.01 (0.97–1.05); 0.58	1.03 (0.97–1.09); 0.32
Waist (cm)	100.5 ± 12.5	100.0 ± 12.4	103.7 ± 12.6	<0.001	1.28 (1.24–1.32); <0.001	1.27 (1.21–1.32); <0.001
Night-time sleep duration (h)	8.8 ± 1.4	8.8 ± 1.3	9.1 ± 1.6	<0.001	1.20 (1.17–1.25); <0.001	1.24 (1.18–1.31); <0.001
Type 2 diabetes (%)	21.3	18.4	41.1	<0.001	2.77 (2.55–3.01); <0.001	2.53 (2.57–2.85); <0.001
Metabolic syndrome (%)	60.0	58.0	73.9	<0.001	1.97 (1.79–2.16); <0.001	1.95 (1.72–2.22); <0.001
Obstructive sleep apnoea (%)	4.2	3.9	6.2	<0.001	1.30 (1.10–1.54); 0.002	1.48 (1.19–1.85); <0.001
Cigarette smoking (%)	13.0	12.6	15.7	<0.001	1.24 (1.09–1.40); 0.001	1.24 (1.05–1.48); 0.012
Obesity (%)	42.5	42.3	55.9	<0.001	1.11 (1.02–1.21); 0.011	1.20 (1.07–1.34); 0.002
Anaemia (%)	9.2	8.5	20.1	<0.001	2.92 (2.40–3.55); <0.001	2.70 (2.07–3.52); <0.001
Albuminuria (%)	15.2	13.7	24.6	<0.001	2.52 (2.26–2.80); <0.001	2.56 (2.22–2.96); <0.001
CKD (%)	24.7	20.7	51.7	<0.001	3.58 (3.30–3.89); <0.001	3.43 (3.06–3.84); <0.001
Previous CVD event (%)	8.8	6.3	26.3	<0.001	4.14 (3.78–4.55); <0.001	5.11 (4.52–5.78); <0.001
Clinical laboratory test values						
Glucose (mg/dL)	106.4 ± 31.0	104.9 ± 28.2	118.7 ± 46.7	<0.001	1.30 (1.26–1.33); <0.001	1.28 (1.23–1.33); <0.001
Creatinine (mg/dL)	1.04 ± 0.80	1.01 ± 0.82	1.58 ± 1.41	<0.001	1.04 (1.03–1.05); <0.001	1.04 (1.02–1.05); <0.001
Uric acid (mg/dL)	5.7 ± 1.9	5.6 ± 1.9	6.2 ± 1.9	<0.001	1.13 (1.11–1.15); <0.001	1.13 (1.10–1.15); <0.001
Total cholesterol (mg/dL)	206.0 ± 42.7	207.7 ± 41.9	191.6 ± 46.4	<0.001	0.68 (0.65–0.72); <0.001	0.71 (0.66–0.76); <0.001
Triglycerides (mg/dL)	130.0 ± 97.9	129.9 ± 99.9	130.9 ± 79.8	0.69	1.02 (0.98–1.05); 0.27	1.02 (0.98–1.07); 0.32
HDL-cholesterol (mg/dL)	53.1 ± 15.6	53.7 ± 15.6	48.6 ± ± 14.7	<0.001	0.73 (0.70–0.77); <0.001	0.75 (0.70–0.81); <0.001
LDL-cholesterol (mg/dL)	126.7 ± 37.4	127.9 ± 36.9	117.9 ± 39.9	<0.001	0.88 (0.87–0.90); <0.001	0.89 (0.86–0.91); <0.001
Haemoglobin (g/dL)	14.2 ± 3.0	14.2 ± 3.1	13.8 ± 1.8	<0.001	0.62 (0.54–0.72); <0.001	0.71 (0.58–0.87); 0.001
eGFR	80.5 ± 24.0	83.0 ± 22.1	59.5 ± 28.4	<0.001	0.48 (0.47–0.50); <0.001	0.49 (0.47–0.52); <0.001
eGFR <60 (%)	17.1	13.4	47.8	<0.001	4.73 (4.31–5.18); <0.001	4.46 (3.93–5.06); <0.001
Albumin/creatinine ratio, mg/gCr, median (interquartile range)	6.7 (3.6–17.0)	6.4 (3.5–15.1)	11.0 (4.6–60.3)	<0.001	1.11 (1.09–1.14); <0.001	1.12 (1.09–1.15); <0.001
Office[a] and ambulatory BP						
Office SBP (mmHg)	145.8 ± 20.5	144.9 ± 19.5	151.7 ± 25.9	<0.001	1.30 (1.25–1.35); <0.001	1.34 (1.27–1.41); <0.001
Office DBP (mmHg)	84.6 ± 12.1	85.1 ± 11.7	81.2 ± 13.9	<0.001	0.74 (0.71–0.77); <0.001	0.76 (0.72–0.81); <0.001
Office PP (mmHg)	61.2±17.2	59.8 ± 16.1	70.5 ± 20.7	<0.001	1.58 (1.53–1.64); <0.001	1.60 (1.53–1.68); <0.001

Continued

Table 1 *Continued*

Variables	All participants	Participants with no event	Participants with event	P between groups	Standardized unadjusted HR of total events (95% CI); *P*-value	Standardized unadjusted HR of CVD outcome (95% CI); *P*-value
Office heart rate (b.p.m.)	72.9 ± 12.4	73.0 ± 12.2	72.1 ± 13.9	<0.001	0.91 (0.87–0.94); <0.001	0.89 (0.84–0.94); <0.001
Awake SBP mean (mmHg)	133.2 ± 14.7	132.8 ± 14.0	135.8 ± 18.1	<0.001	1.24 (1.19–1.29); <0.001	1.28 (1.21–1.35); <0.001
Asleep SBP mean (mmHg)	119.9 ± 15.3	118.8 ± 14.3	127.6 ± 19.7	<0.001	1.55 (1.50–1.61); <0.001	1.62 (1.54–1.69); <0.001
48 h SBP mean (mmHg)	128.6 ± 14.1	127.9 ± 13.3	133.0 ± 17.7	<0.001	1.38 (1.33–1.43); <0.001	1.43 (1.36–1.50); <0.001
Sleep-time relative SBP decline (%)	9.8 ± 7.5	10.4 ± 7.1	5.9 ± 9.0	<0.001	0.66 (0.64–0.68); <0.001	0.64 (0.61–0.67); <0.001
Awake DBP mean (mmHg)	79.8 ± 11.1	80.5 ± 10.8	74.8 ± 11.9	<0.001	0.61 (0.58–0.64); <0.001	0.63 (0.59–0.67); <0.001
Asleep DBP mean (mmHg)	68.0 ± 10.0	68.2 ± 9.8	66.9 ± 11.2	<0.001	0.87 (0.83–0.90); <0.001	0.91 (0.86–0.96); 0.001
48 h DBP mean (mmHg)	75.7 ± 10.3	76.2 ± 10.0	72.0 ± 11.2	<0.001	0.67 (0.64–0.69); <0.001	0.69 (0.65–0.74); <0.001
Sleep-time relative DBP decline (%)	14.4 ± 8.2	15.0 ± 7.8	10.3 ± 9.4	<0.001	0.64 (0.62–0.66); <0.001	0.63 (0.60–0.66); <0.001
Awake PP mean (mmHg)	53.4 ± 12.0	52.3 ± 11.1	61.0 ± 14.9	<0.001	1.73 (1.68–1.79); <0.001	1.75 (1.67–1.82); <0.001
Asleep PP mean (mmHg)	51.9 ± 11.9	50.6 ± 10.7	60.7 ± 15.3	<0.001	1.77 (1.72–1.82); <0.001	1.80 (1.73–1.87); <0.001
48 h PP mean (mmHg)	52.9 ± 11.7	51.7 ± 10.7	61.0 ± 14.7	<0.001	1.78 (1.72–1.83); <0.001	1.80 (1.73–1.88); <0.001
Sleep-time relative PP decline (%)	2.2 ± 10.0	2.6 ± 9.7	-0.3 ± 11.6	<0.001	0.80 (0.77–0.83); <0.001	0.78 (0.74–0.82); <0.001
Awake heart rate mean (b.p.m.)	74.7 ± 10.7	75.1 ± 10.5	72.6 ± 11.8	<0.001	0.80 (0.76–0.83); <0.001	0.78 (0.73–0.82); <0.001
Asleep heart rate mean (b.p.m.)	64.7 ± 9.3	64.5 ± 9.0	65.7 ± 10.7	<0.001	1.11 (1.07–1.15); <0.001	1.08 (1.02–1.14); 0.006
48 h heart rate mean (b.p.m.)	71.1 ± 9.8	71.3 ± 9.6	70.1 ± 11.1	<0.001	0.88 (0.85–0.92); <0.001	0.86 (0.81–0.91); <0.001
Sleep-time relative heart rate decline (%)	13.1 ± 7.5	13.7 ± 7.3	9.1 ± 7.7	<0.001	0.60 (0.57–0.62); <0.001	0.59 (0.56–0.63); <0.001
Non-dipper (%)	46.4	43.6	65.8	<0.001	2.21 (2.02–2.40); <0.001	2.40 (2.13–2.71); <0.001

Values shown as mean ± SD, unless otherwise indicated. Metabolic syndrome: National Cholesterol Education Program Adult Treatment Panel III (ATP-III) revised definition.[17] Obesity: body mass index (BMI) ≥30 kg/m^2. Albuminuria: Albumin/creatinine ratio ≥30 mg/gCr. CKD: eGFR <60 mL/min/1.73 m^2, albuminuria, or both, in at least two occasions ≥3 months apart.[18] eGFR (mL/min/1.73 m^2) was estimated using the CKD-EPI equation.[19] Sleep-time relative BP decline, index of BP dipping, defined as percent decrease in mean BP during night-time sleep relative to mean BP during daytime activity, calculated as: [(awake BP mean - asleep BP mean)/awake BP mean] × 100. Non-dipper: individuals with sleep-time relative SBP decline <10%, using data sampled by ABPM for 48 consecutive hours. Total events: composite of death from all causes, myocardial infarction, coronary revascularization, heart failure, ischaemic and haemorrhagic stroke, angina pectoris, acute arterial occlusion of the lower extremities, thrombotic occlusion of the retinal artery, and transient ischaemic attack. CVD outcome: composite of CVD death, myocardial infarction, coronary revascularization, heart failure, ischaemic stroke, and haemorrhagic stroke.

