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ARTICLE

Risk of incident chronic kidney disease is better reduced by bedtime than upon-awakening ingestion of hypertension medications

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Abstract

This trial investigated whether therapy with the entire daily dose of ≥1 hypertension medications at bedtime exerts a greater reduction in the risk of incident chronic kidney disease (CKD) than therapy with all medications upon awakening. We conducted a prospective, open-label, blinded endpoint trial of 2078 hypertensive patients without CKD (1017 men/1061 women, 53.6 ± 13.7 years of age) randomized to ingest all their prescribed hypertension medications upon awakening ($n = 1041$) or the entire daily dose of ≥1 of those medications at bedtime ($n = 1037$). During a 5.9-year median follow-up, 368 participants developed CKD. Patients of the bedtime, compared with the morning, treatment group showed (i) significantly lower asleep blood pressure (BP) mean, greater sleep-time relative BP decline, and attenuated prevalence of non-dipping at the final evaluation (38 vs. 55%; $P < 0.001$); and (ii) a significantly lower hazard ratio of CKD, adjusted for the significant influential characteristics of age, serum creatinine, urinary albumin, type 2 diabetes, previous cardiovascular event, asleep systolic BP mean, and sleep-time relative systolic BP decline (0.27 (95% confidence interval: 0.21–0.36); event-rate 8.3 vs. 27.1% in the bedtime and morning-treatment groups; $P < 0.001$). Greater benefit was observed for bedtime than awakening treatment, with angiotensin converting enzyme inhibitors and angiotensin receptor blockers. In hypertensive patients without CKD, ingestion of ≥1 BP-lowering medications at bedtime, mainly those modulating or blocking the effects of angiotensin II, compared with ingestion of all such medications upon-awakening, resulted in improved ambulatory BP control (significant further decrease of asleep BP and enhanced sleep-time relative BP decline) and reduced risk of incident CKD.

Introduction

Pharmacological blockade of the renin-angiotensin-aldosterone system (RAAS) by angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) reduces albuminuria and blood pressure (BP) [1–3], although the potential benefits of RAAS blockade on renal outcomes is uncertain [4]. Multiple prospective clinical trials reviewed elsewhere [5, 6] document bedtime ingestion of hypertension medications and their combinations, including those modulating or blocking the effects of angiotensin II, significantly improves sleep-time BP control and reduces adverse effects. In particular, because the RAAS is highly circadian rhythmic and activates during nighttime sleep [7, 8], bedtime ingestion, relative to upon-awakening dosing, of ARBs and ACEIs results in a greater therapeutic effect on asleep BP mean, independently of medication terminal half-life [5, 6]. This discrepancy has also been documented for the bedtime vs. morning regimen of the ARB-calcium channel blocker (CCB), ACEI-CCB, and ARB-diuretic combination therapies [5, 6]. Importantly, bedtime, but not morning, ingestion of valsartan [9], candesartan [10, 11], and olmesartan [12], also significantly reduces urinary albumin excretion, which correlates strongly with the magnitude of treatment-induced reduction in asleep BP mean and increase in sleep-time relative BP decline [9].

Control of asleep BP by a proper choice of hypertension treatment time is clinically relevant. Several studies have documented the sleep-time BP determined by ambulatory BP (ABP) monitoring (ABPM), but neither ABPM-derived awake BP mean nor daytime office BP measurements (OBPM), is a significant prognostic marker of incident chronic kidney disease (CKD) [13–16]. Most importantly,

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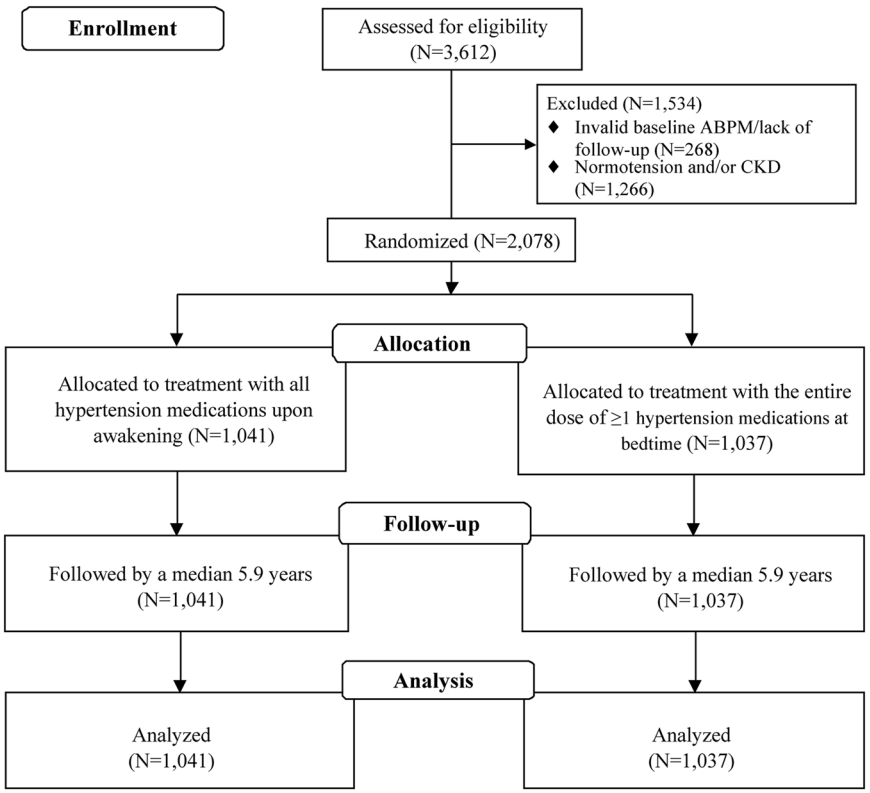


Fig. 1 Flow diagram of participants in the study

the progressive treatment-induced decrease in asleep BP mean, but not in OBPM, and increase in sleep-time relative BP decline toward a more dipper BP pattern might be a significant method for reducing CKD risk and progression, as recently documented [16]. Furthermore, findings of numerous independent prospective studies and meta-analyses demonstrate that elevated sleep-time BP constitutes a significant cardiovascular disease (CVD) risk factor, independently of daytime OBPM and ABPM-derived awake or 24 h BP means, both in patients without [17–19] and those with CKD [20–22].

