SLEEP AND HYPERTENSION (SJ THOMAS, SECTION EDITOR)

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Chronotherapy for Hypertension

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Abstract

Purpose of Review Given the emerging knowledge that circadian rhythmicity exists in every cell and all organ systems, there is increasing interest in the possible benefits of chronotherapy for many diseases. There is a well-documented 24-h pattern of blood pressure with a morning surge that may contribute to the observed morning increase in adverse cardiovascular events. Historically, antihypertensive therapy involves morning doses, usually aimed at reducing daytime blood pressure surges, but an absence of nocturnal dipping blood pressure is also associated with increased cardiovascular risk.

Recent Findings To more effectively reduce nocturnal blood pressure and still counteract the morning surge in blood pressure, a number of studies have examined moving one or more antihypertensives from morning to bedtime dosing. More recently, such studies of chronotherapy have studied comorbid populations including obstructive sleep apnea, chronic kidney disease, or diabetes.

Summary Here, we summarize major findings from recent research in this area (2013–2017). In general, nighttime administration of antihypertensives improved overall 24-h blood pressure profiles regardless of disease comorbidity. However, inconsistencies between studies suggest a need for more prospective randomized controlled trials with sufficient statistical power. In addition, experimental studies to ascertain mechanisms by which chronotherapy is beneficial could aid drug design and guidelines for timed administration.

Keywords Hypertension · Chronotherapy · Blood pressure · Non-dipping · Sleep · Circadian rhythms

Introduction

Chronotherapy with medication involves the tailored timing of doses to match the body's natural daily rhythms and behavioral patterns in order to increase beneficial effects and/or minimize any adverse medication effects across the day and night. The daily patterns of behaviors, including the sleep-wake, rest-activity, and fasting-feeding cycles, influence the daily fluctuations of gastric pH, gastric emptying, gastrointestinal transit time, organ blood flow, liver enzyme activity, and renal function [1–4]. The extent to which the internal circadian system also orchestrates these physiological variations is not well understood, although likely to be an important factor that interacts with these daily patterns of behaviors [5]. The sum of these daily circadian (24-h) and behavioral physiological patterns can therefore affect a medication's bioavailability and duration of action through absorption, distribution, metabolism, and elimination. A medication's effects are also dependent on receptor site availability and function [6], which can also be affected by the circadian system and by prior behaviors, such as exercise [4]. Currently, very few medications are administered based on the time of day in order to optimize beneficial effects or reduce side effects. Moreover, internal biological time (circadian phase) can differ between people in relation to external clock time [7], yet, since it is difficult to instantaneously assess circadian phase, there are virtually no medications currently administered based on internal biological time. However, recent examination of 12 different organs in a mouse model demonstrates that the protein targets of 56% of the top-selling and World Health Organization essential medicines oscillate with circadian profiles [8]. This suggests that chronotherapy, either in terms of external clock time or internal biological time, is underutilized and could be a major consideration to improve modern personalized medicine.

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Hypertension (HTN) is a primary risk factor for adverse cardiovascular (CV) events [9]. Given the well-documented 24-h pattern of arterial blood pressure (BP) in humans, with a morning surge and a decrease during sleep [10], as well as the recognition of increased risk for adverse CV events in the morning [11], chronotherapy for HTN has actually been studied since the late 1980s. According to the recent 2017 American College of Cardiology and American Heart Association guidelines for prevention and treatment of HTN [12], the prevalence of HTN among US adults is 46%. Although almost three quarters of these adults use antihypertensive medications, only half maintain their mean BP at an acceptable level [9]. Thus, improvement in therapy for HTN is warranted, and chronotherapy offers great promise in this regard. BP usually increases during daytime activities and decreases (~ 10–20%) during nocturnal sleep [13, 14]. The degree to which BP rises or falls during sleep and daytime behaviors, measured using 24-h ambulatory BP monitoring (ABPM), is associated with varying risk for all-cause mortality [15], CV events [16], and stroke [17, 18]. Based on 24-h profiles of BP, people with HTN can be broadly classified into four patterns: the (1) normal healthy dipping BP (10–20% drop in average nocturnal vs. daytime BP); (2) extreme-dipping (> 20% drop in average nocturnal vs. daytime BP); (3) non-dipping BP (< 10% drop in average nocturnal vs. daytime BP); and (4) reverse dipping (average nighttime BP is higher than daytime BP [19, 20]). A non-dipping BP profile, prevalent in 32–46% of adults with HTN [21], is associated with impaired cardiac function including increased left atrial systolic volume and left ventricular wall thickness, and lower right atrial ejection fraction [22–24]. Non-dipping BP is also associated with numerous chronic conditions including autonomic dysfunction [25], renal insufficiency [26], glucose intolerance [27], and obstructive sleep apnea [28]. Although less common, reverse dipping BP, prevalent in 5–19% of adults with HTN [21], is associated with severe renal dysfunction, CV injuries, carotid plaque formation, and lacunar infarction in hypertensive patients [29–31]. Patients with extreme dipping BP, prevalent in 4–20% of adults with HTN [21], have an increased risk of silent cerebral infarcts [18]. Additionally, a meta-analysis suggests that among patients who are untreated at baseline, extreme dippers have an increased risk of total CV events compared to normally dipping hypertensive patients [21].