[a]Values correspond to average of three conventional BP measurements obtained per participant at the clinic in the morning before initiating 48 h ABPM.

Results

Demographic characteristics and laboratory variables

During the median follow-up period of 5.1 years (range 1.0–8.4 years), 2311 individuals had any of the listed registered events, including 1209 experiencing the main CVD outcome (CVD death: 227; myocardial infarction: 205; coronary revascularization: 217; heart failure: 295; stroke: 265). Event-subjects were predominantly men, of older age, and at baseline were likely to have type 2 diabetes, metabolic syndrome, anaemia, CKD, and/or history of previous CVD event (*Table 1*). In addition, at baseline they had greater OBPM SBP and PP (but lower OBPM DBP), plus laboratory findings of higher glucose, creatinine, uric acid, and urinary albumin/creatinine ratio, but lower eGFR and HDL-cholesterol (*Table 1*). At baseline, the 48 h mean of SBP was significantly greater and that of DBP significantly lower among event-subjects (*Table 1*). The largest difference between the event and non-event cohorts was in the asleep SBP mean. Moreover, the sleep-time relative SBP decline was significantly lower ($P < 0.001$) and prevalence of non-dipping significantly higher, 66 vs. 44%, among event-subjects ($P < 0.001$; *Table 1*). All differences between groups reported in *Table 1* with a *P*-value <0.001 would remain significant after correction for multiple testing.

Office blood pressure measurement and ambulatory blood pressure monitoring-derived characteristics as markers of cardiovascular disease risk

Beyond BP, increased risk of CVD outcome was jointly associated with male gender [HR 1.56 95% confidence interval (CI) (1.36–1.81), $P < 0.001$]; older age [1.32 (1.28–1.36), $P < 0.001$, per 5 years]; presence of type 2 diabetes [1.20 (1.04–1.37), $P = 0.012$]; presence of CKD [2.07 (1.79–2.39), $P < 0.001$]; cigarette smoking [1.54 (1.26–1.89), $P < 0.001$]; reduced HDL-cholesterol [0.90 (0.86–0.94), $P < 0.001$, per 10 mg/dL]; and history of previous CVD event [2.36 (2.03–2.75), $P < 0.001$]. Additionally, consistent with previous findings,[11] hypertensive patients assigned to take at least one BP-lowering medication at bedtime (intention-to-treat analysis) had a significantly lower HR of CVD outcome than those ingesting all such medications upon awakening [0.47 (0.42–0.54); $P < 0.001$]. There were no statistically significant differences at baseline between these two balanced treatment-groups in prevalence of metabolic syndrome, type 2 diabetes, obstructive sleep apnoea, CKD, history of previous CVD events, and obesity, plus all evaluated anthropometric and clinical laboratory test variables (Supplementary material online, *Table S1*). OBPM, average ABP values, and prevalence of non-dipping at baseline were also not significantly different between groups (Supplementary material online, *Table S1*). There were no differences at the end of the study in the classes and number of hypertension medications (usually at maximum doses) prescribed for therapy between patients of the two treatment-time schemes (Supplementary material online, *Table S2*). The most frequent treatment-schemes in monotherapy were ARB or ACEI (69%) and CCB (12%); combinations of ARB/ACEI with either diuretic (43%) or CCB (26%) in double therapy; and combinations of ARB/ACEI-diuretic with CCB (60%) or ß-blocker (28%) among patients treated with ≥3 medications. Data of the last ABPM evaluation revealed significantly lower asleep, but not awake, SBP/DBP means in participants of the bedtime than morning-treatment regimen ($P < 0.001$; Supplementary material online, *Table S2*). The sleep-time relative SBP/DBP decline was significantly greater among those of the bedtime-treatment regimen; accordingly, the proportion of patients with the non-dipper BP pattern was significantly lower in the bedtime than the morning-treatment group (32 vs. 50%; $P < 0.001$).

Table 2 (left column) reports the Cox proportional-hazard model derived adjusted-HR of CVD outcome calculated on the basis of the baseline OBPM and ABP evaluations per participant. The asleep SBP mean was the most significant BP marker of CVD risk [per 1-SD elevation, HR 1.34 (1.27–1.40), $P < 0.001$; *Table 2*, left column]. Interestingly, a greater either morning or pre-awakening BP surge calculated as previously defined[23] was significantly associated with lower, not higher, CVD risk (*Table 2*, left column), a finding consistent with the highly significant association between greater sleep-time relative BP decline and attenuated risk. The merit of the asleep SBP mean as marker of CVD risk was highly significant independent of absence/presence of hypertension therapy at baseline [HR 1.30 (1.18–1.42), $P < 0.001$; and 1.31 (1.24–1.38), $P < 0.001$, respectively] or treatment-time schedule during follow-up, i.e. for hypertensive participants of the awakening [HR 1.27 (1.20–1.35), $P < 0.001$] vs. bedtime-treatment-schedule groups [1.39 (1.27–1.53), $P < 0.001$] analysed separately. The same conclusions regarding the significantly greater value of asleep SBP as risk marker were also obtained from analysis of total events (including death from any cause and all others listed above) as outcome variable.

Table 2 (centre column) reports the HR of CVD based on OBPM and ABPM of the final evaluation. The findings are similar to those described above for the corresponding baseline evaluation (*Table 2*, left column), thereby providing further evidence for the greater value of the asleep BP mean and sleep-time relative BP decline compared to any of the other ABP characteristics analysed separately as potential individual markers of CVD risk (*Figure 1A*).

We next explored the potential combined contribution to CVD risk of the multiple BP parameters listed in *Table 2*. When the asleep SBP mean was jointly evaluated as an additional confounding variable with either OBPM-derived SBP or any other ABPM-derived SBP parameter, only the former was a significant marker of CVD risk [1.29 (95% CI 1.22–1.35) per SD elevation in asleep SBP, $P < 0.001$; 1.03 (0.97–1.09) per SD elevation in OBPM SBP, $P = 0.32$; and 1.02 (0.94–1.10) per SD elevation in awake SBP mean, $P = 0.68$; *Figure 1B*]. The joint contribution with the asleep SBP mean to CVD risk was significant only for the diminished sleep-time relative SBP decline ($P = 0.042$, *Figure 1B*).

To further investigate the clinical relevance of the awake and asleep BP means on CVD risk, participants were categorized for illustrative purposes into four mutually exclusive cohorts according to ABP level, i.e. normal or high awake and normal or high asleep BP mean, independent of OBPM, using established ABPM thresholds of 135/85 mmHg for awake SBP/DBP means and 120/70 mmHg for asleep SBP/DBP means.[14,15] *Figure 2A* indicates:

Table 2 Adjusted HR of CVD outcome associated with OBPM and ABP

OBPM/ABPM parameter	Baseline BP evaluation	Final BP evaluation	Decrease in BP during follow-up
SBP			
Office	1.19 (1.14–1.26)*	1.15 (1.09–1.21)*	0.85 (0.77–0.93)*
Awake mean	1.20 (1.14–1.26)*	1.25 (1.19–1.31)*	0.78 (0.71–0.86)*
Asleep mean	1.34 (1.27–1.40)*	1.31 (1.25–1.37)*	0.75 (0.69–0.82)*
48 h mean	1.26 (1.20–1.32)*	1.28 (1.22–1.34)*	0.77 (0.70–0.84)*
Sleep-time relative decline	0.81 (0.77–0.85)*	0.86 (0.82–0.91)*	1.21 (1.11–1.32)*
SD, awake	1.25 (1.19–1.31)*	1.23 (1.17–1.29)*	0.99 (0.91–1.09)
SD, asleep	1.09 (1.04–1.15)*	1.10 (1.05–1.16)*	0.92 (0.85–1.03)
SD, 48 h	1.14 (1.08–1.20)*	1.16 (1.10–1.22)*	1.05 (0.96–1.16)
Morning surge	0.92 (0.87–0.97)*	0.94 (0.89–0.99)***	0.94 (0.85–1.04)
Pre-awakening surge	0.87 (0.83–0.92)*	0.93 (0.88–0.97)**	1.10 (0.99–1.22)
Sleep-time fall	0.96 (0.91–1.01)	0.96 (0.91–1.01)	1.15 (1.05–1.27)**
DBP			
Office	1.07 (1.00–1.13)***	1.07 (1.01–1.13)***	0.89 (0.81–0.98)***
Awake mean	0.99 (0.93–1.06)	1.09 (1.02–1.16)**	0.88 (0.79–0.98)***
Asleep mean	1.17 (1.10–1.23)*	1.20 (1.14–1.27)*	0.76 (0.69–0.84)*
48 h mean	1.06 (0.99–1.13)	1.14 (1.07–1.21)*	0.83 (0.75–0.92)*
Sleep-time relative decline	0.81 (0.77–0.86)*	0.85 (0.81–0.90)*	1.29 (1.18 –1.42)*
SD, awake	1.18 (1.12–1.24)*	1.18 (1.11–1.24)*	0.93 (0.84–1.01)
SD, asleep	1.07 (1.01–1.13)***	1.06 (1.01–1.12)***	1.00 (0.91–1.10)
SD, 48 h	1.03 (0.98–1.10)	1.07 (1.01–1.14)***	1.09 (0.98–1.20)
Morning surge	0.95 (0.90–1.00)	0.94 (0.89–0.99)***	1.06 (0.96–1.18)
Pre-awakening surge	0.88 (0.83–0.93)*	0.89 (0.84–0.94)*	1.17 (1.06–1.30)**
Sleep-time fall	0.96 (0.91–1.02)	0.94 (0.89–1.00)***	1.16 (1.06–1.29)**
PP			
Office	1.21 (1.15–1.28)*	1.16 (1.10–1.22)*	0.89 (0.81–0.97)**
Awake mean	1.27 (1.21–1.34)*	1.28 (1.22–1.35)*	0.86 (0.80–0.93)*
Asleep mean	1.32 (1.26–1.39)*	1.30 (1.24–1.36)*	0.84 (0.78–0.91)*
48 h mean	1.30 (1.24–1.37)*	1.29 (1.23–1.36)*	0.87 (0.81–0.94)*
Sleep-time relative decline	0.87 (0.83–0.92)*	0.94 (0.90–0.99)***	1.07 (0.98–1.17)
SD, awake	1.21 (1.15–1.27)*	1.22 (1.16–1.28)*	0.94 (0.86–1.03)
SD, asleep	1.13 (1.08–1.19)*	1.14 (1.09–1.20)*	0.91 (0.84–0.99)***
SD, 48 h	1.23 (1.17–1.29)*	1.22 (1.16–1.28)*	0.96 (0.88–1.05)
Heart rate			
Office	1.05 (0.99–1.11)	1.03 (0.98–1.09)	0.94 (0.85–1.04)
Awake mean	1.03 (0.97–1.09)	0.99 (0.93–1.05)	1.00 (0.91–1.10)
Asleep mean	1.16 (1.10–1.23)*	1.10 (1.05–1.17)*	0.97 (0.89–1.06)
48 h mean	1.08 (1.02–1.14)***	1.03 (0.97–1.09)	0.98 (0.90–1.08)
Sleep-time relative decline	0.81 (0.76–0.86)*	0.81 (0.76–0.86)*	1.12 (1.01–1.23)***
SD, awake	0.93 (0.87–0.98)**	0.90 (0.85–0.96)**	1.13 (1.02–1.25)***
SD, asleep	0.98 (0.93–1.04)	0.96 (0.91–1.01)	1.04 (0.94–1.14)
SD, 48 h	0.88 (0.83–0.94)*	0.88 (0.83–0.93)*	1.10 (0.99–1.22)
AASI	1.24 (1.16–1.33)*	1.20 (1.12–1.28)*	0.85 (0.77–0.93)**

