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Ingestion-time differences in the pharmacodynamics of hypertension medications: Systematic review of human chronopharmacology trials

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ABSTRACT

Pharmacokinetics of hypertension medications is significantly affected by circadian rhythms that influence absorption, distribution, metabolism and elimination. Furthermore, their pharmacodynamics is affected by ingestion-time differences in kinetics and circadian rhythms comprising the biological mechanism of the 24 h blood pressure (BP) pattern. However, hypertension guidelines do not recommend the time to treat patients with medications. We conducted a systematic review of published evidence regarding ingestion-time differences of hypertension medications and their combinations on ambulatory BP-lowering, safety, and markers of target organ pathology. Some 153 trials published between 1976 and 2020, totaling 23,869 hypertensive individuals, evaluated 37 different single and 14 dual-fixed combination therapies. The vast (83.7%) majority of the trials report clinically and statistically significant benefits – including enhanced reduction of asleep BP without inducing sleep-time hypotension, reduced prevalence of the higher cardiovascular disease risk BP non-dipping 24 h profile, decreased incidence of adverse effects, improved renal function, and reduced cardiac pathology – when hypertension medications are ingested at-bedtime/evening rather than upon-waking/morning. Non-substantiated treatment-time difference in effects by the small proportion (16.3%) of published trials is likely explained by deficiencies of study design and conduct. Systematic and comprehensive review of the literature published the past 45 years reveals no single study reported significantly better benefit of the still conventional, yet unjustified by medical evidence, upon-waking/morning hypertension treatment schedule.

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1. Introduction

The diagnosis and treatment of hypertension has long been dominated by the concept of homeostasis, i.e., maintenance of constancy of biological processes and functions. Thus, blood pressure (BP) has been assumed to be more or less constant, with little change during the 24 h, leading to the assumption the time when BP is measured, typically during the wake-time in the doctor's office, is indicative of its level at any time of the activity and sleep spans. This fallacious assumption is in part the rationale for the goal of drug-delivery systems of once-a-day tablet and capsule dosage forms to achieve an as constant as possible medication level throughout the 24 h dosing interval. However, the increasing use of around-the-clock ambulatory BP monitoring (ABPM) methods to conduct BP research and diagnose hypertension reveals systolic BP (SBP) and diastolic BP (DBP) are not at all constant but variable as a predictable-in-time prominent 24 h pattern of typically awake-time higher and asleep-time lower values [1,2]. For many decades such 24 h BP pattern was thought to be representative of the population at large; however, this is not the case. With aging and illness its features, particularly the asleep SBP mean and sleep-time relative SBP decline, i.e., extent of SBP dipping defined as the percent decrease in mean SBP during the sleep span relative to mean SBP during the activity span – calculated as ([awake SBP mean – asleep SBP mean]/awake SBP mean) × 100 – tend to undergo significant alteration [3]. Large ABPM-based clinical studies report more than ≥64% of individuals >60 years of age [3] and those having a diagnosis of type 2 diabetes [4], chronic kidney disease (CKD) [5], or resistant hypertension [6], among other conditions [1,7], is likely to exhibit a non-dipper (sleep-time relative SBP decline <10%) or riser (sleep-time relative SBP decline <0%) 24 h BP profile, often with an abnormally elevated asleep SBP mean that is markedly associated with elevated cardiovascular disease (CVD) risk, regardless of the awake or 24 h BP means [8–18]. Thus, the elevated asleep mean and non-dipping features of the 24 h SBP pattern as identified by around the clock ABPM are considered by an increasing number of investigators as critically important targets of hypertension therapy [15,18].

Chronopharmacology is the study of biological rhythm influences on the pharmacokinetics (PK) and pharmacodynamics (PD) of medications. Chronotherapeutics is the timing of medications (or other forms of treatment) to features of biological rhythms to optimize therapeutic benefits and/or minimize/avert adverse effects. Both are areas of growing interest in medicine, especially as a means to safely improve the control of elevated BP [19–28] and better diminish CVD vulnerability [29–33]. The PK of ingested BP-lowering medications is significantly affected not only by the 24 h cyclic behavior of meal consumption but multiple endogenous circadian rhythms, e.g.: (i) gastric pH and emptying rate, gastrointestinal tract motility, blood perfusion, passive and active transport phenomena, and biliary and pancreatic processes that influence *absorption*; (ii) red and white blood cell count, plasma and tissue protein, passive and active cell membrane transport mechanisms, and tissue perfusion that influence *distribution*; and (iii) hepatic and renal blood perfusion, activity of multiple hepatic enzymes and biochemical pathways, and glomerular filtration and other renal tubular phenomena that influence *metabolism and elimination* [34–37]. On the other hand, the PD of hypertension medications is not only influenced by circadian rhythms that impact their PK but those that: (i) affect the circulating medication free-fraction concentration, cell/tissue receptor number/conformation, and second messengers/signaling pathways of drug targets, e.g., blood vessels and heart and renal tissue; and (ii) comprise the biological mechanisms of the 24 h BP pattern, especially the autonomic nervous system and renin-angiotensin-aldosterone system (RAAS) [1,2,38,39]. Thus, it should not be surprising that the ingestion time of hypertension medications (with reference to the staging of these and other involved circadian rhythms) might affect their duration of action, effects on the 24 h BP profile, and patient tolerability and safety.

Hypertension guidelines do not recommend the time to treat patients with medications [40–42]. Nonetheless, the majority of hypertensive individuals are conventionally advised by healthcare professionals to ingest their BP-lowering therapy in the morning at the commencement of the activity span. This recommendation might derive from large epidemiological studies that reported angina pectoris, myocardial infarction, sudden cardiac death, and hemorrhagic and ischemic stroke occur most frequently during the initial hours of the daily activity span [43–45]. These findings led to the unsubstantiated hypothesis the upon-awakening BP rapid rise being causal of the corresponding-in-time excess manifestation of CVD events. This, in turn, led to the hypothesis that therapeutic attenuation of the upon-awakening BP rapid rate rise reduces CVD vulnerability. These hypotheses posed some three decades ago spurred a new approach to treating hypertension utilizing special drug-delivery systems – marketed as Cardizem LA, COER HS, Verelan PM, and Procardia XL – that when ingested at bedtime, as directed, released medication only after a delay of ~4 h and achieve highest drug concentrations just before and during the expected upon-awakening BP rate of rise [46]. However, the international multicenter Controlled Onset extended-release (COER) Verapamil Investigation of Cardiovascular Endpoints (CONVINCE) trial of the most popular special bedtime-ingested COER-verapamil drug-delivery dosage form did not substantiate the proposed hypothesis of significant difference in the reduction of major CVD events by it vs. morning either β-agonist atenolol or diuretic hydrochlorothiazide (HCTZ) medications, the then considered standard of care hypertension therapies [47]. However, a series of recently conducted prospective investigations that incorporated periodic around-the-clock ABPM patient assessments throughout follow-up to determine the impact of changes in prognostic features of the 24 h BP pattern on CVD morbidity and mortality substantiated treatment-induced decrease of the asleep SBP mean and increase of the sleep-time relative SBP decline are jointly and significantly associated with markedly reduced CVD risk [15,18].

A single Cochrane review published a decade ago that identified only 21 randomized bedtime/evening vs. upon-waking/morning hypertension treatment trials reported no statistically significant ingestion-time differences in adverse effects and only small, although statistically significant, enhanced reduction by 1.71/1.38 mmHg of the 24 h SBP/DBP means with bedtime/evening treatment [19]. This now outdated review, however, did not assess treatment-time-dependent effects on the asleep SBP mean and sleep-time relative SBP decline – reported since then as the most significant BP-derived prognostic markers of CVD risk [8–18] – nor did it assess patient adherence/compliance and target organ pathology. These are, therefore, points of emphasis of this comprehensive review article. More recent, although non-systematic and thus incomplete, reviews involving a larger number of published studies reveal the results and conclusions of ingestion-time hypertension studies are sometimes conflicting due to

differences of investigative methods [20–28]. Accordingly, we conducted an in-depth systematic review of prospective human trials published during the past 45 years that investigated BP-lowering medications for upon-waking/morning vs. bedtime/evening treatment-time differences in safety, adherence, and specific therapeutic effects on the features and characteristics of the BP 24 h pattern, with a view to inform opportunities for future research and development of drug-delivery systems to improve the therapy of hypertension and lessen the risk for its associated pathological effects.