Altered dipping profiles could conceivably be caused in some people by altered behaviors, such as decreased nocturnal sleep raising the nocturnal BP or reduced daytime activity lowering the daytime BP [19, 32–34], both of which would tend towards a non-dipping profile. Pharmacological approaches to improve sleep quality convert only a subset of the non-dipping population into dippers [35], which suggests that the dipping vs. non-dipping is not simply caused by differences in sleep. Despite the association between the degree of day/night BP fluctuation and the risk for adverse CV events,

it remains unclear whether this risk is a result of the decline of BP over the course of a night, low nighttime BP, or the surge of BP upon awakening. Nevertheless, a number of studies have investigated the impact of morning vs. evening dosing of antihypertensive medications on BP dipping profile, 24-h BP control, BP decline during sleep, and/or the reduction of a morning BP surge. Studies conducted from 1987 to 2012 are briefly discussed immediately below, whereas this review will focus on research published in the 5-year period from 2013 to 2017. As previously reviewed in 2010 [36], evening compared to morning ingestion of the common classes of antihypertensive medications generally enhances their BP-lowering effects, these include alpha-adrenoceptor blockers (α-blockers [37–39]); beta-adrenoceptor blockers (β-blockers [40]); angiotensin-converting enzyme inhibitors (ACEI [41–49]); angiotensin II receptor blockers (ARB, [50–54]); diuretics [55, 56]; and calcium channel blockers (CCB, [57–68]). Interestingly, although a low-dose of aspirin (100 mg/day) has traditionally been used as an anticoagulant to prevent CV events [69], when administered at bedtime but not in the morning, it has also been shown to reduce ambulatory systolic BP (SBP) and diastolic BP (DBP) [70–72]. The authors speculate that these findings are related to aspirin's ability to inhibit angiotensin II in a circadian fashion. Additional open-label prospective randomized control trials (RCT) conducted by Hermida and colleagues, including the MAPEC (Ambulatory Blood Pressure Monitoring for Prediction of Cardiovascular Events) study with a total of 2156 hypertensive subjects and a median follow-up of 5.6 years, have consistently shown that by targeting the nocturnal rise in BP there is overall improved 24-h BP control, decreased morning BP surge, decreased prevalence of non-dipping BP, reduced CV morbidity, and improved survival [73–75].

The recent studies reviewed herein extend the above findings by purposefully examining fixed-dose combination therapy, which is generally considered the first line of treatment in individuals with severe HTN (> 180 mmHg SBP and/or > 110 mmHg DBP) [76–78]. Further, recent studies have examined the co-occurrence of HTN with diseases including obstructive sleep apnea, chronic kidney disease, and diabetes. Disease comorbidity may alter underlying physiology including the circadian rhythms of drug targets, necessitating additional examination of any potential benefit or risk of chronotherapy. Moreover, despite the compelling evidence of examined RCTs to date including the comprehensive cardiovascular disease (CVD) and end-organ damage outcomes reported from the MAPEC cohort, routine clinical care in most countries continues to predominately utilize a morning antihypertensive dosing strategy. Physicians generally prescribe multiple medications at increasing doses for individuals with difficult to treat or severe HTN [76–78]. An increased medication load increases the incidence of unwanted side effects and may decrease a patient's adherence to their intended drug regimen

[79, 80]. It seems likely that adverse medication side effects and the number of prescribed medications could be reduced by simply considering the timing of doses relative to the naturalistic rise and fall of BP and regulators of BP.