CVD outcome: Composite of CVD death, myocardial infarction, coronary revascularization, heart failure, ischaemic stroke, and haemorrhagic stroke.
Baseline and final BP evaluation: Standardized adjusted HRs (95% CI) expressed per 1-SD elevation in each evaluated BP parameter either at the baseline evaluation upon recruitment (left column) or at the last available evaluation per participant (centre column). For the individualized analysis of each listed BP parameter, adjustments were always applied for significant influential characteristics of age, sex, diabetes, CKD, cigarette smoking, HDL-cholesterol, hypertension treatment-time, and history of previous CVD event.
Decrease during follow-up: Standardized adjusted HRs (95% CI) expressed per 1-SD decrease in each evaluated BP parameter during follow-up (right column). For the individualized analysis of each listed BP parameter, adjustments were applied for significant influential characteristics of age, sex, diabetes, CKD, cigarette smoking, HDL-cholesterol, baseline values of the tested BP parameter, hypertension treatment-time, and history of previous CVD event. Decrease in BP at each ABPM evaluation from baseline was entered as a time-dependent covariate in the Cox regression models.
Sleep-time relative BP decline, index of BP dipping, is defined as percent decline in BP during night-time sleep relative to mean BP during daytime activity, and calculated as: [(awake BP mean - asleep BP mean)/awake BP mean] × 100. Morning BP surge was calculated as difference between average BP during first 2 h after morning wake-up (i.e. morning BP) and hourly BP average centred on lowest BP reading recorded during night-time sleep (i.e. lowest sleep BP). Pre-awakening BP surge was calculated as difference between average BP during first 2 h after and average BP during 2 h just before morning wake-up. Sleep-time fall was calculated as difference between average BP during the 2 h just before going to bed and hourly average centred on lowest BP reading recorded during night-time sleep.
*$P < 0.001$.
**$P < 0.01$.
***$P < 0.05$.

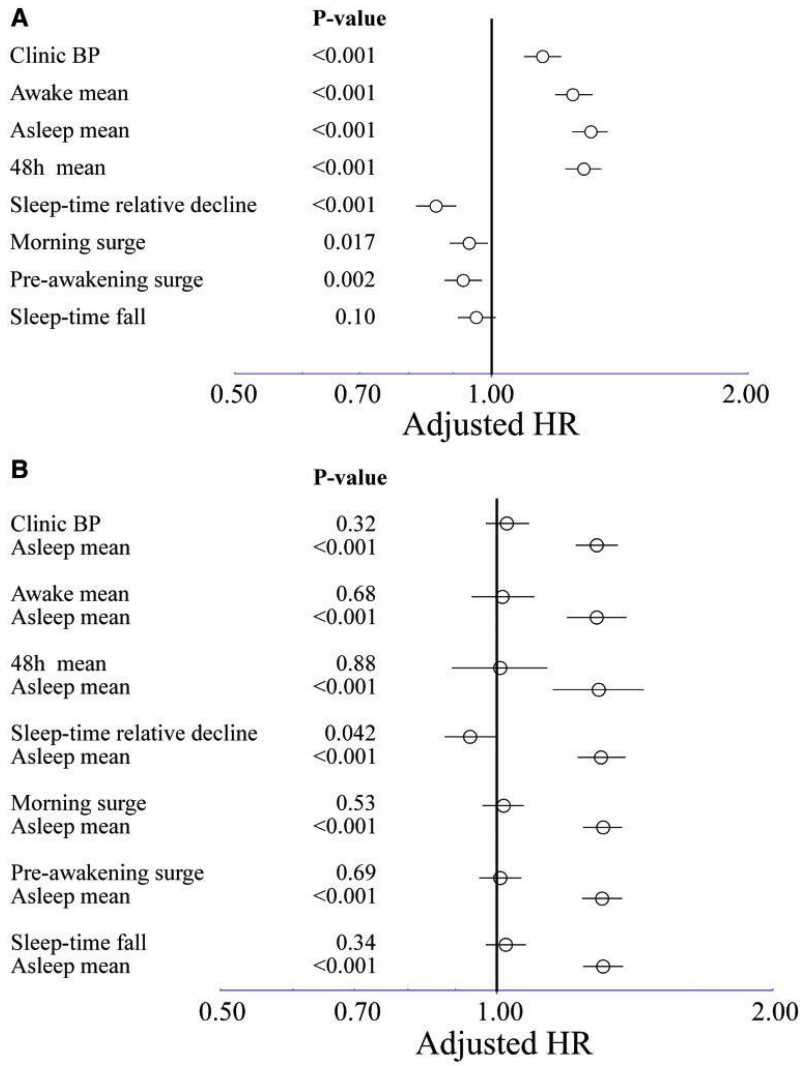

Figure 1 Adjusted hazard ratio (95% CI) of cardiovascular disease outcome per 1-SD elevation in clinic and ambulatory systolic blood pressure. (*A*) Each tested parameter evaluated separately. (*B*) Results for each tested blood pressure parameter adjusted by including asleep systolic blood pressure mean as an additional potentially influential variable in the Cox models. Adjustments were applied for significant influential characteristics of age, sex, diabetes, chronic kidney disease, cigarette smoking, HDL-cholesterol, hypertension treatment-time, and history of previous cardiovascular disease event.

(i) similar adjusted HR for CVD outcome of participants with normal asleep BP whether the awake BP mean is normal or elevated ($P = 0.32$); (ii) equivalent HR in hypertensive patients with high asleep BP whether the awake BP mean is normal or elevated ($P = 0.47$); and (iii) significantly higher adjusted HR of CVD events in participants with elevated than normal asleep BP mean, independent of the awake BP mean being below or above 135/85 mmHg (always $P < 0.001$).

Each of the four cohorts of participants categorized by awake and asleep BP means in *Figure 2A* were further categorized according to either normal or elevated OBPM using the most common 140/90 mmHg thresholds, i.e. yielding in total eight mutually exclusive cohorts. Cardiovascular disease risk was significantly higher in all of the four patient cohorts who had high asleep ABP mean, regardless of whether OBPM or awake ABP mean was normal or elevated, than in all of the other four cohorts of normal asleep ABP mean (*Figure 2B*). Additionally, there were no significant differences in HR for CVD risk of participants with normal vs. high OBPM within each of the four cohorts defined by awake and asleep BP means (always $P > 0.11$, *Figure 2B*).

From the point of view of discrimination/prediction ability of OBPM vs. ABPM, the adjusted Cox regression model that included the asleep SBP mean had the lowest AIC among all other BP parameters tested in *Table 2*. Moreover, difference in AIC with

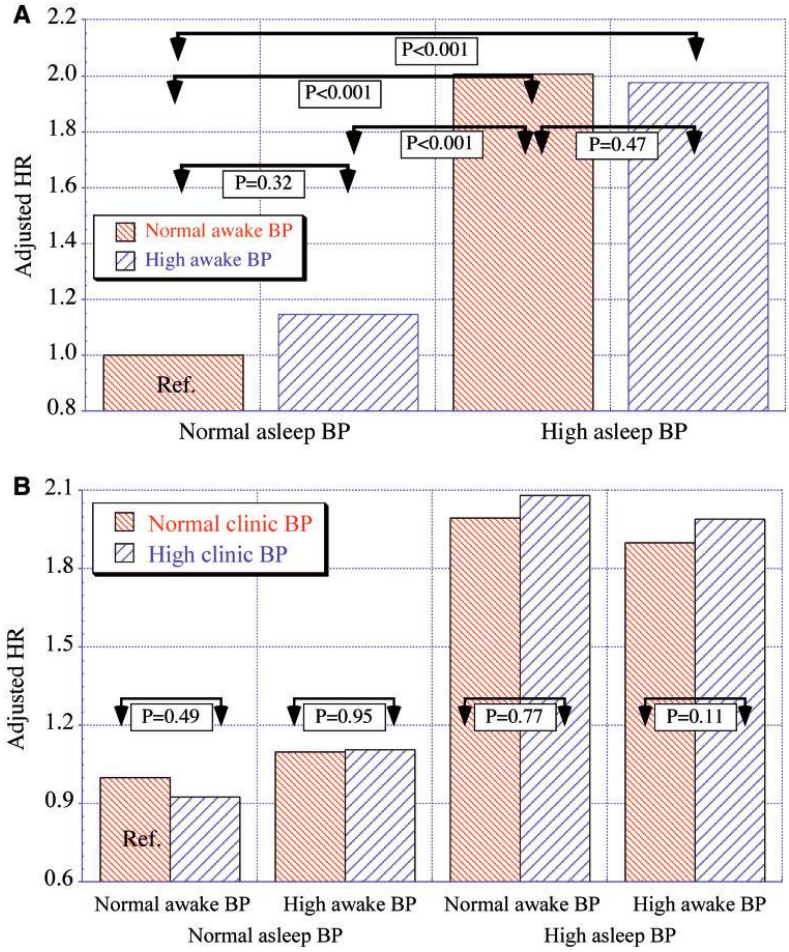

Figure 2 Adjusted hazard ratio of cardiovascular disease outcome as a function of clinic and ambulatory blood pressure. (*A*) Adjusted hazard ratio of cardiovascular disease outcome as a function of awake and asleep systolic blood pressure/diastolic blood pressure means. (*B*) Adjusted hazard ratio of cardiovascular disease as a function of office blood pressure measurements and awake plus asleep systolic blood pressure/diastolic blood pressure means. Awake systolic blood pressure/diastolic blood pressure mean was considered normal if <135/85 mmHg and high otherwise. Asleep systolic blood pressure/diastolic blood pressure mean was considered normal if <120/70 mmHg and high otherwise. Clinic systolic blood pressure/diastolic blood pressurewas considered normal if <140/90 mmHg and high otherwise. Adjustments were applied for the same variables as in *Figure 1*. Ref. means reference group for hazard ratio calculations.