2. Methods of the systematic review

The literature review was conducted in accord with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [48] to identify publications pertaining to ingestion-time differences in the effects of BP-lowering therapies, either trialed as single, fixed-dual combination, or multiple therapies. The protocol for this systematic review is registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42020201220). PubMed, Library of Congress, SCI Web of Science, and DBLP computer science bibliography were searched using combinations of the following terms: chronobiology, chronotherapy, chronopharmacology, chronopharmacodynamics, pharmacology, pharmacodynamics; hypertension, antihypertensive effect, blood pressure lowering, blood pressure reduction; bedtime, awakening, evening, morning, nighttime; plus either ingestion, administration, treatment, or dosing. Articles were limited to studies involving hypertensive adults (≥18 years of age) of both sexes, published in any language, without restriction of duration of therapy, trial design, main outcome, and publication date. We excluded studies relating only to PK, long-term trials on CVD outcomes, reviews, case studies, and commentaries. Systematic review and meta-analysis of long-term trials on CVD outcomes have previously been reported [30,33]. Trials of aspirin, melatonin, and other agents not ordinarily used clinically as antihypertensive medications were also excluded. The reference list of retrieved articles was additionally reviewed to identify publications missed by the above-listed search terms.

We extracted the following details of each trial into a specially designed database: trialed medication(s) and dose(s), treatment times, number of participants/group, inclusion/exclusion criteria, sample size calculation, follow-up duration, study design, primary BP measurement (office BP measurement [OBPM], home BP measurement, or ABPM), primary study endpoint(s), and major findings. When reported, we also extracted quantitative information on: (i) adverse effects and compliance to treatment; and (ii) ingestion-time effects on the 24 h, awake, and asleep SBP means and sleep-time relative SBP decline.

Treatment-time-dependent effects on ambulatory BP (ABP) were evaluated using a random-effects model, given the high likelihood of between-study variance, with heterogeneity assessed by Cochrane $\chi 2$ and I^2 statistics. Publication bias was assessed by Egger's test [49]. Qualitative and, when possible, quantitative analyses were done on the data of the total identified studies plus subgroups of studies categorized according to: (i) medication class, i.e., angiotensin-converting enzyme inhibitor (ACEI), angiotensin-II receptor blocker (ARB), calcium-channel blockers (CCB), ß-blocker, diuretic, α-blocker, adrenergic receptor agonist; (ii) number of trialed agents, i.e., monotherapy, fixed dual-medication combination, polytherapy (≥2 separately ingested medications); and (iii) special populations at elevated CVD risk, i.e., non-dippers and patients with diabetes, CKD, resistant hypertension, or past major CVD event. Main outcomes were ingestion-time-dependent effects on either: (i) asleep SBP mean; (ii) sleep-time relative SBP decline; (iii) markers of hypertension-associated target organ pathology of the kidney – albuminuria, estimated glomerular filtration rate (GFR) – and heart – left ventricular posterior diameter and left ventricular mass; and (iv) adverse events, including sleep-time hypotension. The search of the published literature, screening and identification of trials complying with inclusion/exclusion criteria, and extraction of relevant information were independently conducted by two investigators (RCH, RGHA). Disagreements concerning inclusion/exclusion of studies, retrieved information, and assessment of findings from individual trials were resolved by consensus after consulting with a third investigator (MHS).

3. Ingestion-time differences in the PD of hypertension medications

We identified 168 eligible studies published between 1976 and 2020 (Fig. 1). Some 15 studies were eliminated: one non-randomized open-label study of 164 non-dipper hypertensives incorrectly defined the primary endpoint, namely, extent of sleep-time BP decline, which led to unreliable findings; 2 lacked information on the defined main outcomes; 10 failed to include an upon-waking/morning comparative treatment arm; and 2 reported duplicate information (Supplementary Table S1). Thus, 153 trials, representing 23,869 hypertensive individuals, met criteria for qualitative analyses. Some 59 of them, totaling 5994 hypertensive persons, provided ABPM-based information on ingestion-time-dependent effects of BP-lowering treatment on the awake and asleep BP means and/or sleep-time relative SBP decline and met criteria for quantitative analyses. Supplementary Table S1 summarizes the major features and findings of all of the 153 published ingestion-time hypertension trials.

Among the 153 trials, 25 were classified as "neutral", showing non-inferiority of bedtime/evening vs. upon-waking/morning treatment, while the remaining 128 (83.7%) reported significantly enhanced advantages of bedtime/evening treatment according to the a priori defined main outcomes established for this systematic review: enhanced asleep SBP reduction, increased sleep-time relative SBP decline (dipping), decreased adverse events, and/or improved markers of target organ pathology, including reduced albuminuria, increased GFR, and decreased left ventricular posterior diameter and left ventricular mass. Our comprehensive review found no single study that reported significantly better BP-lowering or other benefits of the most recommended upon-waking/morning treatment-time scheme. Table 1 provides the distribution of trials – with their combined sample size – documenting either superiority or non-inferiority (neutral) of the bedtime/evening vs. upon-waking/morning hypertension treatment regimen categorized by the trialed single, dual-fixed combination, or multiple therapies. Most trials entailed CCB, ACEI, and ARB medications.

Quantitative evaluation of the 59 ABPM-based randomized trials substantiates for bedtime/evening vs. upon-waking/morning therapy statistically significant enhanced reduction of the asleep SBP mean by an average 5.12 mmHg (95%CI [3.96–6.27], $P < 0.001$ between treatment-time groups; $I^2 = 77\%$), but not awake SBP mean (0.71 mmHg, [−0.05–1.46], $P = 0.07$; $I^2 = 48\%$). Consequently, the sleep-time relative SBP decline was significantly further increased by an average 3.23% ([2.40–4.05], $P < 0.001$) towards the low CVD risk normal dipper 24 h BP pattern with bedtime/evening vs. upon-waking/morning treatment. There was no evidence of publication bias ($P = 0.267$). Sensitivity analysis by the leave-one-out approach indicates no single study significantly influenced the global findings; nonetheless, the significantly enhanced reduction of asleep SBP mean with bedtime/evening as opposed to upon-waking/morning treatment was largest for trials entailing: (i) dual-fixed combinations (on average by 8.91 mmHg, [4.62–13.21], $P < 0.001$) and polytherapy (8.53 mmHg, [3.19–13.85], $P < 0.001$); and (ii) non-dippers (8.62, [6.48–10.76], $P < 0.001$) and other high CVD risk populations (8.99 mmHg, [4.49–13.48], $P < 0.001$) compared with hypertensive individuals of the general population (3.99 mmHg, [2.90–5.07], $P < 0.001$).