Methods

An extensive search of the literature was conducted in December 2017 to identify publications regarding the treatment of HTN that also focused on the use of chronotherapeutic principles, namely time of day. PubMed, Google Scholar, and Scopus were used to search for the following keywords and their combinations: "chronotherapy" AND "hypertension"; "chronotherapy" AND "high blood pressure"; "night time" AND "dosing" AND "hypertension"; "evening dosing" AND "hypertension"; "bed time" AND "dosing" AND "hypertension." Articles were limited to the English language and human studies, original articles including case reports, meta-analyses, and systematic reviews, while poster or talk abstracts were excluded. Publications were limited to the 5-year period from January 2013 to December 2017. Abstracts of articles were then scanned for relevance and categorized based on primary HTN ($n = 14$ studies), HTN with a specific comorbid conditions (OSA, chronic kidney disease, diabetes) ($n = 13$), meta-analysis or systematic review ($n = 5$), or chronopharmacology ($n = 4$). Results from original studies are presented in Tables 1 and 2. These tables provide a summary of the following for each study: (1) country of origin; (2) design (e.g., crossover); (3) participant characteristics; (4) how HTN was measured and/or defined; (5) duration of follow-up; (6) class of medication and time of medication administration (i.e., morning vs. evening); (7) measured study outcomes including BP specific outcomes; and (8) study results. The tables are intended for a quick reference, but salient points and distillation of general findings are presented in the text of the "Results" section of this paper. Meta-analyses are presented at the end of each section as these include some of the other listed studies.

Results

2013–2017 Updates on the Effects of Time-Dependent Dosing for Treatment of HTN (Table 1)

The first study listed in Table 1 represents a secondary analysis of the MAPEC RCT and revealed that participants with resistant HTN (suboptimal BP control with more than three antihypertensive medications) have improved ambulatory BP control, a lower incidence of CV events, and reduced mortality over a 5- to 6-year follow-up when they took one or more antihypertensive medications at night compared to all medications in the morning [81••]. Unfortunately, the study was not powered to provide absolute conclusions on the benefit of morning compared to bedtime administration by drug class or the benefits of particular drug combinations. Three cross-sectional studies exploring the efficacy of taking one or more antihypertensive medications at night indicate that bedtime antihypertensive medication reduces asleep SBP, DBP, and prevalence of non-dipping BP, and improves 24-h BP control [85, 90, 110]. A smaller RCT of ARB found no significant effects of treatment timings on morning home BP or office BP [89]. However, this study did not include overnight or sleep measures of BP and included use of various other medications concurrently. Furthermore, there was a mean difference in baseline office SBP of 5 mmHg ($p = 0.052$), which may have led to a negative result in this study. These results are also similar to previous work and could also be attributed to the relatively long half-life (> 12-h) of the ARB olmesartan [111].

A systematic review conducted to evaluate the improved effectiveness of aspirin by changing the timing of administration on the primary and secondary prevention of CVD reported on 12 studies (including nine RCTs) that described outcomes of BP [112, 113••]. In general, studies that examined younger populations with untreated mild HTN or pre-HTN reported reduced 24-h SBP and DBP when aspirin was administered in the evening. Studies that examined populations with treated HTN or with established CVD had no improvements on ABPM regardless of aspirin timing [82, 88, 92]. However, bedtime administration was correlated with lower morning platelet reactivity [82] suggesting that although bedtime aspirin may have limited utility for BP control in patients with advanced HTN, it might be effective to reduce CV risk during the vulnerable morning hours [114]. It is also likely that concurrent administration of two or more drugs can affect pharmacokinetics and drug efficacy. This concept is briefly considered in the "Discussion" section.

In addition to the aforementioned studies, a number of papers have extended prior outcomes by examining the chronotherapeutic effect of antihypertensive combination therapy. Unfortunately, a large percentage of hypertensive individuals are unable to optimally control their BP despite taking two or more antihypertensive medications—although this may be related to a lack of medication adherence [77, 115]. As with monotherapy, it is possible that taking one or all of these medications at bedtime may prove to be a better therapeutic strategy. To this extent, an open-label trial examining the impact of taking all antihypertensive medications at bedtime compared to the morning resulted in improved 24-h BP control [83•]. However, trials on specific drug combinations have demonstrated mixed results. For example, analyses of BP response to morning or evening dosing of a diuretic and an ARB combination showed similarly significant reductions in the