Similarly, the MAPEC Study (Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares, i.e., Ambulatory Blood Pressure Monitoring for Prediction of Cardiovascular Events), a randomized trial specifically designed to investigate whether bedtime, relative to morning hypertension therapy, results in reduced risks of CVD, type 2 diabetes, and incident CKD, documented significantly better reductions of CVD events [23]—including in high-risk patients with CKD [21]—and the risk of developing diabetes in hypertensive patients treated at bedtime [24]. Here we complement those findings by testing the hypothesis, which has never before been prospectively investigated, that bedtime therapy with the entire daily dose of ≥1 hypertension medications offers better protection against development of CKD than morning-time therapy with all medications.

Methods

Inclusion and exclusion criteria

Complete details of the rationale and design of the MAPEC Study are described in previous publications [18, 21, 23]. In summary, the sample consisted of Spanish individuals ≥18 years of age, who adhered to a routine of daytime activity and nighttime sleep. For the present study, we established a priori a minimum of 1-year follow-up per participant. Exclusion criteria were pregnancy, history of drug/alcohol abuse, night/shift-work employment, acquired immunodeficiency syndrome, type 1 diabetes, secondary hypertension, CVD disorders (unstable angina pectoris, heart failure, life-threatening arrhythmia, and grade III–IV retinopathy), nephropathy, intolerance to ABPM, and inability to communicate and comply with all study requirements. This prospective single-center study (clinicaltrials.gov registration number NCT00295542) was approved by the state Ethics Committee of Clinical Research. All participants provided written informed consent.

Participants and diagnostic criteria

Between 2000 and 2007, we recruited 3612 persons, with 3344 (1718 men/1626 women, 52.6 ± 14.5 [mean ± SD] years of age) providing all of the information required for

the study. The remaining 268 individuals were excluded due to inadequate ABPM sampling at baseline without consent for additional ABPM evaluations and lack of the required 1-year minimum follow-up. At the time-of-recruitment, 1266 participants were normotensive and/or already had a diagnosis of CKD and, therefore, were also excluded from analyses. Thus, the final evaluated population for the hypotheses tested herein consisted of 2078 hypertensive patients without CKD, 1017 men/1061 women, aged 53.6 ± 13.7 years (Fig. 1).

Hypertension in untreated participants was defined according to current ABPM criteria, i.e., awake systolic (SBP)/diastolic BP (DBP) mean ≥135/85 mmHg or asleep SBP/DBP mean ≥120/70 mmHg [25, 26]. CKD was defined as either estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2, albuminuria (urinary albumin excretion ≥30 mg/24 h urine), or both, on at least two occasions ≥3 months apart [27]. We also analyzed incident CKD based on diminished eGFR accompanied by a ≥25% eGFR decline from baseline, although this definition applies to CKD progression instead of de novo diagnosis [28]. eGFR (ml/min/1.73 m^2) was estimated by the CKD-EPI equation [29]. 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 [30]. Diagnosis of metabolic syndrome was established by the National Cholesterol Education Program Adult Treatment Panel III (ATP-III) revised definition [31]. Obesity was defined as body mass index ≥30 kg/m^2. Anemia was defined as hemoglobin <13 g/dl in men and <12 g/dl in women. Diagnosis of obstructive sleep apnea (apnea/hypopnea index ≥10) was corroborated by overnight in-hospital polysomnography when the participant reported significant daytime hypersomnia or he/she or his/her bedmate reported loud snoring, choking, interrupted breathing, and/or multiple awakenings during nighttime sleep.

Study design

The MAPEC Study was a single-center, prospective, randomized, open-label, blinded endpoint (PROBE) trial. Hypertensive participants were randomized, using an allocation table constructed by a computerized random-number generator, either to ingest all BP-lowering medications upon awakening (awakening-treatment regimen) or the complete daily dose of ≥1 of those medications at bedtime (bedtime-treatment regimen). Individuals were randomized to treatment-time (upon awakening or at bedtime) separately for each allowed initial individual hypertension medication monotherapy (valsartan, telmisartan, olmesartan, ramipril, spirapril, amlodipine, nifedipine GITS, nebivolol, torasemide, and doxazosin GITS) to ensure the proportion of patients treated in a first step with each medication-class was similar across the two treatment-time arms. If, based on ABPM threshold criteria, the ABP of a given patient remained uncontrolled at any time during follow-up, additional medications could be added in keeping with current clinical practice. The diuretic hydrochlorothiazide (up to 25 mg/day) or a dihydropyridine CCB were the primary choices as second-line therapy (mainly in combination with ARB/ACEI), and either one of these medications or the α-blocker doxazosin were the choices as third-line therapy [23].

Changes in therapeutic scheme during follow-up in uncontrolled patients (those with ABP above the thresholds provided above) were based on results of the periodic evaluations by ABPM. Adherence to the time-of-day schedule of treatment and prescribed medication(s) was enforced at each follow-up visit. Adverse events, including type, duration, seriousness, intensity, and possible relation to hypertension treatment, were registered as spontaneously reported by the patient and/or detected by the investigators through non-directive questioning and physical examination at each follow-up visit.