3.1. Conventional hypertension monotherapies

A total of 24 of the 28 (85.7%) clinical trials of ACEI medications of different terminal half-life – benazepril, captopril, enalapril, imidapril,

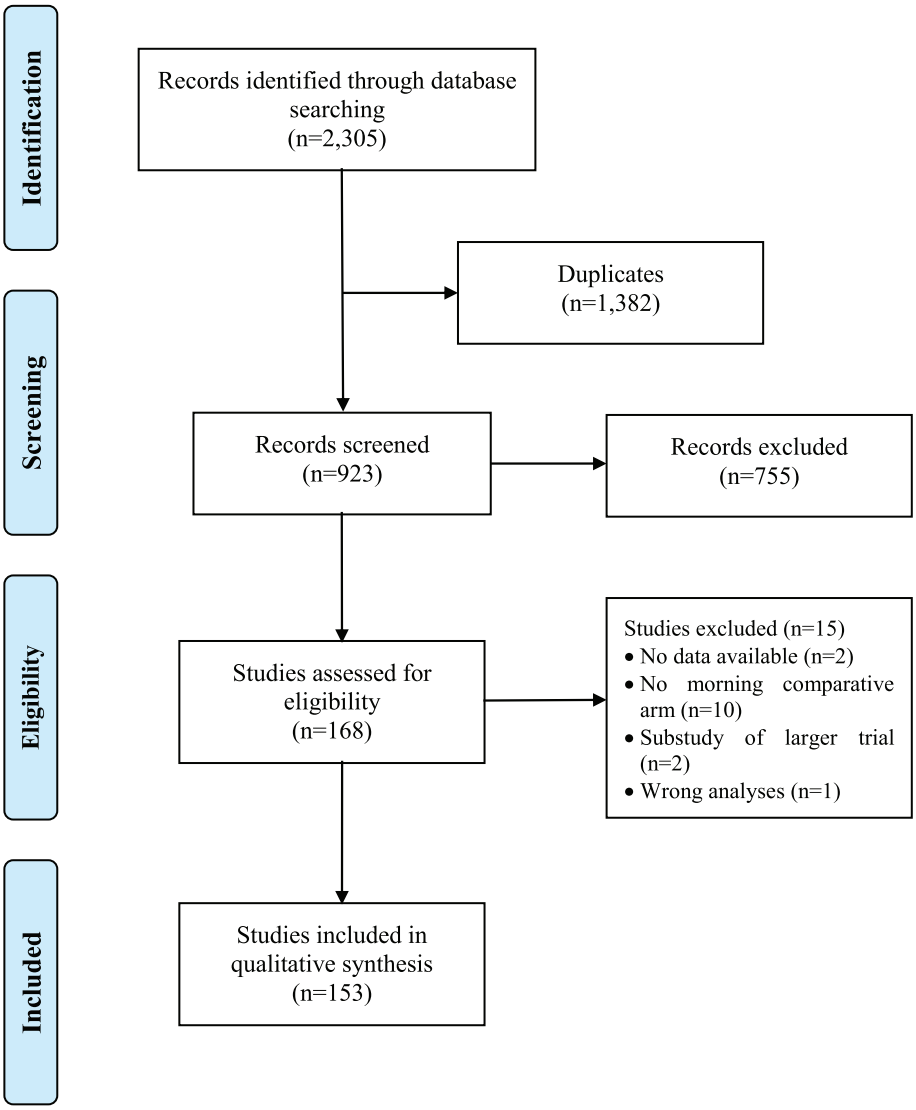

Fig. 1. Study screening flowchart.

lisinopril, perindopril, quinapril, ramipril, spirapril, trandolapril, and zofenopril – when ingested at-bedtime/evening vs. upon-waking/morning reported significantly better: (i) attenuated asleep SBP mean; (ii) normalization of the 24 h SBP dipper profile; and (iii) patient tolerance to treatment, i.e., decreased incidence of adverse effects (Table 1). It is noteworthy that there was no single reported case of sleep-time hypotension with bedtime/evening treatment (Table 1). The remaining 4 ACEI chronotherapy trials were "neutral", i.e., showed non-inferiority of bedtime/evening compared to upon-waking/morning treatment schemes.

Most (19 out of 25, 76.0%) of the published prospective ARB trials on candesartan, irbesartan, olmesartan, telmisartan, and valsartan, validated similar significant ingestion-time differences in therapeutic effects as was found for the ACEI (Table 1), also independent of medication terminal half-life. Again, no cases of sleep-time hypotension were reported with ARB bedtime/evening treatment. Moreover, bedtime dosing of valsartan, olmesartan, and candesartan significantly decreased urinary albumin excretion (UAE) in an amount strongly correlated with the extent of the asleep SBP mean reduction and sleep-time relative SBP decline increase [50–52].

Conventional CCB medications – altiazem, amlodipine, barnidipine, cilnidipine, diltiazem, isradipine, nifedipine, nisoldipine, nitrendipine, and verapamil – as a class were most frequently ($N = 41$ reports) trialed. Although 11 (26.8%) CCB studies report similar homogeneous decrease of BP throughout the 24 h independent of ingestion-time, all of the other 30 (73.2%) document significantly greater reduced asleep SBP mean, increased dipping, decreased left ventricular mass and/or improved safety, primarily significantly decreased risk of peripheral edema, with bedtime/evening treatment (Table 1).

The BP-lowering effect of various other hypertension medications, i.e., α-blocker doxazosin; ß-blockers bisoprolol, carvedilol, nebivolol, penbutolol, and propanolol; diuretics of HCTZ and torasemide; plus methyldopa, guanabenz, and clonidine additionally differs significantly according to ingestion-time. In general, they exert more prolonged BP-lowering effect when ingested at bedtime/evening than upon-waking/morning, and without significant ingestion-time differences in adverse effects (Table 1).

In summary, among the 112 reported trials evaluating BP-lowering monotherapies ingested at different times of the day, either in terms of the nonspecific terminology of "morning" vs. "evening" or, more appropriately from a circadian rhythm perspective, upon-waking vs. at bedtime, 22 were "neutral", i.e., evidenced no treatment-time difference in therapeutic effects. All of the other 90 (80.4%) trials reported significantly better effects by the bedtime/evening treatment schedule,

Table 1
Ingestion-time-dependent differences in the pharmacodynamics of hypertension medications and their combinations.

Medication class	# trials (# patients)	# trials showing significant treatment-time benefits* (# patients)			"bedtime better" % trials (% patients)	Summary of (statistically significant) main findings
		Awakening/morning	Bedtime/evening	Neutral		
ACEI	28 (1254)	0 (0)	24 (1061)	4 (193)	85.7 (84.6)	• Greater: decreased asleep BP mean and morning BP, proportion of controlled patients (by ABPM criteria), enhanced dipping, and corresponding reduced prevalence of non-dipping with bedtime than morning treatment. • Increased GFR and decreased renal vascular resistance only with evening treatment. • Similar or even lower incidence of adverse effects in the bedtime compared to morning-treatment group. Reduced incidence of cough with bedtime treatment. • No reported cases of sleep-time hypotension with bedtime treatment.
ARB	25 (3588)	0 (0)	19 (2085)	6 (1503)	76.0 (58.1)	• Greater: decreased asleep BP mean, proportion of controlled patients (by ABPM criteria), enhanced dipping, and corresponding reduced prevalence of non-dipping with bedtime than morning treatment. • Increased GFR and reduced UAE and UACR with bedtime than morning treatment. • Regression of left ventricular mass index and reduced plaque in the carotid artery with bedtime treatment. • Lessened increase of sympathetic activity with bedtime treatment • No treatment-time difference in incidence of adverse effects. • No reported cases of sleep-time hypotension with bedtime treatment.
CCB	41 (2635)	0 (0)	30 (2093)	11 (542)	73.2 (79.4)	• Greater: decreased asleep BP mean, proportion of controlled patients (by ABPM criteria), enhanced dipping, and corresponding reduced prevalence of non-dipping with bedtime than morning treatment. • Reduced left ventricular mass and improved left ventricular diastolic function with evening treatment. • Similar or even lower incidence of adverse effects in the bedtime compared to morning-treatment group. Reduced incidence of edema with bedtime treatment. • No reported cases of sleep-time hypotension with bedtime treatment.
ß-blocker	7 (791)	0 (0)	7 (791)	0 (0)	100 (100)	• Reversed adverse changes in autonomic nervous system activity and reduced nighttime heart rate with evening treatment. • Administration-time had no effect on ventricular arrhythmia occurrence. • Greater reduction of pre-waking BP following evening/bedtime treatment. • No treatment-time difference in incidence of adverse effects. • No reported cases of sleep-time hypotension in either treatment--time group.
Diuretic	5 (364)	0 (0)	4 (352)	1 (12)	80.0 (96.7)	• Greater decrease in asleep and 24 h ABP means with bedtime treatment. • Enhanced duration of therapeutic effects with bedtime compared to upon-awakening treatment. • Greater percentage of properly controlled patients following bedtime treatment. • Greater decrease in left ventricular posterior diameter and left ventricular mass with evening treatment. • No treatment-time difference in incidence of adverse effects. Mild nocturia reported in ≤7% of patients treated at bedtime.
α-blocker	3 (925)	0 (0)	3 (925)	0 (0)	100 (100)	• Greater decrease in asleep, but not awake, ABP mean, with bedtime treatment. • Extended duration of therapeutic BP-lowering effect following bedtime dosing. • Increased dipping only in non-dippers/risers, but not in extreme--dippers and normal dippers. • Decreased left ventricular mass index, relative wall thickness, and UAE following bedtime therapy.
Adrenergic receptor agonist	3 (147)	0 (0)	3 (147)	0 (0)	100 (100)	• Significant reduction in morning BP after only 2–4 weeks of therapy. • Evening BP reduced mainly in patients with elevated evening BP at baseline. • No treatment-time difference in incidence of adverse effects.
Dual fixed combination	17 (1508)	0 (0)	16 (1485)	1 (23)	94.1 (98.5)	• Greater: decreased asleep BP mean, proportion of controlled patients (by ABPM criteria), enhanced dipping, and corresponding reduced prevalence of non-dipping with bedtime than morning treatment. • Greater reduction on left ventricular mass and left ventricular

