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CONTROVERSIES IN HYPERTENSION

Lowering Nighttime Blood Pressure With Bedtime Dosing of Antihypertensive Medications

Controversies in Hypertension—Pro Side of the Argument

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Key Words: blood pressure ■ chronotherapy ■ circadian rhythm ■ cardiovascular disease ■ pharmacology

Hypertension guidelines recommend wake-time office blood pressure (BP) measurement (OBPM) as the primary mode of diagnosing hypertension and establishing therapeutic goals.[1–4] Many of them now advocate ambulatory BP (ABP) monitoring (ABPM) of adult patients to confirm OBPM-based diagnosis of hypertension because of the well-documented significantly better value of ABPM-derived parameters relative to wake-time OBPM in prognosticating cardiovascular disease (CVD) risk.[5–12] Nonetheless, ABPM is seldom applied in clinical practice and, when it is, there is no consensus yet of which parameter(s) are most appropriate for diagnosis. Most guidelines propose around-the-clock ABPM to derive for diagnostic purpose, solely, either the 24 hours[4] or the daytime systolic BP (SBP) and diastolic BP (DBP) means[1,3] defined according to fixed clock time durations and as opposed to the awake and asleep BP means derived by ascertaining one's actual clock times of the biologically meaningful activity and sleep spans. The disparate criteria of these guidelines, however, are not based on CVD outcomes of properly conceptualized and conducted ABPM investigations. Furthermore, these guidelines suggest ABPM be performed only in selected patient populations according to elevated wake-time OBPM, contrary to the conclusions of the 2015 United States. Preventive Services Task Force report[13] that recommends in adults ≥18 years of age ABPM be the preferred means of making the differential diagnosis of hypertension versus normotension and predicting CVD risk.

Reliance only upon the 24 hours or daytime ABP means for diagnosis seems unsatisfactory. This is because both disregard the much more clinically relevant features of the mostly predictable 24-hour BP pattern plus substantiated stronger relationship than the above BP measures between elevated sleep-time BP and increased CVD risk.[7–10,12] The awake/asleep, that is, activity/rest, synchronized BP temporal variation results from the interrelationship of multiple 24-hour cycles of behavioral and environmental phenomena plus endogenous circadian (≈24 hours) rhythms in neuroendocrine, endothelial, vasoactive peptide and opioid, and hemodynamic parameters, for example, plasma noradrenaline and adrenaline (autonomic nervous system), atrial natriuretic and calcitonin gene-related peptides, and prorenin, plasma renin activity, angiotensin-converting enzyme, angiotensin I and II, and aldosterone (renin-angiotensin-aldosterone system).[14–16] Only around-the-clock, ABPM is able to assess the prognostic features of the 24-hour BP variation that result from the totality of those exogenous cyclic and endogenous rhythmic influences.

Current guidelines also fail to recommend when patients should ingest BP-lowering medication,[1–4] even when, by convention, most are advised by health care

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professionals to ingest it in the morning. Beyond the assumed, although undocumented, improved adherence/compliance to therapy at this versus other times of the day, this recommendation might also, at least partially, mistakenly derive from epidemiological studies that reported angina pectoris, myocardial infarction, sudden cardiac death, and hemorrhagic, and ischemic stroke are most frequent during the initial hours of the daily activity span.[17–19] These findings led to the unsubstantiated hypothesis the upon-awakening BP rapid rise is causal of the corresponding-in-time excess of CVD events. This, in turn, led to the hypothesis that therapeutic attenuation of the upon-awakening BP rapid rate rise reduces CVD vulnerability. However, the CONVINCE trial (Controlled Onset Extended-Release Verapamil Investigation of Cardiovascular End Points) did not corroborate this proposed hypothesis; reduction of major CVD events by targeting morning BP with bedtime ingestion of Controlled Onset extended-release-verapamil was comparable to the morning either ß-agonist atenolol or diuretic hydrochlorothiazide therapy.[20] In actuality, findings of the CONVINCE trial refute the unproven theory of the 1990s that the major goal of therapy be control of the upon-waking BP rate of rise and level during the initial hours of daily activity. Finally, upon-waking, compared with bedtime, ingestion of hypertension medications could hardly prevent both the prewaking BP rise and heightened risk of CVD events following the conclusion of sleep.

Herein, we present updated perspectives of the diagnosis and management of hypertension: (1) who should be treated relative to the understanding of the most significant independent BP determinants of elevated CVD risk upon which the diagnosis of true arterial hypertension should be made; and (2) when, according to biomarkers of endogenous circadian time of each patient, arterial hypertension should be treated, based upon the very large number of published trials confirming ingestion-time differences in effects of hypertension medications on BP regulation and reduction, biomarkers of kidney, heart, and retina target organ damage, patient safety, adherence/compliance, and CVD morbidity and mortality.

SLEEP-TIME BP AS DETERMINANT OF CARDIOVASCULAR RISK

Contrary to the guidelines recommendation to rely on the daytime (preferably awake) or 24-hour ABP means to diagnose hypertension, multiple prospective outcome trials, and meta-analyses substantiate CVD events are much better predicted by the asleep BP mean.[7–10,12] Additionally, the relationship between attenuated sleep-time relative SBP decline—nondipper (sleep-time relative SBP decline <10%) or riser (sleep-time relative SBP decline <0%) 24-hour SBP profile—and increased CVD risk is well documented.[5,7,9,11,12] Thus, elevated asleep SBP mean and blunted sleep-time relative SBP decline (nondipping) constitute joint significant CVD risk factors, independent of wake-time OBPM or awake or 24-hour ABP means. The importance of the asleep SBP mean is exemplified by a meta-analysis of original databases of 9 cohorts representing in total 13 844 patients with hypertension that found wake-time office SBP as well as ABPM-derived awake and asleep SBP means are all significantly associated with elevated CVD risk when each variable is analyzed individually. However, when all 3 SBP measurements are simultaneously included into the survival model, only the asleep SBP mean remains as an independent predictor of CVD events.[10]

The differential importance of the multiple ABPM-derived parameters, compared with wake-time OBPM, as potential risk markers of CVD morbidity and mortality has been further investigated in the large reported primary care-based multicenter Hygia Project,[12] established in 2007 as a multicenter research network comprised of 40 primary care facilities and 292 properly trained clinical investigators that incorporates ABPM as routine procedure to diagnose and manage hypertension, assess response to BP-lowering treatment, and evaluate patient CVD and other risks. Between 2008 and 2018, participating primary-care physicians—properly trained and certified in the proper application of ABPM and conduct of study procedures—referred 21 963 persons for 48-hour ABPM annually, or more frequently when ABP of treated hypertensive participants remained uncontrolled, that is, ≥135/85 or ≥120/70 mm Hg for awake and asleep SBP/DBP means, respectively,[2,21] and for individuals having compelling clinical conditions of elevated CVD risk, including diabetes, chronic kidney disease (CKD), and past CVD event.[12] During the median follow-up of 6.3 years, 1830 individuals experienced the main CVD-outcome of CVD death, myocardial infarction, coronary revascularization, heart failure, ischemic stroke, or hemorrhagic stroke. Corroborating and extending previously reported findings—based upon the Hygia Project cohort of 18 078 individuals recruited up to 2015[12]—Cox proportional-hazard analyses revealed the asleep SBP mean to be the most significant BP marker of CVD risk, independent of absence/presence of hypertension therapy at baseline, treatment-time (upon-waking versus at bedtime) strategy, and patient age, sex, and diagnosis of diabetes or CKD.

To further investigate the relative clinical relevance of the awake versus asleep SBP means on CVD risk, the Hygia Project study population was divided into 4 mutually exclusive nonoverlapping cohorts according to ABP level, that is, normal or elevated awake and normal or elevated asleep BP mean, independent of wake-time OBPM, according to established ABPM thresholds, respectively, 135/85 and 120/70 mm Hg for awake and asleep SBP/DBP means.[2,21] The 4 phenotypes resulting

from comparing awake and asleep ABP means are depicted in Figure 1. Each graph presents the 24-hour SBP pattern of an ABPM-evaluated person (dashed thick line) relative to circadian time-specified tolerance limits of normal SBP (upper and lower continuous thin lines) calculated from a reference population of normotensive individuals as a function of both sex and time during the rest-activity cycle (time expressed relative to hours after awakening from sleep).[21] The shaded dark portion of the bar depicted on the lower horizontal axis designates the sleep span for the represented individual.