ABP, wrist activity, and other assessments

At inclusion and thereafter at scheduled clinic visits for ABPM throughout follow-up, the same investigator obtained six consecutive OBPM from participants after resting in a seated position for ≥10 min using a validated automatic oscillometric device (HEM-705IT, Omron Health Care Inc., Vernon Hills, IL). Immediately thereafter, ABPM was instituted with a properly calibrated and validated SpaceLabs 90207 device (SpaceLabs Inc., Issaquah, WA) 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. 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 usual 24 h, to optimize the reproducibility of results, as accurate determination of ABP characteristics (including mean BP values) and dipping classification depends markedly on ABPM duration [32]. Individuals were instructed to adhere to usual activities with minimal restrictions but to avoid daytime napping and maintain a similar activity-rest schedule during the two consecutive days of monitoring. In keeping with current recommendations [25], BP series were considered invalid for analysis, and thus ABPM was required, if ≥30% of the measurements were missing, data were lacking for an interval of >2 h or obtained when the rest-activity schedule was irregular during the 2 days of monitoring, or nighttime sleep duration was <6 or >12 h.

All participants also wore an actigraph (Mini-Motion-Logger, Ambulatory Monitoring Inc., Ardsley, NY) on the dominant wrist to record the level of physical activity at 1-

min intervals during each 48 h ABPM. Actigraphy data were used to verify the absence of daytime napping and to precisely define the commencement and termination of the daytime awake and nighttime asleep spans of each participant using dedicated software to accurately derive the respective ABP means [33].

Blood and urine samples were obtained at scheduled visits for ABPM. Participants arrived to the clinic between 08:00 and 09:00 h, after overnight fasting, for blood withdrawal from an antecubital vein. Participants collected all their urine voids during the first 24 h of ABPM. Blood and urine samples were analyzed using routine automatic techniques in the hospital laboratory.

Follow-up

Evaluation procedures identical to those described above, including OBPM, 48 h ABPM/wrist activity monitoring, and blood/urine analysis, plus other complementary tests as ordered by physicians (e.g., electrocardiogram, funduscopic examination, echocardiogram, etc.), were scheduled annually or more frequently (3 months after any doctor-ordered change in therapy to improve ABP control). Blood/urine analyses were also performed at intermediate clinic visits, as scheduled by the participating physicians in keeping with current medical practice; in particular, such analyses were repeated within 3 months when showing elevated fasting glucose, albuminuria, or reduced eGFR to allow for proper diagnosis of incident diabetes or CKD as defined above. Investigators blinded to the hypertension treatment scheme of the patients and not involved in clinic evaluations, ABP measurements, or statistical analyses assessed the development of CKD, among other MAPEC Study outcome variables of interest [23]. Complete clinical records of all enrolled participants were reviewed at all visits plus the year following the last ABPM.

Statistical methods

ABPM profiles were 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 minus 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 nighttime sleep as differentiated by wrist actigraphy. To avoid confounding by non-equidistant BP sampling on mean values [25], 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), the percent decrease in mean BP during nighttime sleep relative to mean BP during daytime activity, was calculated as follows: [(awake ABP mean—asleep ABP mean)/awake ABP mean] × 100, utilizing all valid data pertaining to 48 h ABPM. Participants were designated dipper if the sleep-time relative SBP decline was ≥10% and as non-dipper otherwise.

Demographic and clinical characteristics were compared on an intention-to-treat basis among participants randomized to the two treatment-time regimens by a two-sided *t*-test (continuous variables) or non-parametric χ^2-test (proportions). For survival analysis, follow-up was established as either the interval of time to the confirmed diagnosis of CKD or the interval of time to the last clinical evaluation in non-event participants. Survival curves were generated using the Kaplan–Meier product-limit method and compared using the Mantel log-rank test. The Cox proportional-hazard model, adjusted for significant confounding variables, was also used to estimate hazard ratios (HRs), with 95% CI, for events associated with treatment-time regimen and class of hypertension medication. All demographic, anthropometric, and clinical laboratory variables listed in Table 1 were tested as potential confounding variables by stepwise Cox survival analysis. Adjustments were finally applied for the significant influential characteristics of age, serum creatinine, urinary albumin, type 2 diabetes, previous CVD event, asleep SBP mean, and sleep-time relative SBP decline, as these factors were the only ones jointly significant in the Cox regression analyses.

Results

Demographic, laboratory, and BP variables of morning- and bedtime-treatment groups

Among the 2078 participants in this trial, 1041 were randomized to the morning-treatment regimen and 1037 to the bedtime-treatment regimen (Fig. 1). At baseline, there were no statistically significant differences between the two groups with respect to the prevalence of metabolic syndrome, type 2 diabetes, obstructive sleep apnea, anemia, and obesity, plus all evaluated demographic, anthropometric, and clinical laboratory test variables (Table 1). OBPM, average ABP values, and prevalence of non-dipping at baseline were also not significantly different between the two groups (Table 1).