Table 1 (*continued*)

Medication class	# trials (# patients)	# trials showing significant treatment-time benefits* (# patients)			"bedtime better" % trials (% patients)	Summary of (statistically significant) main findings
		Awakening/morning	Bedtime/ evening	Neutral		
						posterior diameter with bedtime than morning treatment. • Decreased UACR following bedtime treatment. • Similar or even lower incidence of adverse effects in the bedtime compared to morning-treatment group. • No reported cases of sleep-time hypotension with bedtime treatment.
Polytherapy	24 (12,657)	0 (0)	22 (12,415)	2 (242)	91.7 (98.1)	• Greater: decreased asleep BP mean, proportion of controlled patients (by ABPM criteria), enhanced dipping, and corresponding reduced prevalence of non-dipping with bedtime than morning treatment. • Bedtime treatment associated with reduced glucose, cholesterol, fibrinogen, UAE, and UACR, plus enhanced GFR. • Greater reduction on left ventricular mass with bedtime than morning treatment. • No treatment-time difference in incidence of adverse effects.
TOTAL	**153 (23,869)**	**0 (0)**	**128 (21,354)**	**25 (2515)**	**83.7 (89.5)**	**Enhanced ABP-lowering efficacy – mainly during sleep-time – increased dipping without induced hypotension, improved renal function, decreased heart damage, and similar/lower incidence of adverse effects when all classes anf hypertension medications and their combinations are routinely ingested at bedtime rather than in the morning.**
Special populations at elevated CVD risk						
Non-dippers	18 (1212)	0 (0)	18 (1212)	0 (0)	100 (100)	• Greater: decreased asleep BP mean, proportion of controlled patients (by ABPM criteria), enhanced dipping, and corresponding reduced prevalence of non-dipping with bedtime than morning treatment. • Reduction of UAE and delayed decline in estimated GFR with bedtime treatment. • Regression of left ventricular mass index and reduced plaque in the carotid artery with bedtime treatment. • No treatment-time difference in incidence of adverse effects. • No reported cases of sleep-time hypotension with bedtime treatment.
Diabetes	9 (3036)	0 (0)	8 (3019)	1 (17)	88.9 (99.4)	• Greater: decreased asleep BP mean, proportion of controlled patients (by ABPM criteria), enhanced dipping, and corresponding reduced prevalence of non-dipping with bedtime than morning treatment. • Increased nocturnal natriuresis and decreased C-reactive proteine with bedtime than morning treatment. • Bedtime treatment associated with reduced glucose, cholesterol, and UACR, plus enhanced GFR. • Regression of parameters of left ventricular structural and functional state following bedtime compared with morning treatment. • No treatment-time difference in incidence of adverse effects. • No reported cases of sleep-time hypotension with bedtime treatment.
CKD	6 (2948)	0 (0)	5 (2801)	1 (147)	83.3 (95.0)	• Greater: decreased asleep BP mean, proportion of controlled patients (by ABPM criteria), enhanced dipping, and corresponding reduced prevalence of non-dipping with bedtime than morning treatment. • Reduction of UAE and delayed decline in estimated GFR with bedtime treatment. • Regression of left ventricular mass index and reduced plaque in the carotid artery with bedtime treatment.
Resistant hypertension	7 (5833)	0 (0)	7 (5833)	0 (0)	100 (100)	• Greater: decreased asleep BP mean, proportion of controlled patients (by ABPM criteria), enhanced dipping, and corresponding reduced prevalence of non-dipping with bedtime than morning--treatment regimen. • Bedtime treatment associated with reduced glucose, cholesterol, fibrinogen, UAE, and UACR, plus enhanced GFR.
Previous CVD event	10 (864)	0 (0)	10 (864)	0 (0)	100 (100)	• Greater reduction of ABP means, central aortic pressure, and stiffness of the vascular wall following evening compared to morning treatment. • Enhanced sleep-time relative BP decline with evening compared to morning treatment. • Increased proportion of controlled patients with bedtime compared to morning treatment. • Greater reduction of UACR with bedtime dosing. • Regression of parameters of left ventricular structural and functional state following bedtime compared with morning treatment. • No treatment-time difference in incidence of adverse effects.

(continued on next page)

Table 1 (*continued*)

Medication class	# trials (# patients)	# trials showing significant treatment-time benefits* (# patients)			"bedtime better" % trials (% patients)	Summary of (statistically significant) main findings
		Awakening/morning	Bedtime/evening	Neutral		
TOTAL	**50 (13,893)**	**0 (0)**	**48 (13,729)**	**2 (164)**	**96.0 (98.8)**	**Enhanced ABP-lowering efficacy – mainly during sleep-time – increased dipping without induced hypotension, improved renal function, decreased heart damage, and similar safety profile when high CVD risk patients routinely ingest hypertension medication (s) at bedtime rather than in the morning.**

ABP: ambulatory blood pressure. ABPM: ambulatory blood pressure monitoring. ACEI: angiotensin-converting enzyme inhibitor. ARB: angiotensin-II receptor blocker. BP: blood pressure. CCB: calcium channel blocker. CVD: cardiovascular disease. CKD: chronic kidney disease. GFR: Glomerular filtration rate. UACR: Urinary albumin/creatinine ratio. UAE: Urinary albumin excretion.
Non-dipper: individuals with sleep-time relative systolic BP (SBP) decline <10%. The sleep-time relative SBP decline, index of BP dipping, is defined as percent decrease in SBP during sleep relative to mean SBP during activity, and calculated as: ([awake SBP mean – asleep SBP mean]/awake SBP mean) × 100.

i.e., improved SBP reduction, mainly during sleep, moderation/reversal of non-dipper 24 h SBP pattern, and/or greater beneficial effects upon the kidney and heart (Table 1). None of the 112 trials found the conventional upon-waking/morning treatment schedule to confer better benefits than the bedtime/evening one.

3.2. Combination hypertension treatment

Some 17 trial, representing a total of 1508 hypertensive patients, investigated differential effects of 14 fixed-combination dual-medication therapies: amiloride-HCTZ, amlodipine-HCTZ, azilsartan-indapamide, captopril-HCTZ, enalapril-HCTZ, fosinopril-amlodipine, losartan-indapamide, olmesartan-amlodipine, perindopril-indapamide, telmisartan-amlodipine (two trials), valsartan-amlodipine (two trials), valsartan-HCTZ, valsartan-indapamide (two trials), and verapamil-trandolapril. Among them, 16 (94.1%) reported better benefits (Table 1) by the bedtime/evening vs. upon-waking/morning schedule; the other single small study (valsartan-amlodipine combination involving only 23 hypertensive patients [53]) was "neutral" i.e., showed no significant treatment-time difference in effects (Table 1).