respect to the model including asleep SBP mean was ≥25 for every other tested BP variable, indicative of their considerably poorer prognostic value. Furthermore, in the survival model including the significant confounders listed above, the addition of asleep SBP mean resulted in significantly better CVD outcome discrimination [C-statistic 0.807 95% CI (0.793–0.821)] than inclusion of either OBPM SBP or awake SBP mean [0.738 (0.723–0.752) and 0.728 (0.713–0.743), respectively, $P < 0.001$]; the discrimination ability of either OBPM SBP or awake SBP mean was significantly improved by adding the asleep SBP mean into the model [0.808 (0.794–0.822) and 0.810 (0.796–0.824), respectively; $P < 0.001$]. On the contrary, adding OBPM SBP or awake SBP to the model already including asleep SBP mean just marginally and non-significantly improved prediction of CVD events ($P > 0.87$).

Decrease in office blood pressure measurement and ambulatory blood pressure during follow-up as markers of reduced cardiovascular disease risk

Table 2 (right column) presents the results of the time-dependent Cox regression analysis—adjusted by the significant confounders of age, sex, diabetes, CKD, cigarette smoking, HDL-cholesterol, baseline BP, hypertension treatment-time, and history of previous CVD event—based upon progressive *decrease* in BP during follow-up, i.e. difference between the values obtained per participant at recruitment and each ABPM determination up to his/her final evaluation. The decrease in the asleep SBP mean was the most significant marker of increased event-free survival, i.e. absence of CVD outcome [0.75

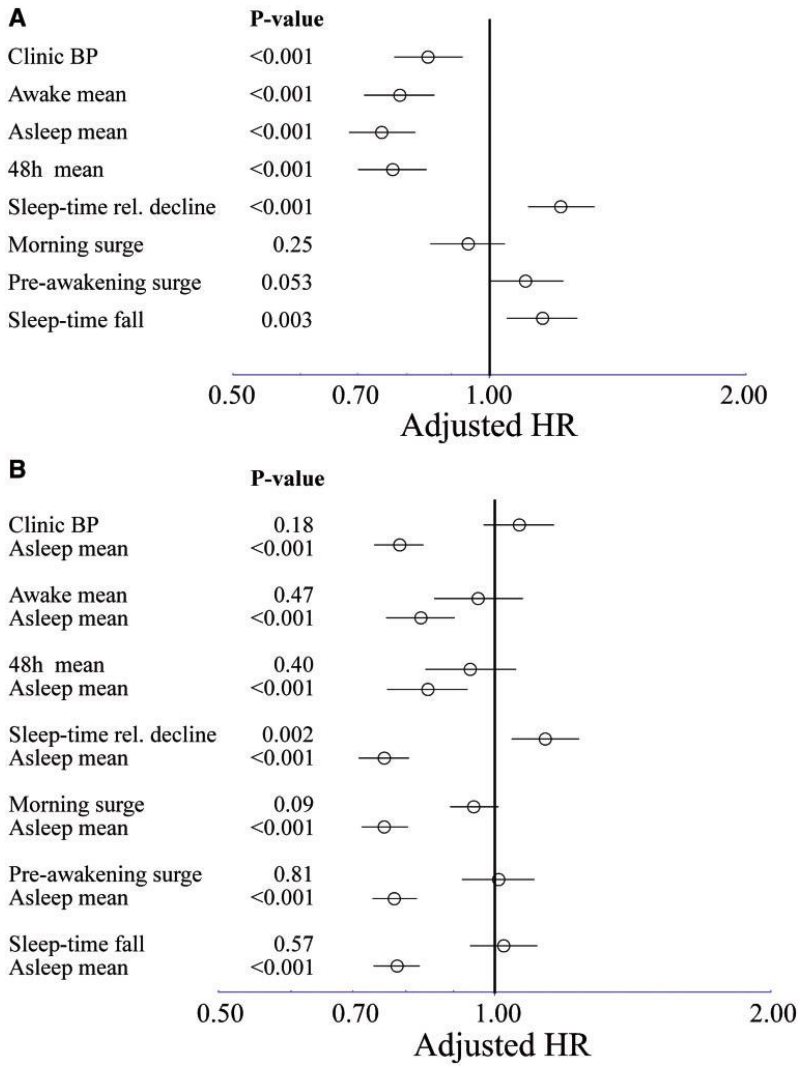

Figure 3 Adjusted hazard ratio (95% CI) of cardiovascular disease per 1-SD decrease from baseline in clinic and ambulatory systolic blood pressure during follow-up. (*A*) Each tested parameter evaluated separately. (*B*) Results for each tested blood pressure parameter adjusted by including the decrease in asleep systolic blood pressure mean as an additional potentially influential variable in the Cox models. Adjustments were applied for significant influential characteristics of age, sex, diabetes, chronic kidney disease, cigarette smoking, HDL-cholesterol, baseline values of the tested blood pressure parameter, hypertension treatment-time, and history of previous cardiovascular disease event.

(95% CI 0.69–0.82) per SD decrease, $P < 0.001$; *Figure 3A*], independent of changes in office [1.07 (0.97–1.17), $P = 0.18$] or awake SBP mean [0.96 (0.85–1.08), $P = 0.47$] during follow-up (*Figure 3B*). Only the decrease in asleep SBP mean and increase in sleep-time relative SBP decline towards the more normal dipper BP pattern remained jointly and significantly associated with reduced CVD risk (*Figure 3B*). The C-statistic of the model including the decrease in asleep SBP mean during follow-up [0.827 (0.814–0.840)] was unchanged when adding the decrease in OBPM SBP [0.827 (0.814–0.840); $P = 0.92$] and reduced when adding the decrease in awake SBP mean [0.813 (0.800–0.827); $P = 0.032$], again reflecting the protective value of increasing the sleep-time relative SBP decline.

Figure 4 shows, for the studied population divided into quintiles, the relationship between CVD outcome and achieved OBPM and ABP at final evaluation, thus suggesting potential outcome-based BP therapeutic targets. For OBPM SBP, the adjusted HR was only slightly higher in the last compared to the first four quintiles. There was a slightly significant increase in CVD risk with progressively higher awake SBP mean (*Figure 4B*). In contrast, across all quintiles there was a highly significant exponential decrease in risk of CVD outcome with progressively lower achieved asleep SBP mean (*Figure 4C*). Additionally, the adjusted HR for CVD outcome increased progressively and significantly when the achieved sleep-time SBP decline was <13% (*Figure 4D*).

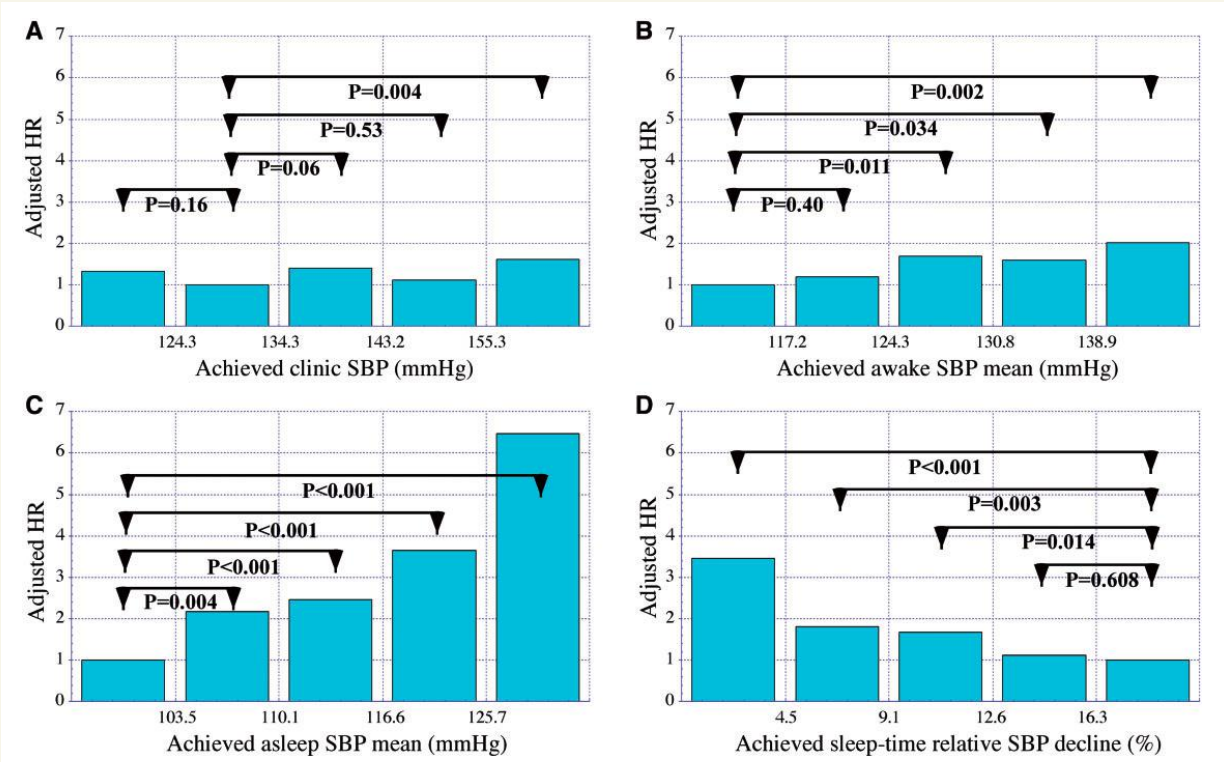

Figure 4 Adjusted hazard ratio of cardiovascular disease outcome as a function of achieved clinic systolic blood pressure (*A*) and ambulatory awake systolic blood pressure mean (*B*), asleep systolic blood pressure mean (*C*), and sleep-time relative systolic blood pressure decline (*D*). Studied population was divided into five classes of equal size (quintiles). Adjustments were applied for the same variables as in *Figure 1*.