In keeping with the study design, there were no differences at the end of the trial in the classes or number of hypertension medications used for therapy between the patients of the two treatment-time groups (Table 2). The

Table 1 Baseline characteristics of investigated participants categorized according to treatment-time regimen (either all hypertension medications upon awakening or the entire daily dose of ≥1 medications at bedtime)

Variable	Awakening	Bedtime	*P* between groups
Demographic, anthropometric, and clinical characteristics			
Participants, *n*	1041	1037	
Age, years	54.0 ± 13.1	53.4 ± 12.5	0.218
Sex, % men	48.9	49.0	0.967
Height, cm	161.7 ± 10.0	162.2 ± 9.9	0.284
Weight, Kg	77.8 ± 15.1	77.7 ± 14.9	0.881
BMI, Kg/m^2	29.7 ± 5.0	29.5 ± 4.9	0.344
Waist, cm	95.8 ± 12.3	95.0 ± 11.9	0.079
Type 2 diabetes, %	16.0	16.6	0.693
Metabolic syndrome, %	54.4	50.7	0.088
Obstructive sleep apnea, %	8.3	8.8	0.675
Cigarette smoking, %	13.1	13.2	0.910
Obesity, %	42.6	40.6	0.342
Anemia, %	5.8	4.4	0.138
Previous CVD events, %	4.3	3.4	0.262
Duration of known hypertension, years	6.8 ± 8.1	6.7 ± 7.9	0.516
Clinical laboratory test values			
Glucose, mg/dl	106.8 ± 30.5	104.3 ± 28.1	0.105
Creatinine, mg/dl	0.94 ± 0.17	0.93 ± 0.16	0.143
Uric acid, mg/dl	5.6 ± 1.5	5.6 ± 1.5	0.456
Total cholesterol, mg/dl	212.5 ± 38.1	211.4 ± 40.5	0.519
Triglycerides, mg/dl	114.1 ± 61.3	112.8 ± 67.8	0.646
HDL-cholesterol, mg/dl	48.7 ± 15.4	48.5 ± 15.1	0.763
LDL-cholesterol, mg/dl	139.8 ± 33.4	139.7 ± 34.5	0.924
Hemoglobin, g/dl	14.2 ± 1.4	14.2 ± 1.3	0.914
Fibrinogen, mg/dl	322.6 ± 78.5	317.1 ± 77.6	0.162
Erythrocyte sedimentation rate, mm	14.0 ± 10.4	13.6 ± 10.6	0.472
Estimated glomerular filtration rate	84.1 ± 14.6	84.8 ± 14.5	0.182
Albumin, mg/24 h urine, median (interquartile range)	9.1 (5.5–14.9)	9.0 (5.7–14.5)	0.575
Clinic[a] and ambulatory BP			
Clinic SBP, mmHg	153.5 ± 20.0	153.4 ± 18.3	0.943
Clinic DBP, mmHg	87.8 ± 10.9	88.2 ± 11.0	0.430
Clinic PP, mmHg	65.7 ± 14.7	65.2 ± 13.6	0.478
Clinic heart rate, beats/min	74.6 ± 12.3	75.2 ± 12.9	0.322
Nighttime sleep duration, h	8.9 ± 1.1	8.8 ± 1.1	0.411
Awake SBP mean, mmHg	136.2 ± 14.6	136.3 ± 13.0	0.883
Asleep SBP mean, mmHg	123.1 ± 15.5	124.3 ± 14.2	0.159
48 h SBP mean, mmHg	132.1 ± 14.1	132.6 ± 12.7	0.400
Sleep-time relative SBP decline, %	9.6 ± 7.6	9.1 ± 7.3	0.211
Awake DBP mean, mmHg	83.2 ± 11.0	83.5 ± 10.5	0.640
Asleep DBP mean, mmHg	71.7 ± 9.8	71.8 ± 9.7	0.419
48 h DBP mean, mmHg	79.5 ± 10.2	79.8 ± 9.8	0.214
Sleep-time relative DBP decline, %	14.2 ± 8.2	14.0 ± 7.8	0.427
Non-dipper, %	49.2	50.1	0.661

Values shown as mean ± SD, unless otherwise indicated. Metabolic syndrome: National Cholesterol Education Program Adult Treatment Panel III (ATP-III) revised definition [31]. Obesity: body mass index (BMI) ≥30 Kg/m^2. Glomerular filtration rate (ml/min/1.73 m^2) was estimated using the CKD-EPI equation [29]. Sleep-time relative BP decline, index of BP dipping, defined as percent decline in mean BP during nighttime sleep relative to mean BP during daytime activity, calculated as: ((awake BP mean—asleep BP mean)/awake BP mean) × 100. Non-dipper: participants with sleep-time relative SBP decline <10%, using data sampled by ABPM for 48 consecutive hours

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

proportions of patients in the morning and bedtime-therapy groups treated with statins (20.6 vs. 19.8%, respectively; $P = 0.654$) or low-dose (100 mg/day) aspirin (11.3 vs. 12.6%; $P = 0.363$) were also similar. At the time-of their final ABPM evaluation, patients in the bedtime-therapy regimen showed lower creatinine, uric acid, erythrocyte sedimentation velocity, and albumin, plus higher eGFR than those treated upon awakening (Table 2).

The data pertaining to the last ABPM evaluation revealed significantly lower asleep, but not awake, SBP and DBP means in participants randomized to the bedtime- rather than morning-treatment regimen ($P < 0.001$; Table 2). The sleep-time relative SBP/DBP decline was significantly greater among those of the bedtime-treatment regimen; accordingly, the proportion of patients with non-dipper BP pattern was significantly lower in the bedtime than the morning-treatment regimen group (38 vs. 55%; $P < 0.001$). Moreover, the proportion of participants with properly controlled ABP, particularly during nighttime sleep, was also significantly greater among those treated at bedtime ($P < 0.001$; Table 2). There were no treatment-time differences in the prevalence of patients reporting adverse effects (5.9 vs. 6.1% for morning and bedtime-treatment regimens, respectively; $P = 0.432$). Due to strict patient control by periodic ABPM during follow-up [23], only three patients in each of the morning and bedtime-treatment groups experienced sleep-time hypotension, as defined by current ABPM criteria; [25] none of them developed CKD.