Figure 2A indicates (1) similar event-rate and adjusted (by significant factors of sex, age, CKD, previous CVD event, and hypertension treatment) hazard ratio (HR) of CVD-outcome in participants with normal asleep BP mean (Figure 1A and 1B), independent of normal or elevated awake BP mean (P=0.895); (2) equivalent adjusted HR in persons with elevated asleep BP mean (Figure 1C and 1D), independent of normal or elevated awake BP mean (P=0.993); and (3) significantly higher adjusted HR of CVD-outcome (P<0.001) in individuals with elevated versus normal asleep BP mean, whether the awake BP mean is below (Figure 1A and 1C) or above 135/85 mm Hg (Figure 1B and 1D). Accordingly, the phenotype of Figure 1B (elevated awake but normal asleep BP), categorized as hypertensive by all hypertension guidelines,[1–4] is, indeed, associated with low CVD risk; on the contrary, the phenotype of Figure 1C (normal awake but elevated asleep BP), categorized as normotensive by most guidelines, is associated with high CVD risk and in need of therapeutic intervention.

The joint contribution with asleep SBP mean to CVD risk was significant only for diminished sleep-time relative SBP decline,[12] but not for wake-time OBPM or awake or 24-hour ABP means, such that at any given asleep SBP level, nondipper individuals showed significantly greater CVD risk than did dipper ones. Participants of the Hygia Project were further divided into 4 mutually exclusive nonoverlapping groups according to the 120 mm Hg threshold for the asleep SBP mean and the arbitrary ≥10% (dipper) or <10% (nondipper) threshold for the sleep-time relative SBP decline. The results depicted in Figure 2B indicate (1) significantly higher adjusted HR of CVD-outcome for nondipper than dipper participants, independent of normal or elevated asleep SBP mean (P<0.001) and (2) essentially equivalent adjusted HR of CVD-outcome for nondipper patients with normal asleep SBP mean and dipper patients with elevated asleep SBP mean (1.36 [95% CI, 1.16–1.58] and 1.42 [1.21–1.67], respectively; P=0.609).

These findings fully corroborate those of the earlier reported tertiary hospital-based MAPEC Study (Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares, ie, ABP monitoring for prediction of cardiovascular events) involving 3344 individuals also evaluated, at least annually, by 48-hour ABPM.[9] The wake-time OBPM, awake SBP/DBP means, and 24-hour SBP/DBP means were not statistically significant predictive variables when both the asleep SBP mean and sleep-time relative SBP decline were simultaneously included in the Cox survival model.[9] The collective evidence of these trials substantiates increased CVD risk is jointly associated with elevated asleep SBP mean—regardless of wake-time OBPM and awake or 24-hour SBP/DBP means—plus nondipper/riser 24-hour SBP pattern—independently of asleep SBP mean—leading to the perspective provided by around-the-clock ABPM of a proposed novel definition of true arterial hypertension based upon these 2 ABP joint significant markers of CVD vulnerability.[12,22]

SLEEP-TIME BP AS THERAPEUTIC TARGET FOR PREVENTION

The MAPEC Study and Hygia Project, unlike other ABPM-based investigations,[5–8,10,11] were specifically designed to permit prospective evaluation of changes in both wake-time OBPM and prognostic features of the 24-hour BP pattern during follow-up on CVD risk by incorporating multiple periodic (at least annual) 48-hour ABPM assessments. Both prospective trials reported progressive treatment-induced attenuation of asleep SBP mean during follow-up to be the most significant marker of decreased CVD risk, independent of changes in OBPM or awake and 48-hour SBP/DBP means. Only decreasing the asleep SBP mean towards or preferably below the hypertension guideline threshold (<120 mm Hg) and increasing the sleep-time relative SBP decline towards the lower CVD risk dipper ABP pattern were jointly and significantly associated with increased patient survival time.[9,12]

Figure 3 shows, for the entire Hygia Project population, so far entailing 21 963 individuals, divided into quintiles, the relationship between the above defined CVD-outcome and per participant treatment-attained awake and asleep SBP means at the final ABPM evaluation—that is, either before a documented CVD event in event-participants or latest assessment in nonevent ones—to explore potential outcome-based ABP therapeutic targets. CVD risk slightly rose with progressively elevated achieved awake SBP mean, although differences in adjusted HR, compared with the first quintile of participants with lowest awake SBP means, were statistically significant only for the last quintile, that is, awake SBP mean ≥140.4 mm Hg (Figure 3A). In contrast, across all quintiles CVD risk with high statistical significance was exponentially reduced with progressive treatment-induced attenuation of the asleep SBP mean, without evidence of J-shaped relationship between achieved asleep SBP mean and CVD risk (Figure 3B), as also documented in the MAPEC Study.[9] Indeed, CVD risk is lowest when the

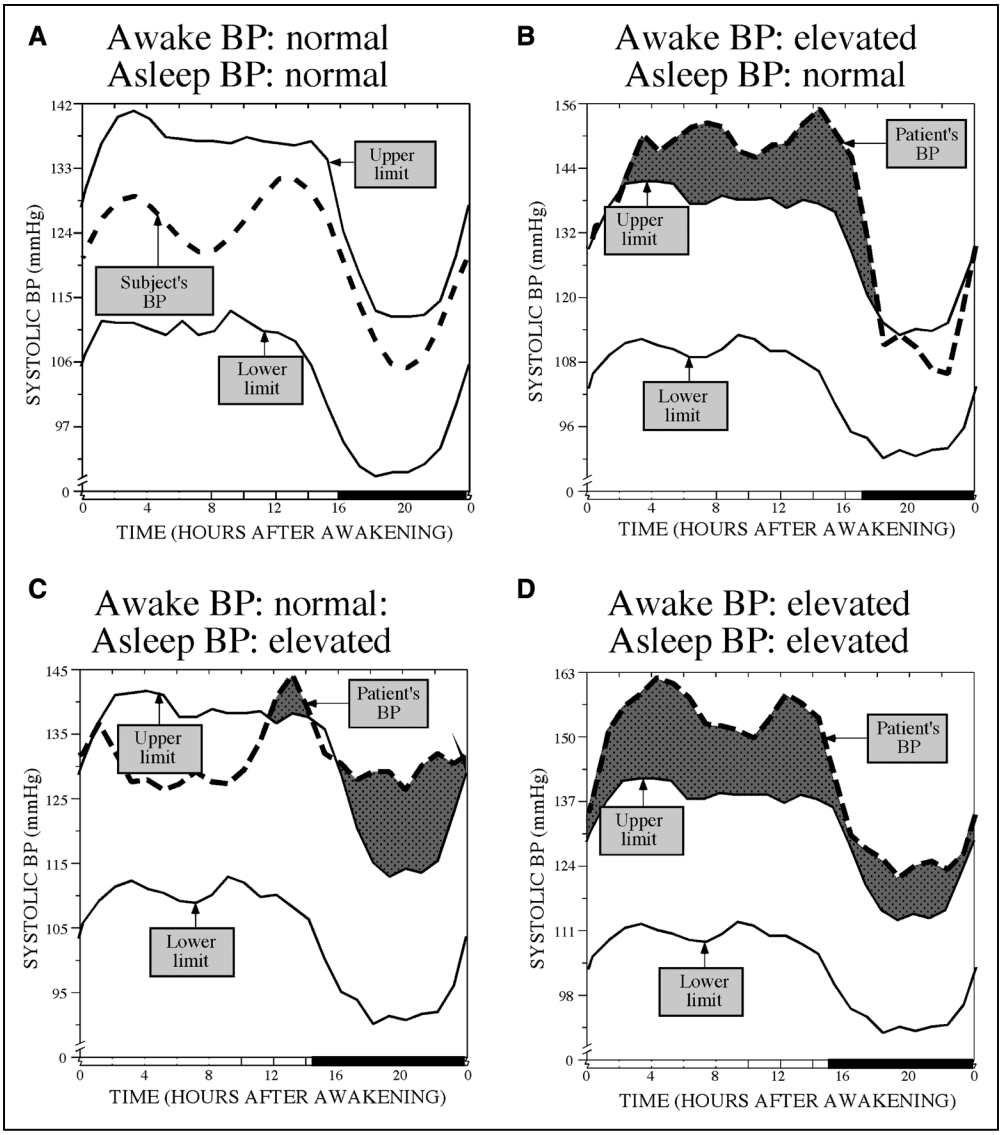

Figure 1. Phenotypes resulting from comparing awake and asleep ABP means: (1) both means normal (A); (2) elevated awake and normal asleep BP (B); (3) normal awake and elevated asleep BP (C); and (4) both means elevated (D).

achieved asleep SBP mean is <104.4 mm Hg, with average asleep SBP mean for persons of this first quintile as low as 98.1±5.6 mm Hg.