Table 1 Effects of time-dependent dosing for treatment of HTN: reviewed studies (2013–2017) of the general populations without emphasis on comorbid conditions

Reference	Country	Study design	Participant details	Follow-up (month)	HTN definition	Morning antihypertensive medications	Evening antihypertensive medications	Measures of BP	Ancillary measures	Results
Ayala et al. 2013 [81••]	Spain	Prospective, open-label, blinded end point, single-center RCT; replacement of one antihypertensive medication with a new medication ingested upon awakening (group 1) vs. at bedtime (group 2)	50% male; aged 61 ± 11 y; groups had similar distributions of T2D (33–34%); OSA (7–8%); metabolic syndrome (70–73%); obesity (53–60%); previous CV events (<8%), otherwise free from CV disorders (total participants, n = 776; group 1, n = 391)	64.8 (6–102)	Resistant HTN: SBP/DBP awake mean ≥135/85 mmHg and/or asleep mean ≥120/70 mmHg (48 h ABPM)	Group 1: All in morning; average 3.2[a] at start and 3.5[a] by end of study. Combination of diuretic with ARB, or ACEI at start, with new medication usually being a CCB or α-blocker. Group 2: Varied	Group 1: None Group 2: ≥1 at bedtime; average 3.2[a] at start and 3.4[a] by end of study. 26% ARB, 13% ACEI, 55% CCB, 17% β-blockers, 13% diuretic, and 41% or α-blocker	48-h ABPM recorded annually (or quarterly if treatment was adjusted)	CV events; CV death; total death	Group 2 ↓asleep SBP/DBP mean, sleep-time relative SBP/DBP decline, prevalence of non-dipping BP[b], hazard ratio of total events and ↑ BP control and increased survival compared to group 1. Ingesting CCB, β-blocker, or ARB at bedtime compared to morning ↓CVD risk; non-significance with other drug classes likely due to limited sample size of individual treatment class
Bonten et al. 2015 [82]	The Netherlands	Prospective, randomized, open-label, blinded end point, 2-period crossover study; comparison of low-dose aspirin administered in the morning vs. bedtime	73% male; aged 64 ± 7 y; previous use of 80–100 mg aspirin for CVD prevention; no antiplatelet, anticoagulant, or NSAID medications (n = 290)	3	Baseline BP ≥120/70 or ≥160/100 mmHg (average of 6 BP measured 2 min apart after 10 min of rest)	Aspirin within 1 h of waking	Same as morning (crossover design); 1 h before bedtime	24-h ABPM	Platelet reactivity	No significant differences in ABPM between morning and bedtime aspirin administration. Bedtime administration ↓morning platelet reactivity
Farah et al. 2013 [83•]	Israel	Prospective RCT; medication upon awakening (group 1) vs. at bedtime (group 2); unclear blinding	67% male; aged 50 ± 2 y; uncontrolled HTN; non-dipping BP[b], BMI <30 kg/m²; no evidence of target organ damage or systemic disease (total participants, n = 60; group 1, n = 30)	4	Uncontrolled HTN: sitting SBP >140 mmHg, sitting DBP >90 mmHg (mean of 3 outpatient visits); and awake BP >135/85 mmHg or nocturnal BP >120/70 mmHg (24-h ABPM)	Group 1: Long-acting CCB or ACEI; 5 of 30 received combined tablet of CCB and ACEI. Group 2: None	Group 1: None. Group 2: Long-acting CCB or ACEI; 5 of 30 received combined tablet of CCB and ACEI	24-h ABPM and office BP	Cholesterol, triglycerides, HDL, LDL, glucose, and creatinine	Group 2 ↓BP, more prominently at night, and controlled 24-h SBP and DBP. Four participants with monotherapy were unresponsive to bedtime dosing, but their BP was controlled by the addition of a 2nd drug at bedtime
Fujiwara et al. 2017 [84]	Japan	Prospective, multicenter, open-label, crossover, non-inferiority, RCT; morning vs. bedtime administration; blinded by independent research center	35% male; aged 68 ± 9 y; 17% T2D; 65% CKD; no HF, coronary heart disease, or cerebrovascular disease at baseline; 17% extreme dipper; 22% non-dipper; and 9% reverse dipper[b] (n = 23)	2	Office SBP ≥140 mmHg or DBP ≥90 mmHg (mean of 2 consecutive BP measurements after ≥2 min of seated rest)	ARB and CCB combination therapy	Same as morning (crossover design)	Nocturnal brachial (ABPM) and central SBP	Adverse events and adherence to medication	Morning administration ↓brachial and central SBP/DBP and bedtime administration ↓ central DBP only compared to baseline.
Hermida et al. 2013 [85]	Spain	Cross-sectional; all medications upon awakening (group 1), full daily dose of ≥1 medications at bedtime (group 2), or split twice daily dose of medications (group 3)	58% male; aged 64 ± 12 y. Resistant HTN: failed to sufficiently lower SBP/DBP with lifestyle changes and prescription of ≥3 HTN medications (group 1, n = 1084; group 2, n = 1436; group 3, n = 379)	N/A	Awake SBP/DBP mean ≥135/85 mmHg and/or asleep SBP/DBP mean ≥120/70 mmHg	Group 1: All medications (3[†] ±1). Group 2: Some medications (3[†] ±1). Group 3: Split twice daily dose of ≥1 medication (4[†] ±1)	Group 1: None. Group 2: Full daily dose of ≥1 medication. Group 3: Split twice daily dose of ≥1 medication	48-h ABPM	Markers of CVD risk: microalbuminuria, CKD, albumin/creatinine ratio, glucose, cholesterol, eGFR	Bedtime dose (group 2) ↓non-dipping and reverse dipping BP[b] and CVD risk compared to group 1 or 2