CKD risk according to hypertension treatment-time regimen

During the median follow-up period of 5.9 years (range 1.3–8.9 years), 368 participants developed CKD. Those ingesting ≥1 hypertension medications at bedtime showed a significantly lower HR of CKD (adjusted by the only significant influential characteristics, among all variables listed in Table 1, of age, serum creatinine, urinary albumin, type 2 diabetes, previous CVD event, asleep SBP mean, and sleep-time relative SBP decline) than those ingesting all medications upon awakening (HR = 0.28 (95% CI: 0.22–0.35); event-rate 8.3 vs. 27.1%, respectively, in the bedtime and awakening-treatment groups; $P < 0.001$). Independently of hypertension treatment-time, increased HR of CKD was jointly associated with older age (1.03 (1.02–1.04), $P < 0.001$, per year); elevated serum creatinine (1.22 (1.18–1.27), $P < 0.001$, per mg/l); elevated urinary albumin (1.25 [1.19–1.31], $P < 0.001$, per $10 \times \log$(mg/24 h urine)), presence of type 2 diabetes (1.39 (1.06–1.81), $P = 0.017$); history of previous CVD event (1.75 (1.15–2.67), $P = 0.010$); elevated asleep SBP mean (1.20 (1.11–1.29), $P < 0.001$, per 10 mmHg), and diminished sleep-time relative SBP decline (0.97 [0.95–0.98], $P < 0.001$, per 1% reduction).

Figure 2 (top left) presents the Kaplan–Meier survival curves for the patients of the two treatment-time groups, demonstrating the highly significant difference between groups in the CKD event-free interval (log-rank 119.7, $P < 0.001$). There was a further benefit in preventing CKD among patients ingesting not just one but all BP-lowering medications at bedtime (event-rate 3.8 vs. 13.5% in patients ingesting medications both upon awakening and at bedtime; $P < 0.001$; Fig. 2, top right). The benefits of bedtime hypertension treatment also included a statistically significant reduction in the incidence of diminished eGFR (Fig. 2, bottom left) and albuminuria (Fig. 2, bottom right) when analyzed separately as outcome variables (HR = 0.27 (0.21–0.36) and 0.30 (0.18–0.50), respectively; $P < 0.001$). Restriction of event-cases to patients within diminished eGFR (<60 ml/min/1.73 m^2) accompanied by a ≥25% eGFR decline from baseline did not change any conclusions regarding the advantages of the bedtime-treatment regimen (HR = 0.25 (0.18–0.35), $P < 0.001$).

CKD risk according to class of hypertension medication and treatment-time regimen

Figure 3 (top) shows the HR of incident CKD for participants of the morning-treatment regimen group categorized according to class of hypertension medication ingested upon awakening. Each category includes all patients ingesting that particular class of hypertension medication upon awakening, either alone or along with other classes of medications also ingested upon awakening. We used patients ingesting an ACEI as the reference group, as this category had the lowest CKD event-rate among all hypertension medications classes. The adjusted HR of CKD was equivalent across all classes of medications when ingested in the morning. Figure 3 (bottom) presents the adjusted HR of incident CKD for participants of the bedtime-treatment regimen group. Patients ingesting mainly an ACEI but also an ARB or ß-blocker (primarily nebivolol) at bedtime had significantly lower HR of CKD than patients ingesting any other medication class also at bedtime (Fig. 3, bottom).

Additionally, we compared the risk of CKD between patients of the two treatment-time regimen groups further categorized as a function of the class of hypertensive medication used for therapy. Figure 4 shows the HR of incident CKD for participants ingesting any given class of hypertension medication upon awakening vs. at bedtime. The comparison for any given class was performed between patients ingesting the tested class of medication upon awakening vs. participants ingesting the same specified class of medication at bedtime. Lower CKD risk was observed for bedtime than for awakening treatment for

Table 2 Final characteristics obtained at the last ABPM evaluation of patients investigated according to treatment-time (either all hypertension medications upon awakening or ≥1 medications at bedtime)