In summary, findings of these 2 prospective outcome ABPM studies document the progressive treatment-induced diminished asleep SBP mean, but not wake-time OBPM or awake SBP/DBP means, and increased sleep-time relative SBP decline are jointly the most highly significant independent prognostic markers of reduced CVD morbidity and mortality. They, therefore, constitute novel therapeutic targets for CVD prevention and prolongation of patient event-free survival. These findings additionally support ABPM be the basis for proper diagnosis of true arterial hypertension and also for evaluating safety (avoidance of sleep-time hypotension) and response to therapeutic intervention.[9,12,22]

INGESTION-TIME DIFFERENCES IN EFFECTS OF HYPERTENSION MEDICATIONS

Chronopharmacology—study of biological rhythm influences on the pharmacokinetics and pharmacodynamics of medications—and chronotherapeutics—timing of medications to features of biological rhythms to optimize therapeutic benefits and minimize/avert adverse effects—are today areas of high relevance to improving control of elevated BP[23–28] and preventing CVD.[29–32] Pharmacokinetics of ingested BP-lowering medications is significantly affected not only by the 24-hour cyclic pattern of food consumption but multiple endogenous circadian rhythms that influence absorption, distribution, metabolism, and elimination.[33–35] Pharmacodynamics, on the contrary, of hypertension medications is not only

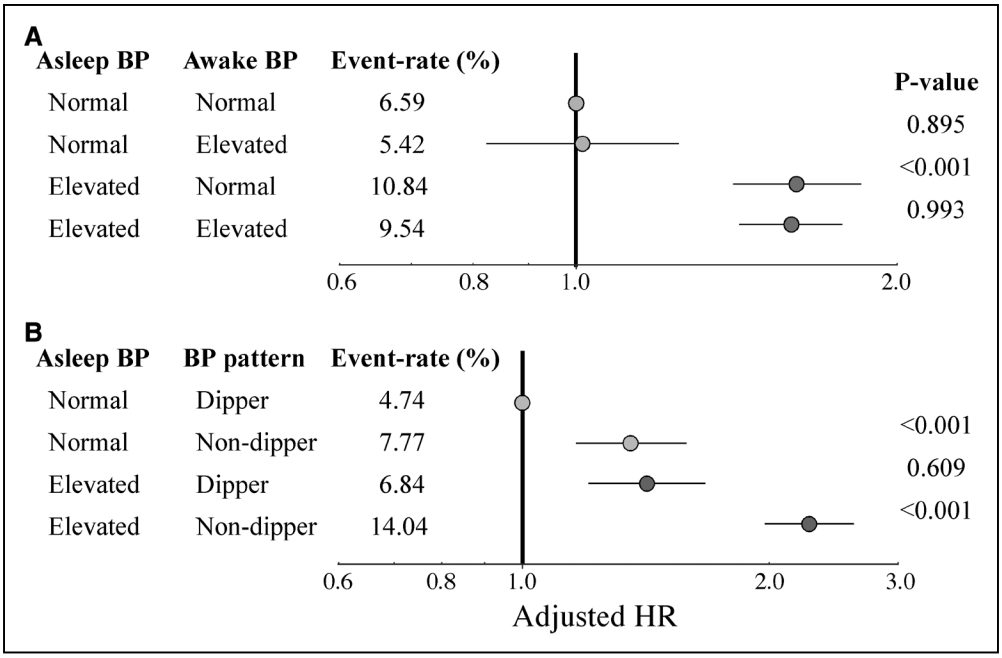

Figure 2. CVD risk according to different ABP phenotypes.
A, Adjusted HR of CVD events in the Hygia Project cohort entailing 21 963 individuals categorized into 4 nonoverlapping groups according to the level (normal or elevated) of the ABPM-derived awake and asleep SBP/DBP means. The ABPM-derived awake SBP/DBP means were considered normal if <135/85 mm Hg and elevated otherwise. The asleep SBP/DBP means were considered normal if <120/70 mm Hg and elevated otherwise. Adjustments were applied, if significant, for sex, age, diabetes, CKD, previous CVD event, and hypertension treatment. **B**, Adjusted HR of CVD events in the Hygia Project participants categorized into 4 nonoverlapping groups according to the level (normal or elevated) of the ABPM-derived asleep SBP mean and the extent of sleep-time relative SBP decline. The asleep SBP mean was considered normal if <120 mm Hg and elevated otherwise. Participants were designated as dipper when the sleep-time-relative SBP decline was ≥10% and as nondippers when <10%, using data sampled by ABPM for 48 consecutive hours. Adjustments were applied for the same variables as in **A**. *P* values are shown for comparison between each pair of consecutive patient groups.

influenced by circadian rhythms that affects pharmacokinetics but also others that (1) affect circulating medication free-fraction concentration, cell/tissue receptor number/conformation, and second messengers/signaling pathways of drug targets, for example, blood vessels and heart, brain, and kidney tissue and (2) comprise biological mechanisms of the 24-hour BP pattern, particularly, the autonomic nervous system and renin-angiotensin-aldosterone system.[14–16] Thus, it should not be surprising when BP-lowering medications are ingested, with reference to the staging of circadian rhythms, affect their duration of action, effects on the 24-hour BP profile, safety, and patient tolerance.

We conducted a comprehensive and systematic review of published human trials that investigated single, dual combination, or multiple hypertension therapies for upon-waking/morning versus bedtime/evening ingestion-time differences in therapeutic effects.[36,37] The protocol, conducted following the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), is registered with PROSPERO (International Prospective Register of Systematic Reviews; No. CRD42020201220). Articles were limited to human studies, published in any language, without restriction of duration of treatment, trial design, main outcome, or publication date. We excluded studies pertaining only to pharmacokinetics studies, long-term trials on CVD outcomes, reviews, case studies, and commentaries. Systematic review and meta-analysis of long-term trials comparing ingestion-time differences of hypertension medications on CVD outcomes have previously been reported[30,32] and are also summarized below. Main outcomes were ingestion-time-dependent effects on either (1) sleep-time SBP mean; (2) sleep-time relative SBP decline; (3) biomarkers of hypertension-associated target organ pathology of the kidney—albuminuria and estimated glomerular filtration rate (GFR)—and heart—left ventricular posterior diameter and left ventricular mass; and (4) adverse medication events, including sleep-time hypotension.[36,37]

We identified 155 valid trials published between 1976 and 2020, representing collectively 23 972 hypertensive individuals. The complete list and references, study features, and major findings of each of these published trials are reported elsewhere.[36] Some 25 of them were classified as neutral, reporting noninferiority of bedtime/evening versus upon-waking/morning treatment, while the remaining 130 (83.9%) reported significantly enhanced advantages of bedtime/evening treatment according to the a priori defined main outcomes of this systematic review. A highly noteworthy finding of our comprehensive review is that no single study found significantly

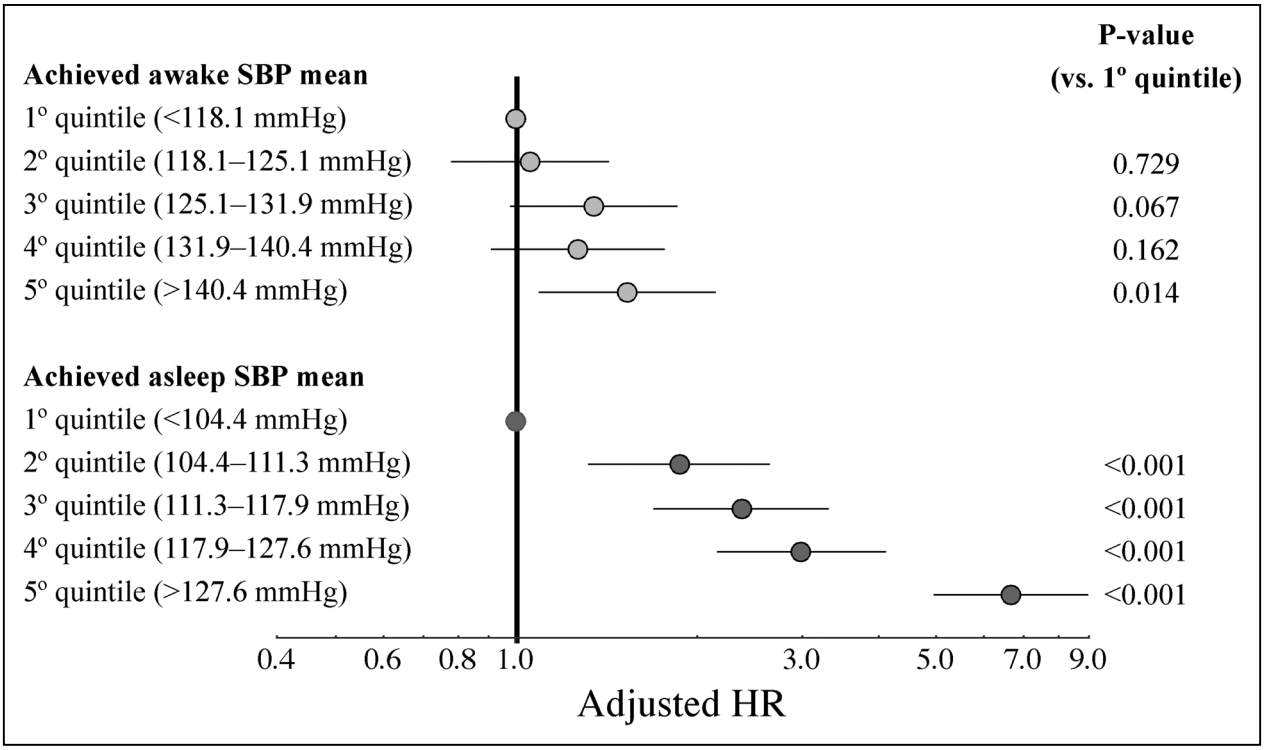

Figure 3. Adjusted HR of CVD events in the Hygia Project cohort entailing 21 963 individuals as a function of the achieved ABPM-derived awake (top) and asleep SBP mean (bottom) at the final evaluation per participant, either before a documented CVD event in event-subjects or latest assessment of nonevent individuals.