Discussion

The Hygia Project is the first outcomes study conducted within primary care-based customary clinical practice to assess prospectively, in the so far largest cohort evaluated by repeated ABPM, the prognostic value for CVD morbidity and mortality not just of OBPM and ABP parameters upon recruitment but, of much more medical relevance, changes in such during sufficient duration follow-up by periodic (at least annual) highly reproducible 48 h ABPM in conjunction with recorded patient diary information, as recommended,[14,15] of bedtime at night and awakening time in the morning to derive individualized awake and asleep BP means plus sleep-time relative BP decline. Results document daytime OBPM is neither an independent significant marker nor proper therapeutic target for reducing CVD risk when the asleep BP mean is taken into account (*Figures 1–3*). *Figure 2* documents the assumed merit of elevated OBPM as risk factor of CVD events derives exclusively from the risk of those individuals who additionally have elevated BP during sleep. Analyses based on the ABP profile obtained per participant both at baseline, as customary in all previous studies entailing ABPM as marker of CVD risk,[2–7] as well as at final evaluation, usually within <1-year of every documented event, indicate the asleep SBP mean is the most significant marker of CVD outcome among the various evaluated ABP parameters (*Table 2*), both individually and jointly when combined with other potential ABP-derived risk factors in the best possible Cox proportional-hazard model (*Figure 1*). In fact, only the diminished sleep-time relative SBP decline might add prognostic value to the Cox model that already includes the asleep SBP mean and corrected for relevant confounding variables (*Figure 1B*). Moreover, when the asleep BP mean was adjusted for the OBPM or awake BP mean, only the former remained a significant predictor of CVD outcome, regardless of whether the OBPM or awake BP mean was normal or elevated (*Figures 1B and 2*). Both office and ambulatory DBP had markedly lower prognostic value than SBP (*Table 2*), in keeping with current knowledge[10,15] and the recognized prognostic value of PP. Relying on OBPM for diagnosing hypertension is associated with a very high 47% misclassification (Groups 2, 4, 5, and 7 from left to right in *Figure 2B*), rendering OBPM no better than flipping a coin to identify individuals at elevated CVD risk and in need of therapeutic intervention.

Despite the limitations of the C-statistic to evaluate the predictive value of highly variable and modifiable factors such as BP,[20] our findings further document asleep SBP mean provides significantly stronger prediction/discrimination of CVD outcome than OBPM or any other ABPM-derived parameter. Indeed, adding OBPM or awake SBP mean to the model already including asleep SBP mean does not improves prediction of CVD outcome, while inclusion of asleep SBP mean significantly increases the prediction and discrimination provided by either OBPM or awake BP mean. Banegas *et al.*[24] also found significantly better prediction of CVD mortality with ABP than

OBPM. On the contrary, Mortensen *et al.*[25] concluded neither ABPM added predictive value to OBPM, nor asleep to awake BP mean; these findings, on a much smaller sample of patients evaluated only once by 24 h ABPM, could be somehow biased, not only by the sparse sampling during sleep (>30-min intervals) in half the patients, but mainly by relying on inaccurate daytime and night-time values calculated assuming arbitrary fixed clock hours that do not reflect the actual rest/activity pattern of each individual. In a recent meta-analysis of nine different cohorts,[7] the difference between the HRs for asleep and awake SBP means was indeed greater and much more significant in studies where asleep was properly defined by either wrist-actigraphy or individualized patient dairy than in those defined by fixed clock-time spans. Nevertheless, taking into consideration, among other facts, the multiple intrinsic and extrinsic factors influencing BP regulation[1] and its modification by hypertension treatment and aging, we believe asleep BP should be preferably used as marker of increased CVD risk, but not as a diagnostic test to attempt prediction of future events.[20]

Beyond agreement on the limited, if any, prognostic value of OBPM compared to ABPM, our findings differ from those by Banegas *et al.*,[24] as they report similar HRs for awake and asleep SBP means (1.54 and 1.55, respectively; $P < 0.001$) when both were adjusted jointly with the non-significant OBPM (HR 1.02, $P = 0.08$) in the same Cox model for CVD mortality. These results, however, might be questionable. First, the HR of awake SBP mean (adjusted by asleep SBP mean and OBPM) reported by Banegas *et al.*[24] for mortality due to ischaemic heart disease, stroke, and heart failure (jointly accounting for 80% of CVD deaths) were 1.025, 1.025, and 1.025, respectively (their Supplementary material online, *Table S3*); accordingly, the adjusted HR of awake SBP mean for total CVD mortality can hardly be the reported 1.54, leading to the conclusion that indeed only asleep SBP mean is a significant marker of CVD mortality. And second, the HRs for OBPM and multiple ABPM-derived parameters reported by Banegas *et al.*[24] are fully identical for CVD mortality and total mortality; this is unsound, as CVD mortality represented 34% of total deaths and non-CVD mortality might not be associated with increased BP in many cases (including cancer, accidents, neurological conditions, etc.). In our study, also conducted in Spain and CVD mortality accounting for a similar 36% of total deaths, the adjusted HRs of OBPM, awake, and asleep SBP analysed jointly in the same Cox model were: for CVD mortality 1.07 (0.94–1.22), $P = 0.33$; 0.89 (0.74–1.07), $P = 0.23$; and 1.48 (1.26–1.73), $P < 0.001$, respectively; for non-CVD mortality 0.87 (0.79–0.97), $P = 0.010$; 0.98 (0.85–1.13), $P = 0.79$; and 1.19 (1.04–1.35), $P = 0.010$; and for total mortality 0.94 (0.87–1.02), $P = 0.14$; 0.94 (0.84–1.06), $P = 0.32$; and 1.30 (1.17–1.43), $P < 0.001$. These findings document the expected strong difference in the prognostic value of BP for CVD and non-CVD mortality, plus the highly significant value of asleep SBP mean as marker not just of CVD outcome (*Figures 1–3*) but also of CVD mortality in particular.

Most important from the perspective of prevention, evaluation of changes in ABP parameters during follow-up documents the progressive *decrease* in asleep SBP mean and *increase* in sleep-time relative SBP decline (towards the more normal dipper BP pattern) are significantly associated with reduced CVD risk (*Figures 3 and 4*). As reported, the relationship between asleep SBP mean decrease and CVD outcome attenuation is significant at all levels of baseline asleep SBP mean, ranging from normotension to hypertension, suggesting benefit even below the asleep SBP/DBP means of 120/70 mmHg, the current diagnostic thresholds for sleep-time hypertension.[14,15] Indeed, analysis of the adjusted HR for CVD outcome in terms of the achieved asleep SBP mean at the last available evaluation per participant reveals significant risk reduction even when the sleep-time SBP mean is <103 mmHg (*Figure 4C*), a finding that requires further investigation specially in high-risk patients.[26] Moreover, CVD risk was also increased significantly in patients with achieved sleep-time relative SBP decline at the final evaluation <13% (*Figure 4D*). This finding suggests the sleep-time relative SBP decline, as a continuous variable, and not just the dipping classification *per se* usually based on an arbitrary 10% threshold value, might be used, jointly with the asleep SBP level, as novel clinical indices to assess and prevent risk for future major CVD events.

The latest update of the guidelines for the clinical management of adult primary hypertension from the National Institute for Health and Clinical Excellence (NICE)[9] in Great Britain recommends ABPM be conducted to corroborate the diagnosis of hypertension in all adults with elevated OBPM. Despite available evidence, here extended and qualified, on the greater prognostic value of asleep than awake BP mean[2–7] the NICE guidelines explicitly recommend such diagnosis be based solely upon the ABPM-derived daytime SBP/DBP means ≥135/85 mmHg.[9] The recent 2015 US Preventive Services Task Force (USPSTF) report[10] concludes: (i) ABPM predicts long-term CVD outcomes independently of OBPM, and (ii) ABPM, rather than OBPM, must be considered *the* reference standard in primary care medicine to diagnose hypertension in adults ≥18 years of age. On the basis of an exploratory meta-analysis showing no apparent difference in HR for CVD risk per 10 mmHg increase between the ABPM-derived night-time, daytime, and 24 h SBP means, a finding we believe is dubious because of methodological limitations of the reviewed investigations,[27] the USPSTF report concludes that anyone of those means might be used to corroborate the diagnosis of hypertension in adults.[10] In contradiction with the recommendations of the NICE and USPSTF reports, current guidelines of the European Society of Hypertension and European Society of Cardiology state 'it is now generally accepted that out-of-office BP is an important adjunct to conventional OBPM, but the latter currently remains the 'gold standard' for screening, diagnosis, and management of hypertension'.[15,28] The 2017 guidelines of the American College of Cardiology and the American Heart Association also rely on OBPM to define hypertension, although establishing lower values of 130/80 mmHg for clinic SBP/DBP as new diagnostic thresholds and therapeutic targets.[29] Using as reference the above discussed USPSTF report,[10] these guidelines state 'out-of-office measurement of BP can be helpful for confirmation and management of hypertension'. Specifically, the guidelines address the importance of identifying persons with masked normotension and masked hypertension; however, these two categories are misleadingly defined by comparing OBPM with *daytime* ABPM or home BP measurements, thus totally disregarding asleep BP as the strongest prognosticator of CVD risk. Contrary to all these guidelines and recommendations, results of the prospective Hygia Project collectively indicate: (i) the asleep SBP mean is the most significant prognostic marker of CVD risk, independent of the other conventional variables here corroborated to be linked with increased CVD risk, such as elevated older age, male gender, diabetes, CKD, and history of previous CVD event[5]; accordingly,

around-the-clock ABPM to derive the asleep SBP mean should be the recommended protocol to diagnose true hypertension and properly assess CVD risk; and (ii) most important, decreasing the asleep SBP mean is significantly protective, thus constituting a novel therapeutic target for reducing CVD risk over and above targeting OBPM or awake BP mean (*Figure 3B*).