Another 24 (of which 9 were cross-sectional in design) trials, totaling 12,657 individuals, addressed ingestion-time difference of hypertension polytherapy. Significantly better benefits of the bedtime/evening vs. upon-waking/morning treatment scheme were documented in 22 of these 24 studies (91.7%; Table 1) in terms of enhanced asleep SBP reduction without inducing sleep-time hypotension, reduced prevalence of SBP non-dipping, larger proportion of controlled patients by ABPM criteria [7,41], improved renal function, and/or reduced cardiac injury.

3.3. Special populations at elevated CVD risk

A total of 50 ingestion-time trials concerned special populations at elevated CVD risk: (i) 18 together comprising 1212 non-dipper hypertensives that consistently documented significant superiority of bedtime/evening treatment time, i.e., better reduction of asleep BP and enhanced sleep-time relative SBP decline – without inducing sleep-time hypotension – plus augmented reduction of UAE and/or regression of left ventricular mass index. (ii) 9 totaling 3036 patients with diabetes of which 8 found significant superior reduction of asleep SBP mean, increased sleep-time SBP decline, enhanced glucose control, decreased UAE, increased GFR, and/or regression of left ventricular hypertrophy; the other trial on only 17 patients [54] disclosed non-inferiority of the bedtime/evening vs. upon-waking/morning treatment scheme. (iii) 6 collectively entailing 2948 CKD patients that showed, with the exception of one of them concerning 147 individuals [55], significant advantages of bedtime/evening treatment, including improved renal function and reduced cardiac injury. (iv) 7 totaling 5833 resistant hypertension patients that all reported greater decrease of ABP, reduced prevalence of non-dipping, and increased proportion of properly controlled BP when ingesting the entire daily dose of ≥1 hypertension medications at bedtime/evening vs. ingesting all of them upon-waking/morning. (v) 10 specifically enrolling a total of 864 patients with past history of CVD events (specifically, congestive heart failure or stroke) that all documented superiority of bedtime/evening therapy, with no reported treatment-time difference in incidence of adverse effects (Table 1).

3.4. Safety and compliance

Quantitative evaluation of the safety of the bedtime/evening and upon-waking/morning treatment-time schedules was reported in 45 of the 153 published trials. Some 16 of them specifically reported absence of sleep-time hypotension episodes with bedtime treatment. 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% vs. 10.9 ± 14.8%, $P = 0.022$), mainly when ingesting ACEI and CCB (Supplementary Table S1). 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) [56]. 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. Finally, only 13 trials reported compliance and adherence data. There was no significant upon-waking/morning vs. bedtime/evening treatment-time difference in average compliance, respectively 94.5 ± 4.1% vs. 93.8 ± 5.9% ($P = 0.169$); moreover, no single randomized study individually reported significant ingestion-time differences in compliance (Supplement Table S1).

4. Discussion

4.1. Differential ingestion-time effects of hypertension medications on BP regulation, target organ damage, safety, and compliance

Our systematic and comprehensive review of the published literature specific to hypertension monotherapies and their combinations identified a large number of clinical trials ($N = 153$) that assessed ingestion-time differences in their PD. The great (83.7%) majority of them, representing 89.5% of the total of 23,869 hypertensive participants, with high consistency document statistically and clinically significant enhanced BP-lowering efficacy, mainly during sleep, plus other favorable effects when medications of different classes and their combinations were ingested at-bedtime/evening rather than upon-waking/morning. The major benefits of the bedtime/evening treatment strategy

include: (i) Significantly enhanced reduction of the asleep SBP mean by an average 5.12 mmHg ($P < 0.001$), without diminished efficacy in reducing the awake SBP mean; this beneficial effect on sleep-time SBP regulation was markedly greater among individuals at high CVD risk, including those requiring multiple medications to achieve adequate ABP control, history of previous CVD events, and those diagnosed with diabetes, CKD, and/or resistant hypertension (Table 1). (ii) Significantly greater increased sleep-time relative SBP decline by 3.23% ($P < 0.001$) towards the normal and lower CVD risk dipper 24 h BP pattern, the effect being greater with fixed dual-medication combinations (5.50% increased sleep-time relative SBP decline, $P < 0.001$) and in high CVD risk cohorts (5.29% increased sleep-time relative SBP decline, $P < 0.001$). (iii) Improved renal function – larger decrease of UAE and increase of GFR – and superior reduction of cardiac and vascular remodeling and damage – greater regression of left ventricular mass index, left ventricular posterior diameter and relative wall thickness, and carotid artery plaque (Table 1). (iv) Similar or even lower – mainly when ingesting ACEI and CCB alone or in combination with other medications – incidence of adverse effects. (v) Lack of risk, i.e., absence of sleep-time hypotension among bedtime-treated individuals. Our systematic review further reveals only 16.3% of the reported trials show non-inferiority of the amount of medical benefits attained by the bedtime/evening vs. upon-waking/morning treatment and, most important, no single trial documents significantly better benefits of the morning treatment regimen (Table 1).

Advantages of the bedtime/evening treatment-regimen in terms of enhanced decrease of asleep SBP mean and increased prevalence of dipping as well as safety were substantiated for: (i) all of the trialed hypertension medication classes, whether single medications (monotherapies) within each class – independent of their PK characteristics (peak plasma concentration, time-to-peak plasma concentration, half-life, and area under the plasma concentration-time curve) – or fixed dual-medication combinations, or polytherapies (≥2 separately ingested medications), and (ii) special patient groups at elevated CVD risk, i.e., those with diabetes, CKD, resistant hypertension, previous CVD event, or non-dipper/riser 24 h BP pattern (Table 1). Such advantages of bedtime BP-lowering therapy will need to be prospectively evaluated in other patient groups of potential clinical interest. For example, the association between the nature, i.e., extent of sleep-time dipping, of the 24 h BP pattern and the worsening of glaucoma is still highly controversial [57–59]. Tokunaga et al. [60] assessed the 4-year progression of visual field defect in either normal-tension or primary open-angle glaucoma patients according to the 48 h ABPM-derived representative awake and asleep BP means and sleep-time relative SBP decline calculated utilizing diary-recorded times of the activity/asleep cycle of each patient. Results, corroborated by other studies as reviewed elsewhere [58], document significantly lower sleep-time BP relative decline – characteristic of non-dipper/riser BP patterning – in progressive compared to stable glaucoma patients ($P = 0.02$). Krasinska et al. [61] evaluated the ingestion-time dependent effects of BP-lowering treatment of 88 hypertensive patients with open-angle glaucoma. On the basis of a 24 h ABPM baseline evaluation and in keeping with the non-randomized open-label study design, dipper participants were assigned to ingest the full dose of all of their medications in the morning (08:00–09:00 h) and non-dippers participants to ingest the entire dose of one of their medications in the evening (20:00–21:00 h) and all of the others in the morning. After 6 months of therapy, patients who ingested one medication in the evening, compared to those who ingested all medications in the morning, had lower mean retinal artery perfusion pressure at night and greater visual field loss. However, the authors did not provide baseline information on nighttime retinal artery perfusion and visual field defect of the (dipper and non-dipper) ingestion-time groups and, accordingly, the reported findings may not be due to ingestion-time treatment schedule but rather differences in disease progression that per se might be dependent upon one's BP dipping phenotype [58]. Interestingly, in the Hygia Chronotherapy Trial [32] discussed below (Section 4.2.) risk of retinal artery thrombotic occlusion during the 6.3-years median follow-up was significantly lower by 44% ($P < 0.001$) with bedtime compared to upon-waking BP-lowering treatment.