Variable	Awakening	Bedtime	*P* between groups
Patients, *n*	1041	1037	
Hypertension treatment			
Number of medications	1.9 ± 1.0	1.9 ± 1.1	0.212
1 medication, %	50.5	47.0	0.104
2 medications, %	19.3	19.4	0.966
≥3 medications, %	30.2	33.6	0.089
ARB, %	55.7	59.8	0.104
ACEI, %	21.5	19.0	0.153
CCB, %	30.9	34.0	0.130
α–blocker, %	14.6	16.1	0.342
ß-blocker, %	20.8	21.3	0.795
Diuretic, %	41.1	37.1	0.063
Blood and urine laboratory test values			
Glucose, mg/dl	108.1 ± 31.6	106.3 ± 28.0	0.178
Creatinine, mg/dl	0.98 ± 0.23	0.93 ± 0.17	<0.001
Uric acid, mg/dl	5.7 ± 1.6	5.6 ± 1.5	0.010
Total cholesterol, mg/dl	207.5 ± 37.2	208.2 ± 39.1	0.678
Triglycerides, mg/dl	116.6 ± 68.0	110.9 ± 61.0	0.051
HDL-cholesterol, mg/dl	47.9 ± 15.5	48.8 ± 15.0	0.183
LDL-cholesterol, mg/dl	135.0 ± 33.1	135.6 ± 33.9	0.703
Hemoglobin, g/dl	14.1 ± 1.4	14.2 ± 1.3	0.922
Fibrinogen, mg/dl	327.1 ± 76.8	324.1 ± 77.0	0.443
Erythrocyte sedimentation rate, mm	14.4 ± 12.6	13.2 ± 11.3	0.032
Estimated glomerular filtration rate	76.5 ± 18.5	82.0 ± 16.3	<0.001
Albumin, mg/24 h urine, median (interquartile range)	9.0 (5.6–18.4)	8.3 (5.7–12.1)	<0.001
Clinic[a] and ambulatory BP			
Clinic SBP, mmHg	144.5 ± 22.6	141.8 ± 19.2	0.003
Clinic DBP, mmHg	82.4 ± 13.0	81.8 ± 11.8	0.238
Clinic PP, mmHg	62.1 ± 15.8	60.0 ± 13.5	0.001
Clinic HR, beats/min	73.0 ± 13.5	73.3 ± 13.5	0.574
Nighttime sleep duration, h	8.9 ± 1.1	8.8 ± 1.1	0.102
Awake SBP mean, mmHg	125.7 ± 14.4	125.4 ± 13.0	0.665
Asleep SBP mean, mmHg	115.1 ± 16.2	111.0 ± 14.6	<0.001
48 h SBP mean, mmHg	122.3 ± 14.1	121.2 ± 12.8	0.072
Sleep-time relative SBP decline, %	8.3 ± 8.9	11.0 ± 7.6	<0.001
Awake DBP mean, mmHg	76.7 ± 10.9	77.0 ± 10.1	0.434
Asleep DBP mean, mmHg	66.8 ± 10.6	64.7 ± 9.8	<0.001
48 h DBP mean, mmHg	73.7 ± 10.3	73.1 ± 9.5	0.592
Sleep-time relative DBP decline, %	13.8 ± 10.4	16.0 ± 9.0	<0.001
Non-dipper, %	55.4	37.8	<0.001
Controlled ambulatory BP, %	52.6	58.1	0.013
Controlled awake BP, %	70.7	72.3	0.412
Controlled asleep BP, %	58.7	68.2	<0.001

Values shown as mean ± SD, unless otherwise indicated. Glomerular filtration rate (ml/min/1.73 m^2) was estimated using the CKD-EPI equation [29]. Sleep-time relative BP decline, index of BP dipping, defined as percent decline in mean BP during nighttime sleep relative to mean BP during daytime activity, calculated as: [(awake BP mean—asleep BP mean)/awake BP mean] × 100. Non-dipper: patients 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. ABP considered controlled if both awake and asleep SBP/DBP means were below those thresholds

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

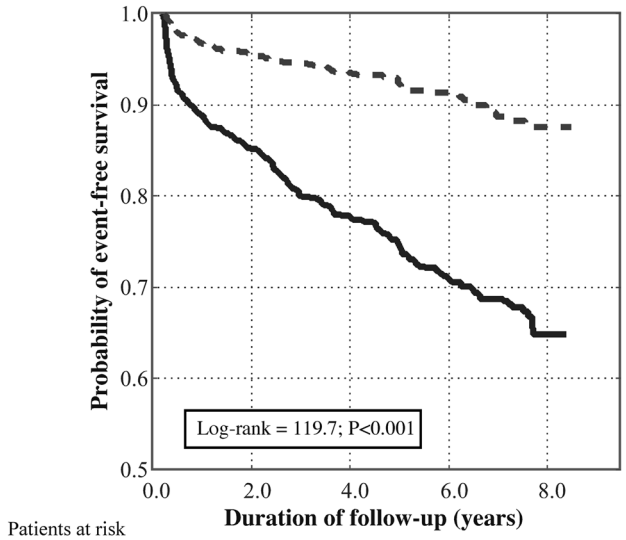
every class of BP-lowering medication; however, the greatest treatment-time differences were observed for ACEIs (HR = 0.20 (0.10–0.38); $P < 0.001$) and ARBs (0.32 (0.21–0.51), $P < 0.001$; Fig. 4).

Discussion

Our study is the first, and to date only, reported outcomes trial with a meaningful follow-up duration to assess prospectively the hypothesis that bedtime treatment with the entire daily dose of ≥1 hypertension medications exerts not only better BP control but better protection against CKD than treatment with all such medications ingested upon awakening. The results document, first, greater ABP control in hypertensive patients ingesting ≥1 BP-lowering medications at bedtime than in those ingesting all such medications upon awakening. The main differences between the bedtime vs. awakening-treatment regimens in terms of ABP control were achievement, in the former, of (i) significantly lower asleep BP mean and (ii) greater sleep-time relative BP decline, without loss-of-awake BP-lowering efficacy (Table 2). The ingestion-time-dependent effects on asleep BP control were strongly associated with attenuated risk of CKD. Indeed, beyond hypertension-treatment time, progressive decrease in the asleep BP mean during the 5.9 median years of follow-up was the most significant predictor of reduced CKD risk, independently of other associated conventional variables, such as older age, elevated serum creatinine and/or urinary albumin, and diagnosis of type 2 diabetes [16]. As documented in a series of prospective controlled trials reviewed elsewhere [5, 6], bedtime hypertension treatment is the simplest strategy for successfully achieving the therapeutic goal of adequate asleep BP reduction and control. One could thus conclude that the significant 72% reduction in CKD risk by ingestion of the entire daily dose of ≥1 BP-lowering medications at bedtime, compared with ingestion of all such medications upon awakening (Fig. 2), is somehow linked to better achievement of this novel hypertension therapeutic goal through improved targeting of the circadian rhythm organized underlying biological mechanisms [7, 8].