Among others, the major limitations of the Hygia Project are: (i) its findings require validation and extrapolation to other ethnic groups; (ii) OBPM was obtained in the presence of the investigator and thus potentially overestimated, although this approach reflects current medical practice also utilized in most previously reported studies[2–7]; and (iii) with regard to the potential increase in CVD event-free survival time with progressive decrease in asleep SBP mean (*Figures 3 and 4*), a confirmatory study randomizing participants to at least two different threshold goals in terms of achieved asleep SBP mean is required to properly validate our findings. Such trial, already designed, approved by the heath authorities, and registered (ClinicalTrials.gov, number NCT03457168) will be conducted with the participation of most clinical sites also involved in the Hygia Project. Yet, our study has several strengths, mainly being the only large outcomes study completely integrated into routine primary care and entailing periodic 48 h ABPM evaluation at least yearly throughout the median 5.1 years of follow-up. This unique approach, used previously only in the single-centre MAPEC study,[5,11] allowed determination of the influence of *changes* during follow-up in relevant ABPM parameters on CVD risk. Additional strengths of the Hygia Project are the use of: (i) 48 h, instead of the most common 24 h, ABPM to increase reproducibility of the BP findings[12]; and (ii) in the absence of wrist-actigraphy as measured in the participants of the MAPEC study,[5,11] properly designed subject diary to ascertain the beginning and end of the activity and sleep spans and thus derive on an individual basis the awake and asleep SBP/DBP means, rather than relying on inaccurate daytime and night-time values calculated assuming common and arbitrary fixed clock hours as used in many previous ABPM studies.[2–4]

In conclusion, according to this prospective evaluation, the asleep SBP mean, but not daytime OBPM or awake ABP mean, is the most significant BP marker of CVD outcome. This finding supports the critical importance of ABPM in routine clinical medicine, as recently concluded by the USPSTF report,[10] but more specifically to accurately detect abnormal sleep-time BP and diagnose true hypertension. More important, therapeutic targeting of elevated asleep SBP mean and diminished sleep-time relative SBP decline, usually most effectively achieved by bedtime ingestion of the full daily dose of one or more hypertension medications[11,30] as also corroborated in this prospective investigation, is associated with significantly lower risk for CVD morbidity and mortality.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Funding

The Hygia Project is an independent investigator-promoted research network supported by unrestricted grants from Ministerio de Ciencia e Innovación, Spanish Goverment (SAF2009-7028-FEDER); Instituto de Salud Carlos III, Ministerio de Economía y Competitividad, Spanish Government (PI14-00205); Consellería de Economía e Industria, Dirección Xeral de Investigación e Desenvolvemento, Galician Regional Government (INCITE08-E1R-322063ES; INCITE09-E2R-322099ES; 09CSA018322PR; IN845B-2010/114); Consellería de Cultura, Educación e Ordenación Universitaria, Galician Regional Government (CN2012/251; GPC2014/078); European Regional Development Fund (ERDF) and the Galician Regional Government under agreement for funding the Atlantic Research Center for Information and Communication Technologies (AtlantTIC); and Vicerrectorado de Investigación, University of Vigo. This funding body has no role in the study design, analysis and interpretation of data, writing of the reports, or the decision to submit articles for publication.

Conflict of interest: none declared.

References

1. Portaluppi F, Tiseo R, Smolensky MH, Hermida RC, Ayala DE, Fabbian F. Circadian rhythms and cardiovascular health. *Sleep Med Rev* 2012;**16**:151–166.
2. Dolan E, Stanton A, Thijs L, Hinedi K, Atkins N, McClory S, Hond ED, McCormack P, Staessen JA, O'Brien E. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. *Hypertension* 2005;**46**:156–161.
3. Fagard RH, Celis H, Thijs L, Staessen JA, Clement DL, De Buyzere ML, De Bacquer DA. Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. *Hypertension* 2008;**51**:55–61.
4. Fan H-Q, Li Y, Thijs L, Hansen TW, Boggia J, Kikuya M, Björklund-Bodegård K, Richart T, Ohkubo T, Jeppesen J, Torp-Pedersen C, Dolan E, Kuznetsova T, Stolarz-Skrzypek K, Tikhonoff V, Malyutina S, Casiglia E, Nikitin Y, Lind L, Sandoya E, Kawecka-Jaszcz K, Imai Y, Ibsen H, O'Brien E, Wang J, Staessen JA. Prognostic value of isolated nocturnal hypertension on ambulatory measurement in 8711 individuals from 10 populations. *J Hypertens* 2010;**28**:2036–2045.
5. Hermida RC, Ayala DE, Mojón A, Fernández JR. Decreasing sleep-time blood pressure determined by ambulatory monitoring reduces cardiovascular risk. *J Am Coll Cardiol* 2011;**58**:1165–1173.
6. Minutolo R, Agarwal R, Borrelli S, Chiodini P, Bellizzi V, Nappi F, Cianciaruso B, Zamboli P, Conte G, Gabbai FB, De Nicola L. Prognostic role of ambulatory blood pressure measurement in patients with nondialysis chronic kidney disease. *Arch Intern Med* 2011;**171**:1090–1098.
7. ABC-H Investigators. Roush GC, Fagard RH, Salles GF, Pierdomenico SD, Reboldi G, Verdecchia P, Eguchi K, Kario K, Hoshide S, Polonia J, de la Sierra A, Hermida RC, Dolan E, Zamalloa H. Prognostic impact from clinic, daytime, and nighttime systolic blood pressure in 9 cohorts on 13,844 patients with hypertension. *J Hypertens* 2014;**32**:2332–2340.
8. Clement DL, De Buyzere ML, De Bacquer DA, de Leeuw PW, Duprez DA, Fagard RH, Gheeraert PJ, Missault LH, Braun JJ, Six RO, Van Der Niepen P, O'Brien E. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. *N Engl J Med* 2003;**348**:2407–2415.
9. National Institute for Health and Clinical Excellence. *Hypertension: The Clinical Management of Primary Hypertension in Adults. NICE Clinical Guidelines 127: Methods, Evidence and Recommendations*. London, UK: National Clinical Guidelines Centre, 2011. http://guidance.nice.org.uk/CG/Wave2/14 (2 November 2017).
10. Piper MA, Evans CV, Burda BU, Margolis KL, O'Connor E, Whitlock EP. Diagnosis and predictive accuracy of blood pressure screening methods with consideration of rescreening intervals: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2015;**162**:192–204.
11. 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**:1629–1651.
12. Hermida RC, Ayala DE, Fontao MJ, Mojón A, Fernández JR. Ambulatory blood pressure monitoring: importance of sampling rate and duration – 48 versus 24 hours – on the accurate assessment of cardiovascular risk. *Chronobiol Int* 2013;**30**:55–67.
13. Hermida RC. Sleep-time ambulatory blood pressure as a prognostic marker of vascular and other risks and therapeutic target for prevention by hypertension chronotherapy: rationale and design of the Hygia Project. *Chronobiol Int* 2016;**33**:906–936.
14. Hermida RC, Smolensky MH, Ayala DE, Portaluppi F, Crespo JJ, Fabbian F, Haus E, Manfredini R, Mojón A, Moyá A, Piñeiro L, Ríos MT, Otero A, Balan H, Fernández JR. 2013 ambulatory blood pressure monitoring recommendations for the diagnosis of adult hypertension, assessment of cardiovascular and other hypertension-associated risk, and attainment of therapeutic goals. *Chronobiol Int* 2013;**30**:355–410.

15. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013;**31**:1281–1357.
16. American Diabetes Association: Standards of Medical Care in Diabetes. Diabetes advocacy. *Diabetes Care 2015* 2015;**38**:S86–S87.
17. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Spertus JA, Costa F. Diagnosis and management of the metabolic syndrome. An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005;**112**:2735–2752.
18. Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Chapter 1: Definition and classification of CKD. *Kidney Inter Suppl* 2013;**3**:19–62.
19. Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; For The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–612.
20. Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. *Circulation* 2007;**115**:928–935.
21. Akaike H. A new look at the statistical model identification. *IEEE Trans Aut Control* 1974;**19**:716–723.
22. Burnham KP, Anderson DR. *Model Selection and Multimodel Inference: A Practical Information-Theoretic Approach*. New York: Springer, 2004.
23. Kario K, Pickering TG, Umeda Y, Hoshide S, Hoshide Y, Morinari M, Murata M, Kuroda T, Schwartz JE, Shimada K. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. *Circulation* 2003;**107**:1401–1406.
24. Banegas JR, Ruilope LM, de la Sierra A, Vinyoles E, Gorostidi M, de la Cruz JJ, Ruiz-Hurtado G, Segura J, Rodríguez-Artalejo F, Williams B. Relationship between clinic and ambulatory blood-pressure measurements and mortality. *N Engl J Med* 2018;**378**:1509–1520.
25. Mortensen RN, Gerds TA, Jeppesen JL, Torp-Pedersen C. Office blood pressure or ambulatory blood pressure for the prediction of cardiovascular events. *Eur Heart J* 2017;**38**:3296–3304.
26. Hermida RC, Ayala DE, Mojón A, Fernández JR. Ambulatory blood pressure thresholds for diagnosis of hypertension in patients with and without type 2 diabetes based on cardiovascular outcomes. *Chronobiol Int* 2013;**30**:132–144.
27. Smolensky MH, Ayala DE, Hermida RC. Ambulatory blood pressure monitoring (ABPM) as THE reference standard to confirm diagnosis of hypertension in adults: recommendation of the 2015 U.S. Preventive Services Task Force (USPSTF). *Chronobiol Int* 2015;**32**:1320–1322.
28. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Løchen ML, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WMM, Binno S; ESC Scientific Document Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**:2315–2381.
29. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmerfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018;**71**:e127–e248.
30. Hermida RC, Ayala DE, Smolensky MH, Fernández JR, Mojón A, Portaluppi F. Chronotherapy with conventional blood pressure medications improves management of hypertension and reduces cardiovascular and stroke risks. *Hypertens Res* 2016;**39**:277–292.