The studied population was divided into 5 classes of equal size (quintiles). Adjustments were applied for the same variables as in Figure 2.

better BP-lowering or other benefits of the most recommended upon-waking/morning hypertension treatment-time scheme. Table 1 lists the distribution of trials, with combined sample size, documenting either superiority or noninferiority (neutral) of the bedtime/evening versus upon-waking/morning treatment regimen categorized by the trialed single, dual combination, or multiple therapies.

Conventional Hypertension Monotherapies

A total of 25 of the 29 (86.2%) trials of ACE (angiotensin-converting enzyme) inhibitor medications of different terminal half-life—benazepril, captopril, enalapril, imidapril, lisinopril, perindopril, quinapril, ramipril, spirapril, trandolapril, and zofenopril—when ingested at bedtime/evening versus upon-waking/morning reported significantly better: (1) attenuated asleep SBP mean without compromised effect on awake or 24h SBP means (Table 2); (2) normalization of 24-hour SBP dipper profile; and (3) patient tolerance to treatment, that is, decreased incidence of adverse effects (Table 1). It is noteworthy that no single case of sleep-time hypotension was reported with bedtime/evening treatment (Table 1).

Similar significant ingestion-time differences in therapeutic effects, also independent of medication terminal half-life, were substantiated for most (19 out of 25, 76.0%) ARB (angiotensin II receptor blocker) trials entailing candesartan, irbesartan, olmesartan, telmisartan, and valsartan (Table 1). Again, not a single case of sleep-time hypotension was reported with bedtime/evening ARB treatment. Moreover, bedtime ARB dosing significantly decreased urinary albumin excretion (UAE) in an amount strongly correlated with the extent of asleep SBP mean reduction and increase of sleep-time relative SBP decline, and additionally increased GFR, decreased renal vascular resistance, and reduced carotid artery plaque size.

Although some (11 out of 41, 26.8%) CCB (calcium-channel blocker) studies found similar homogeneous decrease of BP throughout the 24-hour independent of ingestion-time, all of the other 30 (73.2%)—trialing altiazem, amlodipine, barnidipine, cilnidipine, diltiazem, isradipine, nifedipine, nisoldipine, nitrendipine, and verapamil—reported significantly greater reduced asleep SBP mean, increased dipping, decreased left ventricular mass, and improved safety—mainly significantly decreased risk of peripheral edema—with bedtime/evening treatment (Table 1).

The BP-lowering effect of various other hypertension medications—alpha-blocker doxazosin; ß-blockers bisoprolol, carvedilol, nebivolol, penbutolol, and propanolol; diuretics of hydrochlorothiazide and torasemide; plus methyldopa, guanabenz, and clonidine—additionally were reported to differ significantly according to ingestion-time. Publications entailing these medications generally reported more prolonged BP-lowering effect and more profound asleep BP decrease (Table 2) when ingested at bedtime/evening

Table 1. Ingestion-Time-Dependent Differences in the Pharmacodynamics of Hypertension Medications and Their Combinations

Medication class	No. trials (No. patients)	No. trials showing significant treatment-time benefits* (No. patients)			Bedtime better, % trials (% patients)	Documented significant advantages of bedtime/evening vs upon-waking/morning hypertension treatment schedule						
		Awakening	Bedtime	Neutral		Greater decrease of asleep ABP	Reduced prevalence of nondipping	Greater proportion of controlled patients	Improved kidney function*	Reduced cardiac damage†	Similar/lower incidence of adverse effects	Lack of sleep-time hypotension
ACE inhibitor	29 (1282)	0 (0)	25 (1089)	4 (193)	86.2 (85.0)	✓	✓	✓	✓	Not reported	✓	✓
ARB	25 (3588)	0 (0)	19 (2085)	6 (1503)	76.0 (58.1)	✓	✓	✓	✓	✓	✓	✓
CCB	41 (2635)	0 (0)	30 (2093)	11 (542)	73.2 (79.4)	✓	✓	✓	✓	✓	✓	✓
ß-blocker	7 (791)	0 (0)	7 (791)	0 (0)	100 (100)	✓	✓	✓	Not reported	✓	✓	✓
Diuretic	5 (364)	0 (0)	4 (352)	1 (12)	80.0 (96.7)	✓	✓	✓	Not reported	✓	✓	Not reported
alpha-blocker	3 (925)	0 (0)	3 (925)	0 (0)	100 (100)	✓	✓	✓	✓	Not reported	Not reported	Not reported
Adrenergic receptor agonist	3 (147)	0 (0)	3 (147)	0 (0)	100 (100)	✓	✓	✓	Not reported	Not reported	✓	Not reported
Dual combination	17 (1508)	0 (0)	16 (1485)	1 (23)	94.1 (98.5)	✓	✓	✓	✓	✓	✓	✓
Polytherapy	25 (12732)	0 (0)	23 (12490)	2 (242)	92.0 (98.1)	✓	✓	✓	✓	✓	✓	✓
Total	155 (23972)	0 (0)	130 (21457)	25 (2515)	83.9 (89.5)	✓	✓	✓	✓	✓	✓	✓
Special patient cohorts at elevated CVD risk												
Nondippers	20 (1315)	0 (0)	20 (1315)	0 (0)	100 (100)	✓	✓	✓	✓	✓	✓	✓
Diabetes	9 (3036)	0 (0)	8 (3019)	1 (17)	88.9 (99.4)	✓	✓	✓	✓	✓	✓	✓
CKD	7 (3023)	0 (0)	6 (2876)	1 (147)	85.7 (95.1)	✓	✓	✓	✓	✓	✓	Not reported
Resistant hypertension	7 (5833)	0 (0)	7 (5833)	0 (0)	100 (100)	✓	✓	✓	✓	Not reported	Not reported	Not reported
Previous CVD event	10 (864)	0 (0)	10 (864)	0(0)	100 (100)	✓	✓	✓	✓	✓	✓	Not reported
Total	53 (14071)	0 (0)	51 (13907)	2 (164)	96.2 (98.8)	✓	✓	✓	✓	✓	✓	✓

Nondipper: individuals with sleep-time relative systolic blood pressure (SBP) decline <10%. The sleep-time relative SBP decline, index of blood pressure dipping, is defined as percent decrease in asleep SBP mean relative to awake SBP mean, and calculated as ([awake SBP mean—asleep SBP mean]/awake SBP mean)×100. ABP indicates ambulatory blood pressure; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium-channel blocker; CVD, cardiovascular disease; and CKD, chronic kidney disease.

*Reduced albuminuria (either urinary albumin/creatinine ratio or 24 h urinary albumin excretion), increased estimated glomerular filtration rate, or both.

†Decreased left ventricular mass, left ventricular posterior diameter, or left ventricular relative wall thickness.

than upon-waking/morning, and without significant ingestion-time differences in adverse effects (Table 1).

In summary, among the 113 reported trials evaluating BP-lowering monotherapies ingested at different times of the day, either in terms of the nonspecific terminology of morning versus evening or, more appropriately from a circadian rhythm perspective, upon-waking versus at bedtime, 22 were neutral, that is, evidenced no treatment-time difference in therapeutic effects. All of the other 91 (80.5%) trials reported significantly better effects by the bedtime/evening treatment schedule, that is, improved SBP reduction, mainly during sleep, moderation/reversal of nondipper 24-hour SBP pattern, and greater beneficial effects upon the kidney and heart (Table 1). None of the 113 trials found the conventional upon-waking/morning treatment schedule to confer better benefits than the bedtime/evening one!