The findings of this in-depth review are clinically relevant for multiple reasons. First, independent prospective studies and meta-analyses demonstrate CVD life-threatening and life-ending events are much more accurately predicted by the asleep than the awake or 24 h ABP mean [9–16,18]. Furthermore, the relationship between attenuated sleep-time relative SBP decline, i.e., non-dipper/riser 24 h SBP pattern, and risk for such events, is well documented [8,9,15–18]. Second, prospective ABPM-based investigations designed to evaluate the influence on CVD risk of changes in both OBPM and prognostic features of the 24 h BP pattern achieved by hypertension therapy during several years of follow-up document that the 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 change in the wake-time OBPM and/or the awake SBP mean [15,18]. Third, elevated asleep SBP causes carotid remodeling and also glomerular pathology leading to albuminuria and CKD progression [2]. Cardiac and blood vessel tissues show significant circadian variation in gene expression, metabolism, growth, and remodeling, with cardiovascular growth and remodeling being most active during sleep [62–64]. Together, these plus other factors help explain the better reduction of CVD risk, beyond that expected based on the documented enhanced decrease numerically of the asleep SBP mean and increase of the sleep-time relative SBP decline, achieved by bedtime/evening vs. upon-waking/morning hypertension therapy [29–33], as subsequently further discussed herein.

Several studies report greater compliance, including greater adherence to recommended dosing time, by patients prescribed hypertension therapy delivered by once-a-day dosage forms than those prescribed medications that require more frequent ingestion [65]. Our systematic review found no significant ingestion-time difference in average compliance, i.e., 94.5 ± 4.1% vs. 93.8 ± 5.9%, in patients randomized to upon-waking/morning vs. bedtime/evening treatment, respectively ($P = 0.169$). These findings, though, are inconsistent with the investigation by Vrijens et al. [66], frequently cited in the medical literature to justify the recommendation that hypertension medications be ingested in the morning. It found 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, by comparing a large number of 4149 patients non-randomized to time of treatment who were ingesting their prescribed medications during the author's defined "morning" 12 h long span of 03:00–15:00 h vs. a very small number of only 283 patients who, for unspecific reasons, ingested more than 75% of their prescribed medications during the "evening" equally 12 h long span of 15:00–03:00 h, thereby implying a high proportion of the latter group of patients were likely following a multiple (more than once) daily dosing scheme. Selection of treatment times according to "morning"/"evening" periods or arbitrary designated clock times – rather than according to distinctive biological markers of the staging of circadian rhythms, e.g., upon-waking/bedtime, which properly takes into account individual differences in the activity/sleep 24 h rhythm and associated disparities in the phasing of endogenous circadian rhythms that influence the PD of BP-lowering medications – might negatively influence adherence and obscure the benefits of timed treatment. Improper selection of treatment times in terms of clock hour was a common mistake of many past ingestion-time trials. Indeed, only 70 of the 153 reported ingestion-time trials properly used as reference the upon-waking and bed times to trial differences in the PD of BP-lowering medications. Interestingly, 95.7% of these trials substantiated superiority of the bedtime vs. upon-waking treatment regimen, while in contrast 88.0% of the neutral studies relied on non-specific,

i.e., without reference to the staging of circadian rhythms, morning/evening treatment times. Current guidelines [7] recommend participants of hypertension chronotherapy 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 increase compliance to the allocated hypertension treatment-time schedule. The findings of our systematic review indicate bedtime/evening hypertension therapy does not compromise adherence to medication, inasmuch no single randomized study reported significant treatment-time differences in compliance (Supplement Table S1).

Safety is a highly relevant issue to justify preference of an ingestion-time of hypertension therapy. Our systematic and comprehensive review corroborates the consistent findings of previous publications [19,26], i.e., no single published study found the upon-waking/morning time of BP-lowering therapy to confer better patients safety and compliance than bedtime/evening therapy. On the contrary, adverse events were more prevalent with the current most popular upon-waking/morning treatment scheme, especially when involving ACEI and CCB medications (Table 1).

We hypothesize the inability of the very small number of published trials to substantiate advantages of the bedtime/evening treatment strategy is the consequence of deficiencies of investigative methods, as apparent in the three neutral studies that trialed hypertension polytherapy [55,67] and those that, respectively, concerned high CVD risk patients with CKD [55] and diabetes [54] (Table 1). Among the apparent shortcomings [63] are: (i) "Morning" and "evening" treatment-times were inappropriately defined by expansive clock-hour intervals – e.g., 06:00–11:00 h and 18:00–23:00 h by Poulter et al. [67] and 07:00–09:00 h and 19:00–21:00 h by Kuate et al. [54] – 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 h BP pattern and influence the PD response to hypertension therapy [1,2,39]. (ii) Reliance as primary study endpoint upon the 24 h SBP mean, a parameter of rather low, if any, predictive value of CVD risk when the asleep SBP mean is simultaneously taken into account [15,16,18] and, as extensively documented [19–28], that is minimally affected by the time of hypertension treatment, a finding further corroborated by our systematic review of past published studies. (iii) Secondary study endpoints included non-biologically representative or clinically meaningful "daytime" and "nighttime" BP means improperly determined by investigator-ascribed common fixed clock times of wakefulness and sleep across all participants – respectively, 06:00–00:00 h and 00:00–06:00 h by Rahman et al. [55] and 07:00–22:00 h and 22:00–07:00 h by Kuate et al. [54] and Poulter et al. [67] – rather than the representative actual individualized ones. (iv) The minimum required sample size, established upon the assumed standard deviation of the 24 h SBP mean, was underpowered to reliably evaluate changes in the asleep SBP mean that is characterized by greater between-patient variability [18]. Most important, the stated sample size for the above-specified neutral trials was miscalculated, as valid testing of the stated hypothesis, even if based on 24 h SBP reduction, required almost double the number of participants than recruited – 190 required vs. 147 recruited by Rahman et al. [55]; 175 required vs. 95 recruited by Poulter et al. [67]; and 46 required vs. 17 recruited by Kuate et al. [54]. (v) Participants were diagnosed as hypertensive solely by wake-time OBPM, 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 [18] – a condition that is even more prevalent among patients with diabetes or CKD due to their documented greater proportion of sleep-time hypertension and non-dipper SBP pattern [7]. (vi) Trials by Rahman et al. [55] and Poulter et al. [67] recruited only treated hypertensive persons whose BP was already substantiated to be controlled according to hypertension guidelines. This approach leads to misleading findings when evaluating ingestion-time-dependent effects of BP-lowering therapies [68]. 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 both of these neutral trials, the rather low, i.e., normal, baseline "daytime" and "nighttime" SBP/DBP means of the BP-controlled recruited participants, precluded the findings of the somewhat lower "nighttime" SBP mean achieved by evening in comparison to morning dosing attaining statistical significance [55,67]. Beyond BP-lowering efficacy of hypertension medications being markedly associated with pre-treatment ABP level, diminishing with lower (close to or actually normal) baseline ABP, it is judged unethical to change the treatment regimen of any patient whose BP is already safely and properly controlled according to guideline-recommended threshold values [68].