Asleep Blood Pressure: Significant Prognostic Marker of Vascular Risk and Therapeutic Target for Prevention

Supplementary Appendix

Ramón C. Hermida[1], PhD, FASH; Juan J. Crespo[1,2], MD, PhD; Alfonso Otero[3], MD, PhD; Manuel Domínguez-Sardiña[2], MD, PhD; Ana Moyá[4], MD, PhD; María T. Ríos[1,2], MD, Ph.D.; María C. Castiñeira[1,5], MD; Pedro A. Callejas[1,2], MD; Lorenzo Pousa[1,2], MD, Ph.D.; Elvira Sineiro[1,4], M.D.; José L. Salgado[1,2], MD; Carmen Durán[2], MD; Juan J. Sánchez[1,6], MD; José R. Fernández[1], PhD; Artemio Mojón[1], PhD; Diana E. Ayala[1], MD, MPH, PhD; for the Hygia Project Investigators

[1]Bioengineering & Chronobiology Laboratories; Atlantic Research Center for Information and Communication Technologies (AtlantTIC); University of Vigo, Vigo, Spain.
[2]Estructura de Gestión Integrada de Vigo, Servicio Galego de Saúde (SERGAS), Vigo, Spain.
[3]Servicio de Nefrología, Complejo Hospitalario Universitario, Estructura de Gestión Integrada de Ourense, Verín y O Barco de Valdeorras, Servicio Galego de Saúde (SERGAS), Ourense, Spain.
[4]Estructura de Xerencia Integrada Pontevedra e O Salnés, Servicio Galego de Saúde (SERGAS), Pontevedra, Spain.
[5]Estructura de Gestión Integrada de Lugo, Cervo y Monforte de Lemos, Servicio Galego de Saúde (SERGAS), Lugo, Spain.
[6]Estructura de Gestión Integrada de Santiago de Compostela, Servicio Galego de Saúde (SERGAS), Santiago de Compostela, Spain.

SHORT TITLE: Decreasing sleep-time BP reduces vascular risk.

ADDRESS: Prof. Ramón C. Hermida, Ph.D.
Director, Bioengineering and Chronobiology Labs.
E.I. Telecomunicación
Campus Universitario
VIGO (Pontevedra) 36310, SPAIN
Ph.: 34-986-812148.
Fax: 34-986-812116.
E-mail: rhermida@uvigo.es

REPRINT ADDRESS: Same as above.

HYGIA PROJECT INVESTIGATORS

Hygia Project Scientific Committee: Ramón C. Hermida (President), José R. Fernández (Secretary), Diana E. Ayala, Pedro A. Callejas, María C. Castiñeira, Juan J. Crespo, Manuel Domínguez-Sardiña, Carmen Durán, Artemio Mojón, Ana Moyá, Alfonso Otero, Luis Piñeiro†, Lorenzo Pousa, María T. Ríos, José L. Salgado, Juan J. Sánchez, Elvira Sineiro.

Hygia Project Events Committee: Diana E. Ayala (President), María Fontao (Secretary), Luisa Chayán, María J. Domínguez.

Hygia Project Investigators: Aballe Santos, Luz; Aboal Beato, Miguel Ángel; Aboy Pardal, María del Pilar; Abuín Nieves, Milagros; Aguado Villar, María del Carmen; Aguilar Mateo, Andrea; Aguín Vidal, María Belén; Alonso Alonso, Ignacio; Alonso Estévez, Arsenio; Alonso Martín, María Rosario; Alvarez Ameijeiras, María Antonia; Alvarez Carrera, Cecilia; Alvarez Fernández, Aurelio; Alvarez Pedrouso, Rosa Mª; Alvariño Veiga, Margarita; Ameijeiras Canosa, María; Amorín Ferreiro, Fernanda; Andrade Cochón, Carlos Benito; Antón del Río, María del Consuelo; Arca Quiroga, Silvia; Areán González, Manuel; Armada Fernández, María José; Ayala García, Diana Elva; Baqueiro Carballo, María José; Barbosa Álvarez, Manuel Ángel; Barcia Domínguez, Leonarda María; Barral Andrade, María del Carmen; Barreiro Carretón, Beatriz María; Barreiro Prieto, Andrés; Bartolomé Pérez, Serafín Tadeo; Beceiro Díaz, María Fernanda; Blanco Valdés, Mario A.; Blázquez Ballesteros, María Luisa; Boente Carrera, Carmen; Borrajo Prol, María Paz; Bóveda Fontán, Julia; Brea López, María del Pilar; Bua Eiras, María Concepción; Bustabad Sancho, Belén; Cabanelas Lorenzo, Manuel Angel; Cabo Nuñez, María Isabel; Cadilla Rodríguez, Asunción; Calaza Paz, Celso; Callejas Cabanillas, Pedro Antonio; Camba Caride, María Jesús; Camiño Redondo, María Concepción; Campillo Casais, Carmen; Canda Riobó, María Emilia; Canitrot Míguez, Nuria; Cardalda Freire, Dolores; Carrera López, Jorge Juan; Casares López,

Montserrat; Casariego Barro, Luciano; Castañal Canto, Xulio; Castiñeira Pérez, Carmen; Castro Vázquez, Isabel Regina; Cecilio Montero, Francisco Javier; Chayán Zas, María Luisa; Charle Crespo, Angeles; Cid Sueiro, Marina; Cobas Pacín, Pilar; Conde Freire, María Soledad; Conejo Caridad, Rafael; Constenla Castro, Aurelia; Contreras Vázquez, Rodrigo; Cores Abalo, Margarita; Costa Ribas, Carmen; Costalago Herrera, Ana Isabel; Couto Nogueira, Luciano; Crespo Sabarís, Juan José; Cruces Artero, María Concepción; Cruz Rodríguez, Mercedes; Davila Brun, Carlos; de Jesús Miguez, Pilar; De Jesús Otero, Alba María; Delfín Vázquez, Marta María; Delgado Martín, José Luis; Díaz López, María José; Díaz Mareque, Ana Isabel; Díaz Martínez, María Amparo; Díaz Sanisidro, Eduardo; Diéguez Soengas, Esther; Docampo Millán, Antonio; Domínguez Grandal, Felisa; Domínguez Santalla, María Jesús; Domínguez Sardiña, Manuel; Donado Campos, Francisco; Durán Rodríguez, Carmen; Durán Santos, Carmen; Eguía González, Belén; Eiroa Patiño, Peregrina; Esteban Monlat, Isidro; Estévez Iglesias, Margarita; Facal García, Fernando Luis; Felpete López, Patricia; Fernández Álvarez, Ana; Fernández Areán, Manuel; Fernández Bernárdez, José Ramón; Fernández Bernárdez, Lina; Fernández Crespo, Antonio; Fernández Dacosta, Raquel; Fernández Díaz, María Azucena; Fernández Gago, Miguel; Fernández Herrero, María Teresa; Fernández Sobrino, Carmen María; Ferreiro Serrano, María Teresa; Ferreras Gómez, Amelia; Ferro Castaño, Ana María; Filloy Míguez, Evangelina; Fondevila García, Julio; Fontao Fernández, María José; Fonterosa Fernández, Ana; Fraga Lago, Margarita; Franco Eiras, María Isabel; Gaitero Merino, Juliana; Gallego Martínez, María del Carmen; Gándara Merino, Julia; García Alvarez, Sheila Mónica; García Gutiérrez, Juan Carlos; García Iglesias, María del Carmen; García Palacio, Ana Inés; García Pazos, Alberto; García Recamán, Maricarmen; García Rivas, Domingo; García Soidán, Francisco Javier; Garea Rey, María del Carmen; Gerpe Jamardo, Josefa; Gómara Villabona, Sonia María; Gómez Balboa, Ramón; Gómez Reguera, Ruth; Gómez Villalobos, Juan Antonio; González Blanco, Cristina; González Domínguez, Emilia; González Loureiro, Patricia; González Ríos, Concepción; González Teijeiro, Monserrat; Hermida Domínguez, Ramón C.; Hernaiz Valero, Susana; Iglesias Alonso, Olga; Iglesias Lamas, Elena; Iglesias Mato, Francisco

Javier; Jamardo Varela, Saul; Jueguen Bóveda, Joaquín; Lago Costas, Pedro; Lago Deibe, Fernando Isidro; Lago Durán, María del Valle; Lago Vila, Luz; Lagos Fernández, Ramón; Lama Lama, Aurora; Lareo Tallón, Elisa; Llovo Sáenz, Bárbara; Lois López, Víctor Manuel; López Alarcón, Walter Luis; López Ozores, Yemina; López Pérez, Francisca; López Vilar, José Luis; López Vilar, Rosa; Lorenzo Llauger, Elena; Lorenzo Vidal, Sonia; Lores Romay, Rocío; Lumbreras Márquez, Ana Isabel; Márquez Cortizo, Enrique; Martín Hernández, Florencio; Martínez Barrios, Jesús; Martínez Domínguez, Cristina; Martínez Iglesias, María del Mar; Martínez Magadán, Rita; Martínez Trelles, María José; Meijide Calvo, Luis María; Méndez Fernández, Zita; Méndez Salgado, Mónica; Mendía Sanmartín, Mercedes; Menduiña Sanín, Jesús; Mera González, Elisa; Miniño Couto, Gerardo; Miranda Vázquez, Marcelina; Mojón Ojea, Artemio; Molina Poch, Dolores; Moliner de la Puente, José Ramón; Montero Gamarra, Gardenia; Moraes de Passos, Graziella; Moreno Molinero, María Montserrat; Mosquera Nogueira, Jacinto; Moyá Álvarez, Ana; Nadal González, Laura; Navas Almodóvar, Rosario; Názara Otero, Carlos Alberto; Nieto Jácome, Ana; Nieto Vázquez, Jesús Carlos; Nogueiras Santás, Concepción; Noguerol González, María Teresa; Novoa Fernández, Enrique; Novoa Rodríguez, Juan Francisco; Orro Arcay, Carolina; Otero Bouzada, Cristina; Otero González, Alfonso; Outeiro Rodríguez, Carmen; Padín Montoto, Fernando; Pardo Planas, Irene; Pardo Teijeiro, Bernardino; Parrado Nsang, Esperanza; Patrón Catalán, Luis; Pazo Ferreiro, María Dolores; Pereira Lorenzo, Alfredo; Pereiras Bernárdez, Jesús; Pérez Álvarez, Roberto; Pérez Mayán, Concepción; Pérez Meixeira, Sara; Pérez Melón, Cristina; Pérez Pérez, Carlos; Pérez Rodríguez, Adolfo Telmo; Pérez Rodríguez, Juan Antonio; Pérez Romero, Minerva; Pernas Rodríguez, Carmen; Piñeiro Gómez-Durán, Luis; Piñeiro Moyá, Juan; Platero Vázquez, María Victoria; Polo Infante, Begoña; Porritt Lueiro, María Begoña; Portas Moledo, Alicia; Porteiro Fernández, César; Pousa Estévez, Lorenzo; Prieto Casado, María Angeles; Puga Sarmiento, Elías; Pugés Dorca, María Antonia; Quintela Martínez, José; Ramos Durán, Concepción; Reboreda Rivera, Mónica; Regueira Rey, José Manuel; Regueiro Martínez, Antonio Ángel; Rey García, Jesús; Rey Tasende, José María; Rial Verde, Consuelo I; Rico Padín, María del