Combination Hypertension Treatment

Some 17 trials, representing a total of 1508 patients with hypertension, investigated differential ingestion-time-dependent effects of 14 dual-combination therapies: amiloride-hydrochlorothiazide, amlodipine-hydrochlorothiazide, azilsartan-indapamide, captopril-hydrochlorothiazide, enalapril-hydrochlorothiazide, fosinopril-amlodipine, losartan-indapamide, olmesartan-amlodipine, perindopril-indapamide, telmisartan-amlodipine (2 trials), valsartan-amlodipine (2 trials), valsartan-hydrochlorothiazide, valsartan-indapamide (2 trials), and verapamil-trandolapril. Among them, 16 (94.1%) reported better benefits by the bedtime/evening than upon-waking/morning schedule (Table 1).

Another 25 (9 being cross-sectional in design) trials, totaling 12732 hypertensive participants, concerned

Table 2. Enhanced Reduction of Asleep SBP Mean and Increased Dipping With Bedtime/Evening vs Upon-Waking/Morning Hypertension Treatment

Medication type or class/ patient cohort	Office SBP	24 h mean	Awake mean	Asleep mean	Sleep-time relative decline
All studies (n=62)	1.99 [0.85 to 3.14]; <0.01	1.99 [1.14 to 2.85]; <0.01	0.71 [−0.04 to 1.46]; 0.06	5.17 [4.04 to 6.31]; <0.01	3.22 [2.42 to 4.02]; <0.01
ACE inhibitor (n=14)	0.66 [−1.49 to 2.82]; 0.55	0.67 [−0.45 to 1.80]; 0.24	−0.47 [−1.64 to 0.70]; 0.43	4.58 [2.54 to 6.62]; <0.01	3.42 [1.77 to 5.07]; <0.01
ARB (n=15)	1.64 [−0.43 to 3.70]; 0.12	0.68 [−0.23 to 1.59]; 0.14	−0.73 [−1.58 to 0.13]; 0.10	4.10 [2.03 to 6.18]; <0.01	3.54 [1.72 to 5.36]; <0.01
CCB (n=12)	4.56 [1.77 to 7.34]; <0.01	1.64 [0.37 to 2.92]; 0.01	1.01 [−0.28 to 2.30]; 0.12	3.11 [1.58 to 4.63]; <0.01	1.43 [0.40 to 2.45]; <0.01
Other monotherapies (n=5)	0.80 [−5.45 to 7.04]; 0.80	3.14 [−0.69 to 6.97]; 0.11	2.20 [−1.73 to 6.13]; 0.27	4.76 [1.65 to 7.87]; <0.01	1.84 [0.63 to 3.04]; <0.01
Dual combination (n=8)	0.89 [−2.31 to 4.08]; 0.59	4.75 [0.65 to 8.86]; 0.02	2.28 [0.06 to 4.50]; 0.04	8.91 [4.62 to 13.21]; <0.01	5.50 [3.42 to 7.57]; <0.01
Polytherapy (n=8)	1.63 [−0.53 to 3.78]; 0.14	3.89 [0.24 to 7.53]; 0.04	3.50 [0.13 to 6.88]; 0.04	8.46 [3.66 to 13.25]; <0.01	3.58 [1.68 to 5.49]; <0.01
Special populations at elevated CVD risk					
Special populations (n=17)	2.81 [0.16 to 5.46]; 0.04	4.03 [1.27 to 6.80]; <0.01	2.42 [0.24 to 4.60]; 0.03	7.91 [5.08 to 10.74]; <0.01	4.08 [2.74 to 5.42]; <0.01
Nondippers (n=9)	5.00 [0.77 to 9.23]; 0.02	2.76 [0.65 to 4.87]; <0.01	2.66 [−1.11 to 6.42]; 0.17	8.30 [6.39 to 10.21]; <0.01	3.34 [1.02 to 5.67]; <0.01
Other special groups (n=8)	1.40 [−2.00 to 4.80]; 0.42	4.81 [0.68 to 8.94]; 0.02	2.26 [−0.62 to 5.13]; 0.12	7.99 [3.03 to 12.95]; <0.01	4.67 [2.99 to 6.34]; <0.01
Nonspecial populations (n=45)	1.89 [0.62 to 3.16]; <0.01	1.29 [0.58 to 2.00]; <0.01	0.20 [−0.49 to 0.89]; 0.57	4.20 [3.09 to 5.31]; <0.01	2.92 [2.04 to 3.79]; <0.01

Data of 62 randomized clinical trials entailing in total 6120 patients with hypertension. Special populations at elevated CVD risk: individuals with nondipper 24 h SBP pattern, diabetes, chronic kidney disease, resistant hypertension, or previous CVD event. Nondipper: individuals with sleep-time relative SBP decline <10%. The sleep-time relative SBP decline, index of blood pressure dipping, is defined as percent decrease in asleep SBP mean relative to awake SBP mean, and calculated as ([awake SBP mean—asleep SBP mean]/awake SBP mean)×100. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker; CVD, cardiovascular disease; and SBP, systolic blood pressure.

Results shown as differential effect [95% CI] in mm Hg between bedtime/evening vs upon-waking/morning treatment; *P* value for ingestion-time difference. Positive value for differential effect indicates greater decrease in office. Twenty-four hour, awake, or asleep SBP mean (mm Hg) and increase in sleep-time relative SBP decline (%) with bedtime/evening than upon-waking/morning hypertension treatment.

ingestion-time-dependent effects of BP-lowering polytherapy. Significantly better benefits of the bedtime/evening versus upon-waking/morning treatment scheme were documented in 23 studies (92.0%; Table 1) in terms of enhanced asleep SBP reduction without inducing sleep-time hypotension, reduced prevalence of SBP nondipping, larger proportion of controlled patients by ABPM criteria, improved kidney function, or reduced cardiac injury.

Special Patient Cohorts at Elevated CVD Risk

A total of 53 ingestion-time trials concerned special patient populations at elevated CVD risk, reporting with high consistency significant superiority of bedtime/evening versus upon-waking/morning treatment regimen (Table 1): (1) 20 involving nondipper hypertensives that showed better attenuation of asleep SBP mean and increased sleep-time relative SBP decline—without causing sleep-time hypotension—plus augmented reduction of UAE and regression of left ventricular mass index; (2) 9 on patients with diabetes, of which 8 found significantly superior reduction of asleep SBP mean, increased sleep-time SBP decline, enhanced glucose control, decreased UAE, increased GFR, or regression of left ventricular hypertrophy; the other trial of only 17 patients was neutral[38]; (3) 6 on patients with CKD that showed, with one exception,[39] significant advantages, including improved kidney function and reduced cardiac injury; (4) 7 on resistant hypertension patients that all reported greater benefits when ingesting the entire daily dose of ≥1 hypertension medications at bedtime/evening versus all of them upon-waking/morning; and (5) 10 on patients with past history of CVD events (specifically, congestive heart failure or stroke), all documenting superiority of bedtime/evening therapy (Table 1).

Ingestion-Time Dependent Effects on ABP

Among the identified 155 ingestion-time hypertension studies, 62 trials totaling 6120 hypertensive persons provided ABPM-based data on effects on the awake and asleep BP means and sleep-time relative SBP decline enabling quantitative meta-analyses (Table 2). Some 51 (82.3%) disclosed significantly enhanced advantages of bedtime/evening treatment; the other 11 (17.7%) were

neutral, that is, showed noninferiority of this versus upon-waking/morning schedule.[37]

Quantitative evaluation of these ABPM-based randomized trials substantiates for bedtime/evening versus upon-waking/morning therapy statistically significant enhanced reduction of the asleep SBP mean by an average of 5.17 mm Hg (95% CI, 4.04–6.31), $P<0.01$ between treatment-time groups, but not awake SBP mean (0.71 mm Hg [95% CI, −0.04 to 1.46], $P=0.06$; Table 2). Consequently, the sleep-time relative SBP decline was significantly further increased by an average 3.22% (95% CI, 2.42–4.02; $P<0.01$) towards the normal dipper 24-hour BP pattern. No evidence of publication bias was detected ($P=0.148$). Nonetheless, enhanced reduction of asleep SBP mean with bedtime/evening treatment was largest for trials of (1) dual combinations (average of 8.91 mm Hg [4.62–13.21], $P<0.01$) and polytherapy (8.46 mm Hg [3.66–13.25], $P<0.01$); and (2) nondippers (8.30 mm Hg [6.39–10.21], $P<0.01$) and other high risk (diabetes, CKD, and previous CVD events) patient populations (7.99 mm Hg [3.03–12.95], $P<0.01$) relative to hypertensive individuals of the general population (4.20 mm Hg [3.09–5.31], $P<0.01$; Table 2). In contrast, there were only small and often nonsignificant ingestion-time dependent effects on wake-time OBPM and awake SBP mean (Table 2).[37]