4.2. Effects of bedtime (chrono)therapy on CVD outcomes

Despite the evidence summarized above substantiating bedtime hypertension treatment with conventional hypertension medications best achieves BP control, particularly during sleep, and improves markers of target organ pathology of the kidney and heart, few long-term outcomes studies have specifically assessed its impact on CVD prevention. The Syst-Eur trial, involving 4695 elderly persons with isolated SBP hypertension diagnosed by OBPM, alone, found evening CCB nitrendipine therapy, versus placebo, reduced after 2 years of follow-up the primary endpoints of total and non-fatal stroke, respectively, by 42% ($P = 0.003$) and 44% ($P = 0.007$), CVD mortality by 27% ($P = 0.07$), and total CVD outcomes by 31% ($P < 0.001$) [69]. The Syst-China trial of almost identical protocol, comprising 2394 elderly patients followed for 2 years, reported evening nitrendipine treatment diminished total stroke by 38% ($P = 0.01$), total and CVD mortality each by 39% ($P = 0.003$), stroke mortality by 58% ($P = 0.02$), and total fatal and non-fatal CVD outcomes by 37% ($P = 0.004$) [70]. The Heart Outcomes Prevention Evaluation (HOPE) trial, consisting of a cohort of 9297 high-risk individuals ≥55 years of age, found adding the ACEI ramipril at bedtime, relative to placebo, to an existing preventing strategy that included BP-lowering and cholesterol-lowering medications, significantly reduced CVD death, myocardial infarction, and stroke, despite a very minor better 3/2 mmHg reduction of wake-time office SBP/DBP with ramipril than placebo [71]. Interestingly, a small around-the-clock ABPM substudy of HOPE patients found the bedtime ingestion of ramipril exerted profound lowering of the "nighttime" SBP/DBP means by an average 17/8 mmHg ($P < 0.001$ compared to placebo) that translated into significant increase by 8% of the sleep-time relative SBP decline [72]. The Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET) randomized a small cohort of 380 hypertensive patients with diabetes to fosinopril in the morning or amlodipine in the evening and followed them for up to 3.5 years; if OBPM was not controlled by the first study medication, the second study medication was added at an unspecified time of day. Patients initially randomized to morning-time fosinopril had lower risk of CVD events, although the number of reported events was too few (14 vs. 27 for fosinopril and amlodipine, respectively) to be relevant [73]. The prematurely terminated CONVINCE trial found no significant difference in the primary outcomes of myocardial infarction, stroke, or CVD death between COER-verapamil – a specially designed delayed onset, extended release CCB formulation intended for bedtime ingestion to achieve highest drug concentration upon awakening so as to attenuate the rate of rise and level of BP during the initial hours of the activity span – and morning-treatment with either atenolol or HCTZ [47]. Bedtime COER-verapamil exerts significant 2-fold greater reduction in the awake than asleep SBP/DBP means [74], resulting in the undesired effect of significant reduction of sleep-time relative BP decline, thereby inducing a non-dipping 24 h BP pattern, which based upon published findings increases CVD risk [8,15,17,18]. Accordingly,

the results of the CONVINCE trial, which involved a unique bedtime-ingested delayed-onset, extended release CCB delivery system designed to specifically target the expected upon-waking BP surge, cannot be considered evidence against the merit of bedtime chronotherapy that entails conventionally formulated once-a-day medications to target the asleep BP level, the BP parameter when abnormally elevated is found to be most strongly linked with increased CVD risk and also tissue and organ pathology [9–16,18]. In actuality, findings of the CONVINCE trial refute the unproven theory of the 1990s that therapy should target as major goal control of the upon-waking BP rate of rise and level during initial hours of the daily activity span.

We must emphasize the protocols of the above-discussed evening/bedtime nitrendipine, ramipril, amlodipine, and COER-verapamil trials did not incorporate around-the-clock ABPM at baseline to certify subjects as arterial hypertensive to qualify them for participation or periodic ABPM patient assessments during follow-up to enable quantification of the effects of timed treatment on the prognostic features of the 24 h BP pattern. Most important, these protocols do not qualify as valid hypertension ingestion-time or chronotherapy trials, because none of them included an awakening-time treatment arm of the same tested medication as reference to compare effects upon BP control and CVD risk reduction. To address this deficiency, Roush et al. [30] conducted a meta-analysis of the extent of CVD reduction reported for the bedtime/evening treatment trials of Syst-Eur, Syst-China, HOPE, FACET, and CONVINCE, using as reference that reported for another 170 reported prospective CVD outcome trials in which participants ingested therapy in the morning [30,75]. The authors found the bedtime/evening, relative to the upon-waking/morning, hypertension medication strategy markedly reduced by 48% ($P = 0.008$) the relative risk of CVD events. Gupta et al. [33] recently extended the meta-analysis by Roush et al. [30] by incorporating results of both the MAPEC Study [29] and Hygia Chronotherapy Trial [32] discussed below, concluding once again bedtime/evening vs. upon-waking/morning hypertension treatment is significantly more protective against major CVD events, including stroke. The critical importance of targeting control of asleep BP is reinforced by the investigation of Sobiczewski et al. [31], who evaluated the benefits of bedtime hypertension treatment in a high-risk cohort of 1345 coronary heart disease patients assessed by 24 h ABPM. Cox survival analysis of the data of this median 6.6-year follow-up trial revealed the asleep ABP mean – but not elevated OBPM or awake ABP mean – non-dipper SBP profile, and lack of bedtime-treatment were, apart from age and diabetes, the only significant joint predictors of all-cause mortality.

The clinical relevance of the bedtime treatment strategy that specifically targets normalization of the asleep SBP level and sleep-time relative SBP decline, i.e., BP dipping, in comparison to the upon-waking treatment strategy that specifically targets normalization of the wake-time BP has seldom been properly evaluated in trials that simultaneously assessed CVD and other hypertension-associated outcomes. The MAPEC Study, conducted at a single tertiary hospital, was the first prospective, randomized, CVD endpoint trial designed to explicitly test the clinically relevant hypothesis that bedtime hypertension chronotherapy with conventional one-a-day medications better reduces CVD risk than the same conventional once-a-day therapies ingested upon-waking therapy [29]. Hypertensive patients ($N = 2156$) – according to ABPM criteria [7,41] regardless of OBPM – randomized to ingest the entire daily dose of ≥1 BP-lowering medications at bedtime vs. the 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 non-dipping, and, of upmost importance, significantly attenuated adjusted hazard ratio (HR) for major CVD events, including CVD death, myocardial infarction, and ischemic and hemorrhagic stroke [29].

The much larger multicenter prospective, randomized, blinded-endpoint Hygia Chronotherapy Trial 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 to either ingest the entire daily dose of ≥1 prescribed hypertension medications at bedtime or all of them upon awakening [32]. 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 period those randomized to the bedtime treatment regimen additionally had significantly lower adjusted HR (0.55 [95%CI 0.50–0.61], $P < 0.001$) of the primary CVD-outcome variable – composite of CVD death, myocardial infarction, coronary revascularization, heart failure, and stroke. Furthermore, adherence and compliance to treatment was not diminished by the bedtime treatment schedule; poor adherence was found in 2.8% of those who ingested all their medications upon awakening vs. 2.9% of those who ingested ≥1 of them at bedtime ($P = 0.813$). Finally, the bedtime treatment regimen was well tolerated; adverse effects throughout the 6.3-years median follow-up period were experienced by 6.7% of the upon-awakening-treatment cohort vs. 6.0% of the bedtime-treatment cohort ($P = 0.061$). Manifestation of sleep-time hypotension defined by current ABPM criteria [7], which affected only 0.3% of all participants, also did not differ between the two treatment-time regimens ($P = 0.114$ between groups). The low incidence of sleep-time hypotension may in part reflect the adopted clinical protocol of the trial that required 48 h ABPM several weeks after initiating or changing hypertension therapy to ensure proper patient response and safety [32]. The consistent findings of these two large outcome trials are in line with those expected based on the extensive review presented herein of the published literature pertaining to ingestion-time differences in effects of hypertension medications (Table 1). Nonetheless, they await future corroboration, especially by properly designed future studies incorporating ethnic groups other than Caucasians evaluated by periodic ABPM assessment – starting at baseline for the diagnosis of true arterial hypertension as the required inclusion criterion [18,76] – in conjunction with 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 [29,32].