Table 1 (continued)

Reference	Country	Study design	Participant details	HTN definition	Follow-up (month)	Morning antihypertensive medications	Evening antihypertensive medications	Measures of BP	Ancillary measures	Results
Huangfu et al. 2015 [86]	China	Randomized, single-blinded, and parallel-controlled; comparison of morning, evening, and split administration of diuretic and ARB	45% male; aged 56 ± 13 y; grade II or III HTN untreated ≥ 2 weeks (group 1, n = 20; group 2, n = 21; group 3, n = 23; group 4, n = 22)	24-h mean SBP/DBP ≥ 130/80 mmHg, the diurnal mean value ≥ 135/85 mmHg, or the nocturnal mean value ≥ 120/70 mmHg	3	Morning medications taken 6–8 AM. Group 1: Diuretic and ARB. Group 2: None. Group 3: Diuretic. Group 4: ARB	Bedtime medications taken 7–9 PM. Group 1: Diuretic and ARB. Group 2: None. Group 3: ARB. Group 4: Diuretic	24-h ABPM	N/A	Group 2 ↓morning surge in BP from baseline. No significant changes in dipping[b] status or 24-h mean BP
Kario et al. 2016 [87]	Japan	Prospective, multicenter, open-label, RCT; morning (group 1) vs. bedtime (group 2) administration; unclear blinding	62% male; aged 75 ± 9 y; HTN patients with paroxysmal AF confirmed with electrocardiography; free from severe liver or kidney disease, persistent or permanent AF prior to randomization; no HF, stroke or MI within 6 months of study initiation (total completing study, n = 81; group 1, n = 41; 91% completed study)	SBP ≥ 140 mmHg (office) or SBP ≥ 135 mmHg (home), and/or DBP ≥ 90 mmHg (office) or DBP ≥ 85 mmHg (home). Office BP: mean of 3 consecutive measures. Home BP: mean of morning or evening BP for 5 consecutive days	3	Group 1: ARB + CCB combination tablet. Group 2: None	Group 1: None. Group 2: ARB + CCB combination tablet	24-h ABPM	High-sensitivity troponin T, plasminogen activator inhibitor-1, N-terminal pro-brain natriuretic peptide, and the urinary albumin/creatinine ratio from baseline	Compared to baseline, groups 1 and 2 ↓ 24 h, nighttime, morning, pre-awake, morning and evening home SBP/DBP and home BP variability. Group 2 ↓ high-sensitivity troponin T, N-terminal pro-brain natriuretic peptide, and the urinary albumin/creatinine ratio
Lafeber et al. 2014 [88]	The Netherlands	Open-blinded end point, three-period crossover, RCT; comparison of a fixed-dose combination pill (polypill) administered in the morning (period 1) vs. evening (period 2) vs. individual pill components administered in morning and evening (period 3)	85% male; aged 67 ± 8 y; 100% established atherosclerotic CVD + indication for the use of CV medication (n = 81)	N/A	1.5–2	Morning administration between 5 and 11 AM. Period 1: Polypill (containing aspirin, statin, ACEI, and diuretic). Period 2: None. Period 3: Aspirin, ACEI, and diuretic	Evening administration between 9 PM–12 AM. Period 1: None. Period 2: Polypill. Period 3: Statin	24-h ABPM	LDL cholesterol, anti-platelet function, medication adherence	No difference in ABPM between polypill dose time (period 1 and 2) compared to individual agents. Polypill (period 1 and 2) ↑ adherence compared to individual agents. Polypill in evening (period 2) ↓ LDL compared to morning dosing
Mori et al. 2013 [89]	Japan	Prospective RCT; morning (group 1) vs. bedtime (group 2) administration of ARB with increasing dosing and/or addition of long-acting CCB for BP control; blinded by numbered containers	56% male; aged 62 y; untreated primary HTN; 9% on diabetic medications; 6% CKD. Participants were free from secondary HTN, severe liver dysfunction, stroke, bilateral renal artery stenosis, hyperpotassemia, and had > 1 kidney present. Groups did not vary on baseline characteristics (total completing study, n = 188; group 1, n = 96)	Office SBP ≥ 140 mmHg, DBP ≥ 90 mmHg-measured after sitting ≥ 10 min. Excluded if SBP ≥ 180 mmHg	6	Group 1: Baseline dose of ARB, 14 ± 5 mg; 6 month dose, 22 ± 11 mg. Baseline number of antihypertensive drugs, 1.1; 6 months number of antihypertensive drugs 1.4 including ACEI, CCB, β-blockers, diuretics, and spironolactone. Group 2: None	Group1: None Group 2: Baseline dose of ARB, 14 ± 5 mg; 6-month dose, 21 ± 12 mg. Baseline number of antihypertensive drugs, 1.2; 6 months number of antihypertensive drugs 1.4 including ACEI, CCB, β-blockers, diuretics, and spironolactone	Office BP and morning home BP obtained after 2 min of sitting rest within 1 h of waking from nighttime sleep	Renal function: glomerular filtration rate, sCR, albumin-to-creatinine ratio; C-reactive protein; pulse rate; cardiothoracic ratio; total voltage of the S wave of V_1 + R wave of V_5 (SV_1 + RV_5); dose amount	Compared to baseline, groups 1 and 2 ↓ office and morning SBP and DBP, SV_1 + RV_5, and albumin-to-creatinine ratio with no difference between dose time. Office and morning pulse rate ↓ in group 1 but not group 2. Compared to baseline, group 1↓ glomerular filtration rate, and group 2 ↓ cardiothoracic ratio. There was no significant difference in dose of ARB between groups or number of drugs administered