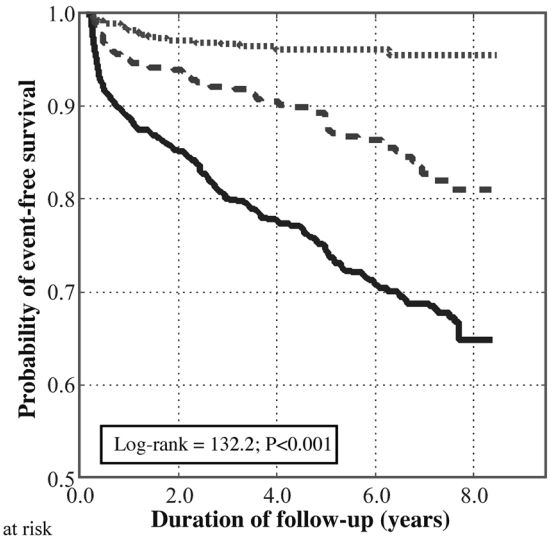
The randomization for this trial, performed independently for each of the allowed choices of hypertension medications, and the heretofore unique approach of systematic, periodic (at least annual) patient evaluation by highly reproducible 48 h ABPM to determine the features of the 24 h SBP/DBP pattern and to guide required changes in therapy, also allowed for a comparative investigation of the influence of different classes of hypertension medications on CKD risk. The findings summarized in Figs. 3 and 4 document significant differences in such risk between individual classes of hypertension medications when treatment time is considered. The adjusted HR of CKD across all the tested classes of hypertension medications were equivalent in those patients randomized to ingest all medications as full daily doses upon awakening (Fig. 3, top). However, among patients randomized to the bedtime regimen, ingestion of the full daily dose of an ACEI, ARB, or ß-blocker was associated with significantly lower HR of CKD compared with ingestion of any other class of medication also at bedtime (Fig. 3, bottom). We wish to emphasize that the ß-blocker mostly prescribed to participants in the MAPEC Study was nebivolol; in fact, nebivolol was only ß-blocker allowed for first randomization among previously untreated patients. Nebivolol is a third-generation, long-acting ß-blocker medication that exerts endothelium-dependent vasodilation through activation of the L3-arginine/nitric oxide pathway and the regulatory effect of the RAAS [34]. Accordingly, our findings might not be extrapolated to all ß-blockers as a class, an issue that requires further investigation. These considerations notwithstanding, the results indicate that reduced risk of CKD might be associated with RAAS blockade therapy ingested at bedtime but not upon awakening.

Our study has some potential limitations. First, the sample size of the single-center MAPEC Study does not permit evaluation of the potential predictive value of the different prescribed hypertension medications within each of the therapeutic classes. Second, the reported findings require validation and extrapolation to other ethnic groups. Finally, the use of a PROBE design might also be considered a limitation; however, the PROBE design was specifically developed for the conduct of long-term outcome trials, although it is also frequently used for the conduct of short-term efficacy clinical studies in patients evaluated in a blinded manner by ABPM. Our study also has several strengths [18, 23], mainly that it is the first trial yet to (i) provide results based on systematic periodic, at least annual, multiple evaluations by ABPM simultaneously with wrist actigraphy to precisely determine the commencement and termination of the activity and sleep spans of each participant to enable accurate derivation of the awake and asleep SBP/DBP means and sleep-time relative BP decline throughout the median 5.9 years of follow-up; (ii) define hypertension as an inclusion criterion based solely on ABP measurements, as now recommended; [25, 35] (iii) prescribe changes in therapeutic intervention during follow-up to improve control of ABP, instead of daytime OBPM; and (iv) randomize patients either to ingest all BP-lowering medications upon awakening or the complete daily dose of ≥1 of those medications at bedtime, i.e., according to the individualized rest/activity cycle that synchronizes the documented predictable-in-time 24 h changes in RAAS activation and BP patterning [7].



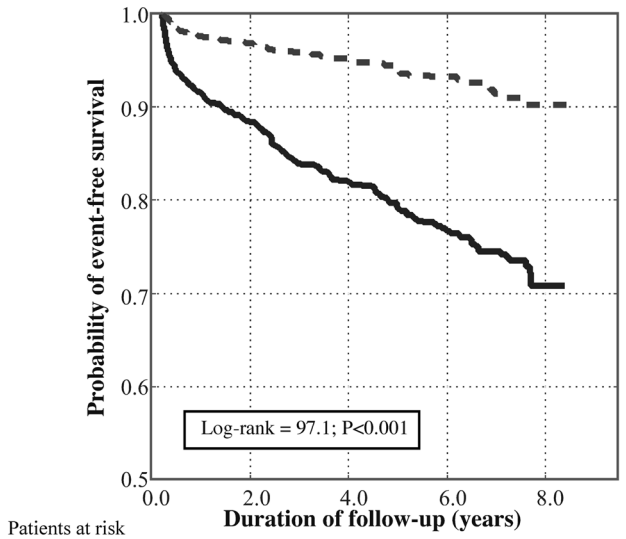
Patients at risk

Awakening	1041	889	636	434	146
Bedtime	1037	978	727	476	209



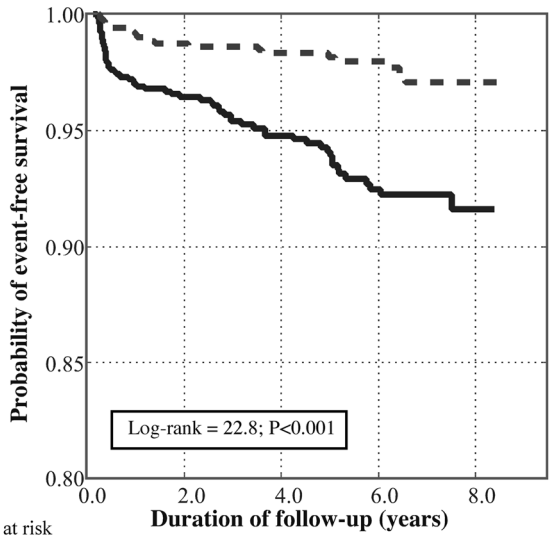
Patients at risk

Awakening	1041	889	636	434	146
Awak.+bedtime	483	448	334	227	100
Bedtime	554	530	393	249	109