METHODOLOGICAL ASPECTS OF REPORTED INGESTION-TIME HYPERTENSION TRIALS

We hypothesize the inability of the quite small number of reported trials to substantiate advantages of the bedtime/evening treatment strategy to be the consequence of deficiencies of investigative methods, as exemplified by 3 of the neutral studies that trialed hypertension polytherapy[39,40] and those that concerned high-risk patients, respectively, with CKD[39] and diabetes[38] (Table 1). In keeping with current guidelines for the design and conduct of clinical trials on chronotherapy on BP-lowering medications,[41] among the apparent shortcomings are (1) reliance solely on wake-time OBPM to certify participants as arterial hypertensive, which makes probable inclusion into the trial of >20% low CVD risk persons with so-called isolated-office hypertension (elevated BP in the office setting but normal BP outside it) and exclusion of >27% persons at high CVD risk with so-called masked hypertension (normal BP in the office setting but elevated BP outside it),[12] a condition even more prevalent among patients with diabetes or CKD due to their documented greater proportion of sleep-time hypertension and nondipper 24-hour SBP pattern.[21] (2) Morning and evening treatment-times that were either unspecific[39] or inappropriately defined by expansive clock-hour intervals—for example, 06:00 to 11:00 hours and 18:00 to 23:00 hours by Poulter et al[40] and 07:00 to 09:00 hours and 19:00 to 21:00 hours by Kuate et al[38]—instead of meaningful individualized biological ones linked to the bed and wake times of each individual participant that are indicative of the staging of circadian rhythms that both regulate the 24-hour BP pattern and influence the biological response to hypertension therapy.[14–16] (3) Reliance as primary study end point upon the 24-hour SBP mean that is a parameter of rather low, if any, predictive value of CVD risk when the asleep SBP mean is simultaneously taken into account[9,10,12] and that is minimally affected by time of hypertension treatment,[23–28] as corroborated by our systematic review of published ingestion-time studies (Table 2).[37] (4) Secondary study end points included nonbiologically representative or clinically meaningful daytime and nighttime BP means improperly determined by investigator-defined common fixed clock times of wakefulness and sleep across all participants—respectively, 06:00 to 00:00 hours and 00:00 to 06:00 hours by Rahman et al[39] and 07:00 to 22:00 hours and 22:00 to 07:00 hours by Kuate et al[38] and Poulter et al[40]—rather than actual individualized ones. (5) The minimum required sample size of these neutral trials was miscalculated, as valid testing of the stated hypothesis of ingestion-time difference in reduction of the 24-hour SBP mean actually required almost double the number of participants than recruited—46 required versus 17 recruited by Kuate et al[38]; 190 required versus 147 recruited by Rahman et al[39]; and 175 required versus 95 recruited by Poulter et al.[40] (6) In the trials by Rahman et al[39] and Poulter et al,[40] recruitment restricted to treated hypertensive participants whose BP was already controlled according to medical guidelines likely led to misleading findings when evaluating ingestion-time-dependent effects of BP-lowering therapies.[41] Indeed, in both studies the mean ABP values were actually higher after both morning and evening treatment than at baseline. In addition to the insufficient sample size of these neutral trials, the rather low, that is, normal or near normal, baseline daytime, and nighttime SBP/DBP means of the BP-controlled recruited participants, precluded detection of statistical significance of the somewhat lower nighttime SBP mean achieved by evening in comparison to morning therapy.[39,40] Beyond the BP-lowering efficacy of hypertension medications being markedly associated with pretreatment ABP level, diminishing with lower baseline ABP, it is judged unethical to change the treatment regimen of any patient whose BP is already safely and properly controlled according to ABPM guideline-recommended threshold values.[41] These neutral studies[39,40] are frequently used by some, without critical discussion of their many pitfalls and limitations, to argue BP-lowering time of treatment does not matter,[42] in spite of convincing evidence summarized herein of 130 trials (83.9% of all published ones) entailing several thousand patients clearly showing superiority of the clinical benefits derived by bedtime hypertension therapy (Table 1).[36]

INGESTION-TIME EFFECTS OF HYPERTENSION TREATMENT ON CVD OUTCOMES

Despite the quite consistent published evidence during the past 45 years summarized above substantiating bedtime hypertension treatment best achieves ABP control, particularly during sleep, and improves markers of target organ pathology, especially of the kidney and heart, few long-term outcomes studies specifically assessed its impact on CVD prevention. The MAPEC Study, conducted

at a single tertiary hospital, was the first prospective, randomized, CVD end point trial designed to specifically test the hypothesis that bedtime hypertension treatment with conventional once-a-day medications better reduces CVD risk than upon-waking therapy.[29] Patients with hypertension (N=2156) diagnosed according to ABPM criteria, regardless of OBPM, randomized to ingest the entire daily dose of ≥1 BP-lowering medications at bedtime versus entire daily dose of all such medications upon-awakening exhibited, after a median follow-up of 5.6 years, significantly lower asleep BP mean, lesser prevalence of nondipping, and, of greatest importance, significantly attenuated adjusted HR for major CVD events, including CVD death, myocardial infarction, and ischemic and hemorrhagic stroke.[29]

The subsequent much larger multicenter prospective, randomized, blinded-end point Hygia Chronotherapy Trial—one of the several ABPM-based studies nested within the Hygia Project—conducted in the primary care setting extended the findings of the relatively small cohort MAPEC Study. It involved 19 084 ABPM-diagnosed hypertensive patients randomized either to ingest the entire daily dose of ≥1 prescribed hypertension medications at bedtime or all of them upon awakening.[31] Patients of the bedtime treatment group had significantly lower asleep SBP/DBP means and higher prevalence of the normal dipper SBP pattern, plus lower creatinine, LDL-cholesterol, and UAE, and higher HDL-cholesterol and GFR. Most important, over the 6.3 years median follow-up those randomized to the bedtime versus upon-waking treatment regimen evidenced significantly lower adjusted HR (0.55 [95% CI, 0.50–0.61], $P<0.001$) of the primary CVD-outcome variable—CVD death, myocardial infarction, coronary revascularization, heart failure, and stroke—and each of its single components.[31] The number of documented events per treatment-time group, relative risk (ratio of event-probabilities per treatment-time group), absolute risk reduction (difference between percent event-rates per treatment-time group), adjusted HR, and number needed to treat (number of patients who need to be treated to prevent one outcome) are listed in Table 3.

Findings of the meta-analysis conducted by Roush et al[30] are consistent with the above-discussed results of the MAPEC Study and Hygia Chronotherapy Trial. They compared the extent of CVD reduction reported by the earlier reported Syst-Eur, Syst-China, HOPE, FACET, and CONVINCE investigations in which trialed hypertension treatment was ingested at bedtime/evening—but without an awakening-time treatment arm of the same tested medication as reference—versus such achieved in 170 prospective CVD-outcome trials in which participants ingested therapy in the morning.[30] The bedtime/evening, relative to the upon-waking/morning, hypertension treatment strategy markedly reduced by 48% ($P=0.008$) the relative risk of CVD events. Gupta et al[32] extending this meta-analysis by incorporating results of both the MAPEC Study[29] and Hygia Chronotherapy Trial,[31] once again found bedtime/evening hypertension treatment to be significantly superior in protecting against major CVD events and stroke.

The critical importance of targeting control of asleep BP control is reinforced by the findings of Sobiczewski et al,[43] who evaluated the benefits of timed hypertension treatment in a high-risk cohort of 1345 coronary heart disease patients assessed by 24-hour ABPM. Cox survival analysis of the data of this median 6.6-year follow-up trial revealed the asleep ABP mean—but not elevated wake-time OBPM or awake ABP mean—nondipper 24-hour SBP profile, and lack of bedtime treatment, apart from age and diabetes, to be the only significant joint predictors of all-cause mortality.

At least 2 additional studies—Bed-Med Trial (URL: https://www.clinicaltrials.gov; Unique identifier: NCT02990663) and TIME (Treatment in Morning Versus Evening)[44]—were initiated after publication of the results of the MAPEC Study[29] to evaluate potential differences in CVD risk according to BP-lowering treatment time. These 2 pragmatic clinical trials recruited only persons already treated with BP-lowering medications and diagnosed as hypertensive solely by OBPM without performing as recommended ABPM at baseline to correctly certify participants as hypertensive,[1] or during follow-up to properly evaluate efficacy and safety (sleep-time hypotension avoidance) of the timed therapy regimens. The TIME study,[44] which comprises a cohort of self-enrolled persons followed by internet without participation of their prescribing physicians, does not evaluate adherence, compliance, or safety, and CVD events are to some extent self-reported utilizing the web-based platform. Further, doubling of sample size from the initially stated 10 269 participants and allocation of them to treatment-time without knowledge and endorsement of the prescribing physicians are concerning. Most important, TIME is not a chronotherapy trial, that is, entailing treatment synchronized to internal circadian time denoted by markers of the rest/activity cycle as the conceptual basis for chronotherapeutics,[14–16] but instead a broadly defined morning (06:00–10:00 hours) versus evening (20:00–00:00 hours) span comparison of external time-of-day-based treatment effects. These and other methodological limitations call into question the clinical relevance, if any, of whatever findings might emanate from these studies.