Carmen; Riera Taboas, Laura; Río Orgeira, José Antonio; Ríos Cerviño, María Dolores; Ríos Rey, María Teresa; Rivas Quelle, Maite; Rodríguez Fernández, José Benito; Rodríguez Figueiras, María Dolores; Rodríguez Madrid, Concepción; Rodríguez Marquina, Isaura; Rodríguez Mouriz, María del Carmen; Rodríguez Rodríguez, Elisa; Rodríguez Sarandeses, Javier; Rodríguez Souto, Amelia; Romero Rodríguez, Francisco; Romero Rodríguez, Graciela; Ropero Mengibar, Caridad; Ropero Mengibar, Concepción; Rúa Fuentes, Pilar; Ruíz Rivas, Andrés; Salas Aguilera, Encarnación; Salgado Conde, José Luis; Sánchez Castro, Juan José; Sánchez Luces, Concepción; Sánchez Sánchez, Rubén; Sanisidro Vilaso, Francisco José; Sanmartín Fernández, Marcelo; Sanmartín Portas, Luis; Santiago Nieto, José Emilio; Santidrián Arias, Santiago; Santos Folgar, Myriam; Santos Nores, Juan; Sardón Lorenzo, Angeles; Sineiro Galiñanes, Elvira; Soler Martín, Rita; Soneira Soneira, María Francisca; Soto Davila, Carmen; Tato Fontaiña, María; Tocino Martín, María Pilar; Tojal del Casero, Félix; Túñez Bastida, Carmen; Turienzo Rio, Nieves; Ucha Fernández, José; Uribe Moya, Silvia Cristina; Varela Alonso, José Carlos; Varela Groba, María Isabel; Varela Prado, María Esther; Varela Ramos, Milagros; Vázquez Couso, Francisca; Vázquez Gregorio, María Dolores; Vázquez Pérez, Angela María; Vázquez Seijas, Enrique José; Veiga Domínguez, Juan Ramón; Velhas Pereira, Moncho J.; Velicia Peñas, María del Carmen; Vidal Macía, Alejandra; Vidal Sobral, Dolores; Villar Moreira, Olga María; Yun Casalilla, María Teresa.

Table S1. Baseline characteristics of participants categorized according to treatment-time regimen (all hypertension medications upon awakening or taking ≥1 of them at bedtime).

Variable	Awakening	Bedtime	P between groups
Demographic and clinical characteristics			
Participants, n	7848	7826	
Age, years	60.5±13.9	60.3±13.5	0.34
Sex, % men	56.0	54.8	0.14
Height, cm	162.8±9.6	162.6±9.6	0.11
Weight, Kg	78.6±15.3	79.0±15.0	0.25
BMI, Kg/m^2	29.6±4.8	29.7±4.6	0.15
Waist, cm	101.0±12.7	101.0±11.9	0.92
Nighttime sleep duration, h	8.8±1.4	8.8±1.4	0.30
Type 2 diabetes, %	23.1	23.7	0.47
Metabolic syndrome, %	63.6	63.5	0.87
Obstructive sleep apnea, %	4.4	4.1	0.37
Cigarette smoking, %	15.4	15.0	0.48
Obesity, %	42.1	43.0	0.28
Chronic kidney disease, %	27.8	27.5	0.67
Previous CVD events, %	9.6	9.2	0.42
Duration of known hypertension, years	8.5±8.3	8.7±7.9	0.20
Clinical laboratory test values			
Glucose, mg/dl	107.9±32.2	107.5±31.7	0.45
Creatinine, mg/dl	1.04±0.52	1.02±0.86	0.14
Uric acid, mg/dl	5.8±1.9	5.7±1.9	0.24
Total cholesterol, mg/dl	204.4±43.3	206.1±42.6	0.59
Triglycerides, mg/dl	131.5±81.2	131.2±77.7	0.83
HDL-cholesterol, mg/dl	52.5±15.6	52.9±13.9	0.23
LDL-cholesterol, mg/dl	125.5±37.3	126.0±37.1	0.45
Estimated glomerular filtration rate	78.6±24.1	79.6±22.1	0.16
Estimated glomerular filtration rate <60, %	17.8	16.7	0.06
Albumin/creatinine ratio, mg/gCr, median (interquartile range)	6.5 (3.0-19.7)	6.3 (3.0-16.5)	0.77
Office* and ambulatory BP			
Office SBP, mmHg	149.9±20.6	149.5±19.7	0.45
Office DBP, mmHg	86.0±11.8	85.6±12.2	0.30
Office PP, mmHg	63.9±16.8	63.9±16.5	0.68
Office heart rate, beats/min	73.1±12.4	72.8±12.2	0.21

Awake SBP mean, mmHg	135.6±14.9	135.5±14.0	0.56
Asleep SBP mean, mmHg	122.5±15.5	122.7±14.7	0.44
48h SBP mean, mmHg	131.1±14.2	131.0±13.3	0.77
Sleep-time relative SBP decline, %	9.5±7.8	9.3±7.6	0.08
Awake DBP mean, mmHg	81.3±11.6	80.9±11.3	0.33
Asleep DBP mean, mmHg	69.7±10.2	69.6±10.0	0.28
48h DBP mean, mmHg	77.2±10.6	76.9±10.3	0.21
Sleep-time relative DBP decline, %	13.8±8.4	13.7±8.2	0.24
Non-dipper, %	50.1	50.9	0.23

Values shown as mean±SD, unless otherwise indicated. Sleep-time relative BP decline, index of BP dipping, defined as percent decrease in mean BP during nighttime sleep relative to mean BP during daytime activity, calculated as: ([awake BP mean – asleep BP mean]/awake BP mean) x 100. Non-dipper: individuals with sleep-time relative SBP decline <10%, using data sampled by ABPM for 48 consecutive hours.

*Values correspond to average of three conventional BP measurements obtained per participant at the clinic in the morning before initiating 48h ABPM.

Table S2. Final characteristics of patients investigated categorized according to treatment-time regimen (either all hypertension medications upon awakening or taking ≥1 medications at bedtime).

Variable	Awakening	Bedtime	P between groups
Participants, n	7848	7826	
Hypertension treatment			
Number of medications	1.9±1.0	1.9±0.9	0.16
ARB, %	49.4	49.8	0.62
ACEI, %	19.0	19.5	0.39
CCB, %	31.7	31.1	0.43
ß-blocker, %	16.0	15.9	0.81
Diuretic, %	37.4	36.8	0.39
Clinical laboratory test values			
Glucose, mg/dl	108.2±33.1	108.1±31.2	0.90
Creatinine, mg/dl	1.07±0.60	1.03±0.87	<0.001
Uric acid, mg/dl	5.8±2.0	5.7±2.1	0.10
Total cholesterol, mg/dl	201.4±42.5	202.4±41.8	0.16
Triglycerides, mg/dl	131.0±79.4	130.5±75.8	0.67
HDL-cholesterol, mg/dl	52.4±15.8	53.3±15.0	<0.001
LDL-cholesterol, mg/dl	122.1±40.9	122.3±37.2	0.84
Estimated glomerular filtration rate	76.1±27.0	80.5±23.5	<0.001
Estimated glomerular filtration rate <60. %	23.7	17.5	<0.001
Albumin/creatinine ratio, mg/gCr, median (interquartile range)	6.3 (3.0-20.0)	6.0 (3.1-15.4)	0.40
Office* and ambulatory BP			
Office SBP, mmHg	143.2±21.3	139.7±19.0	<0.001
Office DBP, mmHg	82.5±12.5	80.8±11.8	<0.001
Office PP, mmHg	60.7±16.6	58.9±15.6	<0.001
Office heart rate, beats/min	72.1±12.7	72.0±12.3	0.78
Awake SBP mean, mmHg	129.8±14.8	129.6±12.9	0.66
Asleep SBP mean, mmHg	117.8±16.7	113.2±14.0	<0.001
48h SBP mean, mmHg	125.7±14.6	123.8±12.4	<0.001
Sleep-time relative SBP decline, %	9.1±8.4	12.5±7.5	<0.001
Awake DBP mean, mmHg	77.1±10.7	76.9±10.0	0.71
Asleep DBP mean, mmHg	66.1±10.1	63.6±9.2	<0.001

48h DBP mean, mmHg	73.3±9.9	71.8±9.2	<0.001
Sleep-time relative DBP decline, %	13.8±9.4	17.0±8.4	<0.001
Non-dipper, %	49.5	31.8	<0.001
Controlled awake BP, %	61.2	63.0	0.12
Controlled asleep BP, %	53.8	64.6	<0.001
Decrease in ambulatory BP from baseline			
Awake SBP mean, mmHg	5.8±14.4	5.9±14.6	0.34
Asleep SBP mean, mmHg	4.7±13.7	9.5±14.6	<0.001
48h SBP mean, mmHg	5.4±13.4	7.2±13.7	<0.001
Sleep-time relative SBP decline, %	0.4±6.9	-3.2±7.6	<0.001
Awake DBP mean, mmHg	4.2±8.8	4.0±8.8	0.69
Asleep DBP mean, mmHg	3.6±8.6	6.0±9.0	<0.001
48h DBP mean, mmHg	3.9±8.1	5.1±8.2	<0.001
Sleep-time relative DBP decline, %	0.0±7.9	-3.3±8.5	<0.001

Values shown as mean±SD, unless otherwise indicated. Sleep-time relative BP decline, index of BP dipping, defined as percent decrease in BP during nighttime sleep relative to mean BP during daytime activity, calculated as: ([awake BP mean – asleep BP mean]/awake BP mean) x 100. Non-dipper: individuals with sleep-time relative SBP decline <10%, using data sampled by ABPM for 48 consecutive hours. Awake SBP/DBP mean considered controlled if <135/85 mmHg. Asleep SBP/DBP mean considered controlled if <120/70 mmHg.

*Values correspond to average of three conventional BP measurements obtained per participant at the clinic in the morning before initiating 48h ABPM.

†A negative value indicates increase from baseline (e.g., in sleep-time relative BP decline towards a more dipper BP pattern in the bedtime-treatment group).