Patients at risk

Awakening	1041	921	673	421	170
Bedtime	1037	990	736	483	225



Patients at risk

Awakening	1041	988	745	536	241
Bedtime	1037	1005	780	577	290

Fig. 2 Kaplan–Meier survival curves for incident chronic kidney disease (CKD; top left), diminished glomerular filtration rate (bottom left), and albuminuria (bottom right) as a function of time of day of hypertension treatment, i.e., for participants ingesting either all their prescribed blood pressure-lowering medications upon awakening (continuous line) or the entire daily dose of ≥1 of those medications at bedtime (dashed line). For CKD risk evaluation, the bedtime-treatment group was further divided into two groups: participants ingesting either all their prescribed BP-lowering medications at bedtime (dotted line) or the entire daily dose of ≥1 of those medications at bedtime and the remaining ones upon awakening (dashed line) (top right)

According to this prospective evaluation, in hypertensive patients without CKD, ingestion of the entire daily dose of ≥1 BP-lowering medications at bedtime compared with ingestion of all such medications upon awakening results in significantly improved asleep ABP control and prevention of CKD. Moreover, the levels of safety of the bedtime- and morning-treatment regimens were similar, a finding consistent with previous publications reporting that bedtime compared with morning BP therapy significantly improves ABP reduction without any increase in adverse effects [36]. Finally, antagonism of the RAAS by reduction of angiotensin II formation and blockade of its receptors achieved

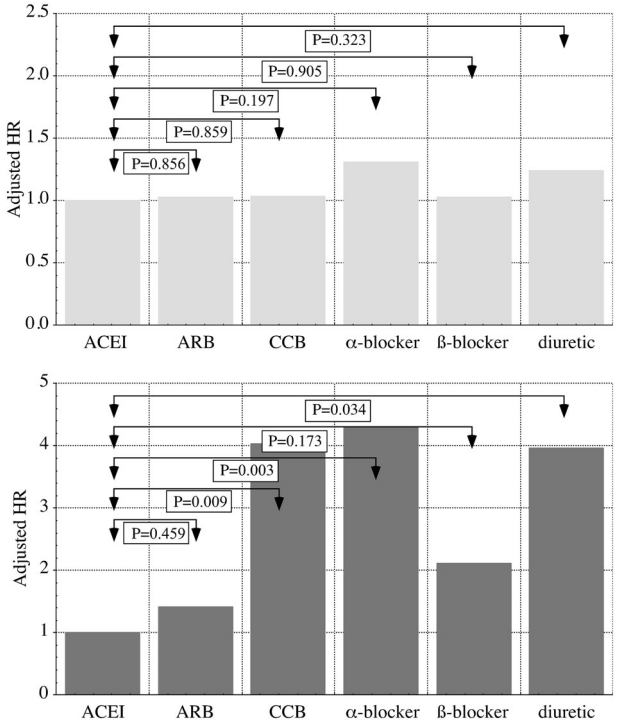


Fig. 3 Adjusted hazard ratio (HR) of incident chronic kidney disease as a function of class of hypertension medication included in the therapeutic scheme of hypertensive patients ingesting all hypertension medications upon awakening (top) or the entire dose of ≥1 of those medications at bedtime (bottom). ACEI: angiotensin converting enzyme inhibitor. ARB: angiotensin-II receptor blocker. CCB: calcium-channel blocker

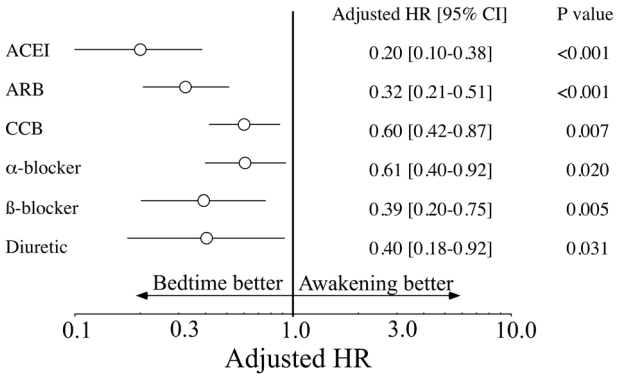


Fig. 4 Adjusted hazard ratio (HR) with 95% confidence interval (CI) of chronic kidney disease as a function of medication class and hypertension treatment-time regimen, i.e., for participants ingesting either all medications upon awakening or the entire dose of ≥1 of those medications at bedtime. Comparisons for any given class of hypertension medications was performed between participants ingesting the tested medication upon awakening alone or along with other medications ingested also upon awakening vs. participants ingesting the same class of medication at bedtime. ACEI: angiotensin converting enzyme inhibitor. ARB: angiotensin-II receptor blocker. CCB: calcium-channel blocker

either by a bedtime ACEI or ARB ingestion strategy might be superior to any other treatment scheme for reducing CKD risk. Future prospective intervention trials that incorporate periodic, annual, or more frequent, ABPM assessments during long-term follow-up evaluation, as performed in the MAPEC Study and the currently ongoing multicenter Hygia Project [37], are necessary to confirm the benefits of bedtime hypertension chronotherapy on CKD risk reduction.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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