The consistent findings of the above-discussed published large CVD-outcome trials and meta-analyses, although in line with those expected based on the extensive review of the literature presented herein (Tables 1 and 2), await corroboration, especially by properly designed studies incorporating ethnic groups other than Whites evaluated by periodic ABPM assessment—starting at baseline for the diagnosis of true arterial hypertension as

Table 3. Number of Events, RR, RRR, ARR, adjusted HR, and NNT as a Function of Treatment-Time Regimen (Either Upon-Waking or Bedtime) in the Hygia Chronotherapy Trial

Outcome variable	No. of events		RR	RRR	ARR [95% CI]	Adjusted HR [95% CI], *P* value	NNT [95% CI]
	Awakening treatment	Bedtime treatment					
Participants	9552	9532					
Total events	2068	1178	0.571	0.43	9.29 [8.23 to 10.35]	0.58 [0.54 to 0.62], <0.001	10.76 [9.66 to 12.14]
Total CVD events	1566	888	0.568	0.43	7.08 [6.13 to 8.02]	0.57 [0.53 to 0.62], <0.001	14.13 [12.46 to 16.30]
Total death	631	326	0.518	0.48	3.19 [2.57 to 3.80]	0.55 [0.48 to 0.63], <0.001	31.39 [26.29 to 38.93]
CVD outcome	1133	619	0.548	0.45	5.37 [4.55 to 6.18]	0.55 [0.50 to 0.61], <0.001	18.63 [16.17 to 21.97]
CVD death	221	89	0.404	0.60	1.38 [1.02 to 1.74]	0.44 [0.34 to 0.56], <0.001	72.47 [57.54 to 97.85]
Myocardial infarction	166	108	0.652	0.35	0.60 [0.27 to 0.94]	0.66 [0.52 to 0.84], <0.001	165.34 [106.13 to 373.90]
Coronary revascularization	189	113	0.599	0.40	0.79 [0.44 to 1.15]	0.60 [0.47 to 0.75], <0.001	126.08 [87.18 to 227.63]
Heart failure	328	193	0.590	0.41	1.41 [0.95 to 1.87]	0.58 [0.49 to 0.70], <0.001	70.97 [53.45 to 105.57]
Stroke	229	116	0.508	0.49	1.18 [0.80 to 1.56]	0.51 [0.41 to 0.63], <0.001	84.71 [64.18 to 124.55]
Ischemic stroke	178	96	0.541	0.46	0.86 [0.52 to 1.19]	0.54 [0.42 to 0.69], <0.001	116.77 [83.78 to 192.64]
Hemorrhagic stroke	51	20	0.393	0.61	0.32 [0.15 to 0.50]	0.39 [0.23 to 0.65], <0.001	308.55 [201.32 to 660.14]
Minor events	525	322	0.615	0.39	2.12 [1.53 to 2.70]	0.60 [0.52 to 0.69], <0.001	47.21 [37.01 to 65.16]
Angina pectoris	168	111	0.662	0.34	0.59 [0.25 to 0.93]	0.65 [0.51 to 0.83], <0.001	168.27 [106.99 to 393.87]
Peripheral artery disease	192	104	0.543	0.46	0.92 [0.57 to 1.27]	0.52 [0.40 to 0.79], <0.001	108.82 [78.78 to 175.84]
Occlusion retinal artery	92	53	0.577	0.42	0.41 [0.16 to 0.65]	0.56 [0.40 to 0.79], <0.001	245.62 [153.05 to 621.65]
Transient ischemic attack	73	54	0.741	0.26	0.20 [−0.03 to 0.43]	0.73 [0.51 to 1.04], 0.078	505.75 [233.44 to 3036.42]

Total events: sum of death from all causes, myocardial infarction, coronary revascularization, heart failure, ischemic and hemorrhagic stroke, angina pectoris, peripheral artery disease, thrombotic occlusion of the retinal artery, and transient ischemic attack. Total CVD events: sum of CVD death, myocardial infarction, coronary revascularization, heart failure, stroke, angina pectoris, peripheral artery disease, and transient ischemic attack. CVD-outcome: sum of CVD death, myocardial infarction, coronary revascularization, heart failure, and stroke. Minor events: sum of angina pectoris, peripheral artery disease, thrombotic occlusion of the retinal artery, and transient ischemic attack. ARR indicates absolute risk reduction; CVD, cardiovascular disease; HR, hazard ratio; NNT, number needed to treat; RR, relative risk; and RRR, relative risk reduction.

the required inclusion criterion[12]—and either wrist actigraphy or diary recording of bed and wake times to enable accurate derivation of the asleep and awake BP means and dipping status, as done in both the MAPEC Study and Hygia Chronotherapy Trial.[29,31]

INGESTION-TIME EFFECTS OF HYPERTENSION TREATMENT ON ADHERENCE AND COMPLIANCE

Our systematic review found no significant ingestion-time difference in average compliance, that is, 95.8±5.9% versus 94.8±8.2%, in patients randomized, respectively, to upon-waking/morning versus bedtime/evening treatment (*P*=0.306).[36] The often cited earlier conducted nonrandomized observational study of Vrijens et al,[45] on the contrary, reported adherence to treatment to be significantly lower in those who took their BP-lowering medications in the evening than morning. This study, however, seems to be flawed, not only because it is based on clock (not circadian) time as reference for the schedule of treatment but also, of greater importance, because of comparing a large number of 4149 patients nonrandomized to treatment-time who were ingesting their prescribed medications during the authors' defined morning—12-hour long span of 03:00 to 15:00 hours – versus a very small number of only 283 patients who, for unspecified reasons, ingested >75% of their prescribed medications during the authors' defined evening—equally 12-hour long span of 15:00 to 03:00 hours—thereby implying a high proportion of patients of the latter group was likely following a multiple, that is, split, daily-dosing scheme per medication. Selection of treatment times according to morning and evening periods or arbitrary designated external clock times—rather than according to distinctive markers of endogenous biological time, for example, upon-waking/bedtime that properly takes into account individual differences in the activity/sleep 24-hour rhythm and associated disparities in the phasing of endogenous circadian rhythms that influence the pharmacodynamics of BP-lowering medications—might negatively influence adherence and obscure benefits of timed treatment.[41] Improper selection of treatment times in terms of clock hour was a common error of many past ingestion-time trials. Indeed, only 72 (46.5%) of the 155 reported such studies (Table 1) appropriately used as reference the upon-waking and bed times

to trial ingestion-time differences in the effects of BP-lowered medications. Interestingly, 95.8% of these 72 trials reported superiority of bedtime treatment regimen, while 88.0% of the 25 neutral studies in contrast relied on nonspecific, that is, without reference to the staging of circadian rhythms, morning/evening treatment times.[36] Current guidelines[21,41] recommend participants of ingestion-time hypertension trials be explicitly instructed upon recruitment and reminded at every clinical visit throughout follow-up to place the prescribed medication(s) on the bedside table and to ingest it/them either immediately upon-waking from sleep or before turning the lights off to retire to sleep as the means to achieve high compliance to the allocated hypertension treatment-time schedule, a recommendation followed by participants of both the MAPEC Study and Hygia Chronotherapy Trial.[29,31] In the latter trial, poor adherence (assessed by the Morisky-Green test) was reported at any visit during follow-up by 2.8% and 2.9% of patients randomized, respectively, to the upon-waking and bedtime treatment regimens (P=0.813). The findings discussed herein of our systematic review further corroborate bedtime/evening hypertension therapy does not compromise adherence to medication, inasmuch as no single randomized study reported significant treatment-time differences in compliance.