4.3. Future required research and drug-delivery opportunities

We believe the findings of this comprehensive review, discussed meta-analyses, plus MAPEC Study and HYGIA Project are relevant to drug-delivery scientists. All of them collectively substantiate the importance of the bedtime/evening treatment strategy to achieve peak concentration of single or dual-fixed hypertension therapies of different classes during the sleep period to best attenuate the asleep SBP as a novel means to meaningfully reduce hypertension-associated pathology of the blood vessels, heart, and kidney and to diminish CVD morbidity and mortality. Current prescription hypertension therapies are engineered to deliver medications in a constant rate to attain as much as possible smooth and consistent drug levels within the upper and lower range of therapeutic efficacy throughout the 24 h dosing interval. This might be achieved by a variety of tablet and capsule-based delivery systems of varying sophistication and complexity, such as core coat system – hydrophilic gel layer surrounding active drug – to enable steady diffusion of medication through the hydrophilic gel matrix coating as the dosage form moves through the gastrointestinal tract (GIT), polysaccharide sodium alginate system that upon absorbing water in the GIT becomes gelatinous, biodegradable geometric system composed of two slow hydrating barriers around a hydrophilic matrix core that disintegrates slowly to enable steady diffusion of medication as it moves through the GIT, and encapsulated beads with coatings of different thickness or polymer composition, with or without immediate release powder to realize steady diffusion of medication [77]. These delivery systems have been proved to perform effectively and be safe releasing

medication in a smooth and safe way without risk for erratic spikes or troughs, thereby precluding during the 24 h too great or too little BP-lowering and risk for adverse effects. These constant medication release systems, nonetheless, are engineered to satisfy the assumption that BP is relatively constant throughout the day and night, which is not the real situation biologically. Indeed, SBP, in particular, often exhibits ≥50 mmHg difference between the occurrence of the typically awake-time maximum and sleep-time minimum values. The vast majority of the past conducted ingestion-time investigations that have trialed once-a-day conventional medications of sustained-release delivery systems have found that a bedtime/evening treatment schedule best controls asleep SBP, best reduces pathology/injury of the blood vessels, heart, and kidney (Table 1), and best protects against CVD incidents and deaths [29–33]. We hypothesize there are two explanations as to why such conventional therapies when ingested at bedtime attain better control of sleep SBP. The first one is bedtime ingestion of such medications, even under steady conditions, gives rise to higher blood and tissue concentrations during the initial hours of the dosing interval, i.e., during sleep. Conversely, we suspect the blood and tissue concentrations of such therapies when ingested upon awakening, even if maintained above the lower range of therapeutic effectiveness, are too low to exert the same extent of beneficial effect, i.e., reduction of asleep SBP mean. The second hypothesis is that bedtime ingestion of conventional medications, exemplified in particular by those of the ACEI and ARB classes, achieves highest circulating and tissue concentrations when certain major circadian mechanisms of 24 h BP control activate or are at near peak or peak activity daily [1,2,38,39].

The findings of the reported trails that overwhelmingly substantiate all classes of BP-lowering monotherapies, dual-fixed combinations, and polytherapies are most effective when ingested at bedtime should be of interest to drug-delivery scientists. Although most, if not all, of the studies reviewed herein involved sustained-release drug-delivery systems designed to attain near constant blood and tissue drug concentration for 24 h, it is yet to be established whether or not such a sustained constant level of medication is necessary and optimal to specifically target as a major goal control of the asleep SBP and reduce the risk of associated deleterious CVD and other pathological outcomes. It was recently suggested [78,79] that short-acting medications delivered at the optimal circadian time to attain peak concentration supportive of favorable drug PK and PD so as to target key circadian regulatory mechanisms of the 24 h BP pattern, theoretically, might improve therapeutic effects and patient outcomes. The development of appropriate next generation drug-delivery systems for hypertension medications is of importance for of all diagnosed hypertensive and of elevated CVD risk, but it is of particular significance for ~20% of the adult working population in the USA and considerably higher proportion of the adult working force of developing nations whose employment requires permanent night, rotating, or irregular shifts [80–82]. Such shift workers, as well as aircraft flight crew personnel and persons who frequently travel across multiple time zones, have inconsistent sleep and wake spans, thereby making it difficult to optimize from one day to the next the treatment-time schedule of conventional medications to successfully control elevated BP, asleep BP in particular [83]. A potential drug-delivery solution, especially for those with such irregular sleep/wake routines, could be biometric-based systems of single or even multiple therapies that are individually or in combination released on demand, e.g., by elements of the RAAS, circadian clock gene products that signal its up-regulation, or other surrogate circadian biomarkers that culminate in control of abnormally elevated asleep SBP and deleterious remodeling of vulnerable blood vessels, kidney, and heart tissue [1,2,38,39,62–64]. As earlier proposed [84], such next generation hypertension drug-delivery systems should be configurable so they (i) require minimum volitional adherence; (ii) respond on demand on a real time basis to one or more specific casual or surrogate stimuli – biomarkers of processes that directly precede or associate with consequent elevated BP and induce pathology – that both vary in a predictable-in-time manner, as manifestations of endogenous regulatory circadian rhythms and/or 24 h behavioral cycles, but also randomly in time during the 24 h to encountered stresses of everyday life, to initiate single or multiple sequential therapeutic pulses; and (iii) are competitively cost-effective to market to patients and managed care organizations. Optimally, such next generation systems must be designed to deliver multiple medications – each delivered by a system uniquely responsive to a specific stimulus – to target one or more key mechanisms of BP control. Such system could thus optimize both medication efficacy and safety as a comprehensive poly-chronotherapy of abnormalities of the 24 h BP pattern as well as (chrono)prevention of end-organ pathology and deleterious CVD outcomes.

5. Conclusions

The design of better performing drug-delivery systems for treatment of hypertension to prevent CVD and other elevated-BP associated pathology requires understanding of circadian and other processes deterministic of the abnormal features of the 24 h BP pattern. This includes knowledge of those endogenous circadian rhythms that both regulate BP and influence response to hypertension therapy. Some of the most important ones are linked to the state of sleep: (i) activation of the RAAS [1,2,38,39]; (ii) elevation of atrial natriuretic and calcitonin gene-related vasoactive peptides and nitric oxide as vasodilators [1,2,85]; and (iii) cardiac remodeling [62–64]. 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) vs. upon-waking *traditional* therapy entailing conventionally drug-delivered BP-lowering medications. The reported better reduction of CVD risk with bedtime than upon-waking hypertension therapy might stem not only from the documented enhanced reduction of the asleep SBP level and increase of sleep-time relative SBP decline [29,32], but from the superior suppression of the RAAS, whose circadian rhythm is expressed at peak or near peak level during sleep and thus most actively inducing cardiac, endothelial, and other tissue remodeling, pathology, and injury at this time during the 24 h [1,2].

Our systematic review reveals the vast majority of the 153 reported ingestion-time hypertension therapy trials (83.7%) with high consistency substantiate statistically and clinically significant ingestion-time differences in the PD of BP-lowering medications. The differences include enhanced asleep BP reduction, increased sleep-time relative SBP decline with corresponding reduced prevalence of the higher CVD risk non-dipper/riser 24 h BP patterning, decreased incidence of adverse events, and improvement in markers of hypertension-associated target organ pathology – reduced albuminuria and increased GFR of the kidney, plus decreased left ventricular posterior diameter and left ventricular mass of the heart – when hypertension medications are ingested at bedtime rather than upon-waking. The inability of the very small number of trials to verify advantages of the bedtime/evening treatment strategy is likely explained by deficiencies of their study design and conduct [68]. Most noteworthy is the finding that no single reported randomized trial documents better BP-lowering and other medical benefits, safety, or compliance of the most recommended, but unjustified by medical evidence, upon-waking/morning ingestion-time schedule of currently marketed conventional hypertension medications.

On the basis of all this collective information, we recommend the diagnosis and management of hypertension be: (i) Baseline around-the-clock ABPM assessment both for proper diagnosis of true arterial hypertension – in terms of elevated asleep SBP mean and/or non-dipper SBP pattern – and establishment of need for therapeutic intervention [18,76]. (ii) Pharmacologic 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 [86]. (iii) As routine clinical procedure, assessment of treatment efficacy and safety (sleep-time hypotension avoidance) 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 [7].

Disclosures

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.addr.2021.01.013.

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