INGESTION-TIME EFFECTS OF HYPERTENSION TREATMENT ON SAFETY

Safety is a highly relevant justification for recommending a preferred time for ingestion of hypertension medications. Quantitative evaluation of the safety of the bedtime/evening versus upon-waking/morning treatment-time schedule was reported in 45 of the 155 published trials.[36] Among them, 16 specifically reported total absence of sleep-time hypotension episodes with bedtime treatment. Moreover, adverse events, on average, occurred in a significantly greater proportion of patients randomized to the upon-waking/morning than bedtime/evening treatment scheme (14.2±14.9% versus 10.9±14.8%, P=0.022), mainly when ingesting ACEI and CCB. One trial of the diuretic torasemide reported mild nocturia in 7.1% of participants randomized to bedtime treatment and other adverse effects in 5.3% of those randomized to upon-waking therapy (P=0.679 between treatment-time groups).[46] Noteworthy is the finding that no single trial reported superiority of the upon-waking/morning treatment scheme in terms of patient safety and tolerance to therapy.[36,37]

In the Hygia Chronotherapy Trial, no treatment-time differences in adverse effects were reported throughout the 6.3-year median follow-up (6.7% versus 6.0% for the upon-waking versus bedtime treatment regimen; P=0.061)[31] among the 19 084 participants. Furthermore, there were no treatment-time differences in cases of sleep-time hypotension defined by current ABPM criteria[21] (0.3% of all participants; P=0.114 between treatment-time groups). Such low incidence of sleep-time hypotension may in part reflect the adopted clinical protocol of the trial that required conduct of 48-hour ABPM several weeks after initiating or altering hypertension therapy to ensure attainment of therapeutic goals.[31] These results, consistent with those of previous publications,[23,26] are further corroborated by findings of our systematic and comprehensive review showing no single study found the upon-waking/morning therapy to confer better patient safety and tolerance than bedtime/evening therapy. On the contrary, adverse events were on average more prevalent, especially when involving ACEI and CCB medications, with the current most popular upon-waking/morning treatment scheme.

DISCUSSION

Our systematic and comprehensive review of the published literature identified a large number of clinical trials (N=155) that assessed ingestion-time differences in the therapeutic effects of BP-lowering medications and their combinations on hypertensive individuals. The great (83.9%) majority of them with high consistency substantiate statistically and clinically significant enhanced BP-lowering efficacy, mainly during sleep, plus other beneficial effects when conventional hypertension medications of different classes and their combinations are ingested at bedtime/evening than upon-waking/morning. The major reported benefits of the bedtime/evening treatment-time strategy include (1) significantly enhanced reduction of the asleep SBP mean, without diminished efficacy in reducing the awake SBP mean; this beneficial effect on sleep-time SBP regulation is markedly greater among individuals at high CVD risk, including those requiring multiple medications to achieve adequate ABP control, those exhibiting the nondipper or riser 24-hour SBP pattern, those having history of previous CVD event(s), and those diagnosed with diabetes, CKD, or resistant hypertension (Table 2).[37] (2) Significantly greater increased sleep-time relative SBP decline towards the normal and lower CVD risk dipper 24-hour SBP pattern, the effect being greater with dual-combination medications and in high CVD risk cohorts (Table 2).[37] (3) Improved kidney function—larger decrease of UAE and bigger increase of GFR—and superior reduction of cardiac and vascular remodeling and damage—greater reduction of left ventricular mass index, left ventricular posterior diameter, relative wall thickness, and carotid artery plaque size (Table 1).[36] (4) Similar or even lower incidence of adverse effects mainly when ingesting ACEI and CCB alone or in combination with other medications. (5) Lack of risk, that is, absence, of sleep-time hypotension among bedtime-treated individuals.[36]

Advantages of the bedtime/evening treatment schedule in terms of superior decrease of asleep SBP mean and increased prevalence of dipping are corroborated for all of the trialed hypertension medication classes—whether single medications (monotherapies) within each class independent of pharmacokinetics characteristics (peak plasma concentration, time-to-peak plasma concentration, half-life, and area under the plasma concentration-time curve), dual combinations, or polytherapies (>2 separately ingested medications)—and for all investigated special patient groups at elevated CVD risk, that is, those with diabetes, CKD, resistant hypertension, previous CVD event, or nondipper/riser 24-hour BP pattern (Tables 1 and 2). Our systematic review found only 16.1% of the reported trials reported noninferiority of the extent of medical benefit of the bedtime/evening versus upon-waking/morning treatment. The inability of this very small number of reported trials to verify advantages of the bedtime/evening treatment strategy is likely explained by deficiencies of study design and conduct. Most noteworthy is the finding that no single reported randomized trial reported better BP-lowering and other medical benefits of the most recommended, but unjustified by medical evidence, upon-waking/morning treatment-time scheme.

The findings of this in-depth review are clinically relevant for multiple reasons. First, independent prospective studies and meta-analyses demonstrate CVD events are much more accurately predicted by the asleep than awake or 24-hour ABP mean.[7–10,12] Second, the relationship between attenuated sleep-time relative SBP decline, that is, nondipper/riser SBP 24-hour SBP pattern, and risk for fatal and nonfatal CVD events, has been consistently reported.[5,7,9,11,12] Third, ABPM-based investigations rigorously designed to evaluate prospectively the influence on CVD risk of changes in both OBPM and prognostic features of the 24-hour BP pattern achieved by hypertension treatment during several years of follow-up document progressive decrease of the asleep SBP mean and increase in the sleep-time relative SBP decline are jointly and significantly associated with increased patient survival time, and independently of therapy-induced change in wake-time OBPM and awake or 24-hour SBP/DBP means.[9,12] Fourth, elevated asleep SBP induces carotid remodeling and also glomerular pathology, leading to albuminuria and CKD progression.[16] Cardiac and blood vessel tissue show significant circadian variation in gene expression, metabolism, growth, and remodeling, with the remodeling, in particular, being most active during sleep.[47,48] Indeed, the peak or near peak staging of many of the most relevant circadian mechanisms of BP regulation is linked to the state of sleep: (1) activation of the renin-angiotensin-aldosterone system[16]; (2) elevation of atrial natriuretic and calcitonin gene-related vasoactive peptides and nitric oxide as vasodilators[16]; and (3) cardiac remodeling.[47,48] These and other rhythmic phenomena might help explain the markedly diminished vulnerability to cardiac and vascular pathology accomplished by bedtime hypertension chronotherapy (medication timed to features of circadian rhythms) versus upon-waking traditional treatment.[29–32] The reported better reduction of CVD risk with bedtime than upon-waking hypertension therapy, particularly with an ARB or ACEI medication,[49,50] might stem not only from the enhanced numerical reduction of the asleep SBP level and increase of sleep-time relative SBP decline,[29,31] but from superior suppression of the renin-angiotensin-aldosterone system, whose circadian rhythm is expressed at near peak or peak level during sleep, thereby resulting in enhanced protection against deleterious cardiac, endothelial, and other tissue remodeling, pathology, and injury, which at this specific time during the 24-hour is considered to be of greatest risk.[14–16]

PERSPECTIVES

On the basis of all the collective information reviewed herein, we recommend the diagnosis and management of hypertension be (1) baseline around-the-clock ABPM assessment—both in previously untreated persons or when clinically feasible after washed-out for ≥2 weeks in previously treated assumed hypertensives—most strongly recommended for everyone ≥55 years of age and those with diabetes, CKD, and history of previous CVD event (due to the high prevalence of sleep-time hypertension and nondipper 24-hour BP pattern in these patient groups), for proper diagnosis of true arterial hypertension—in terms of elevated asleep SBP mean and nondipper SBP pattern—and to establish the need for therapeutic intervention.[12] (2) Pharmacological treatment, preferably at bedtime, in those with true arterial hypertension according to the patient's individualized CVD risk score determined by ABPM and other relevant CVD risk factors.[51] (3) As routine clinical procedure, assessment of treatment efficacy and safety by periodic around-the-clock ABPM, preferably conducted ≈3 months after either instituting or modifying the patient's therapeutic scheme and as proper follow-up at least annually, thereafter, to confirm appropriately controlled ABP.[21]

ARTICLE INFORMATION

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Response to Lowering Nighttime Blood Pressure With Bedtime Dosing of Antihypertensive Medications: Controversies in Hypertension - Pro Side of the Argument

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Hermida et al make a good case about the importance of ambulatory blood pressure monitoring and nocturnal hypertension, with which we agree. Otherwise, in their defense of chronotherapy, they rely on their own duplicate publications of the same systematic review (https://www.crd.york.ac.uk/PROSPERO/; Unique identifier: CRD42020201220), which include a plurality of studies from their own group and are limited by inclusion of cross-sectional, overlapping, and otherwise biased studies. Notably, this review was neither conducted according to the Cochrane methodology nor properly reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidance. Hermida et al continue their inconsistent criticism of other studies with discordant results, casting aspersions on sample size of properly conducted and clearly reported trials (Hellenic-Anglo Research into Morning or Night Antihypertensive Drug Delivery [HARMONY]) and ongoing trials with rigorous protocols (BedMed and TIME [Treatment in Morning Versus Evening]). They accept evening dosing (as opposed to bedtime) when the conclusions align with their own (eg, Roush systematic review) but raise it as a weakness when they do not. More importantly, no further details or explanation are provided for the incredible benefit seen in Hygia for noncardiovascular mortality and the unprecedented lack of adverse effects. The investigation reported by the *European Heart Journal* editors suggests that Hygia was a low-cost trial embedded in routine care that lacked the robust measurement of adherence, adverse events, and event adjudication typically expected from clinical trials. This is the most plausible explanation for their findings, and the medical community should await the results of more rigorous ongoing clinical trials.