Table 1 (continued)

Reference	Country	Study design	Participant details	HTN definition	Follow-up (month)	Morning antihypertensive medications	Evening antihypertensive medications	Measures of BP	Ancillary measures	Results
Santiago et al. 2014 [90]	Portugal	Cross-sectional; observational study; random sampling with replacement; patients with controlled (group 1) vs. uncontrolled (group 2) HTN	52% male; 86% aged <65 y; 65% controlled HTN; $n = 201$	ICPC-2 classification of HTN based on the mean of the last 3 measurements over a minimum of 9 months	N/A	N/A	N/A	Number and type of antihypertensive medications, time of day of medication ingestion, use of NSAIDs	Age, gender, previous CV events, comorbidity	↑Target organ damage and nighttime dosing of antihypertensive medications in group 1; ↑NSAIDs use in group 2
Suomela et al. 2015 [91]	Finland	Prospective; morning vs. evening aspirin administration; unclear blinding	59% male; aged 65 ± 8 y; regular antihypertensive therapy ≥ 1 year; $n = 34$	N/A	3	Before intervention: aspirin taken on awakening	Aspirin taken at bedtime	24-h ABPM, office BP, home morning and evening BP	Arterial pulse wave velocity (PWV), stiffness index, and reflection index	Evening administration ↓office SBP and ↑carotid-femoral PWV, and plasma TG compared to morning administration
Szauder et al. 2015 [92]	Hungary	Prospective; once daily (evening-group 1) vs. twice daily (morning and evening-group 2); unclear blinding	40% male; aged 56 ± 14 y; newly diagnosed primary HTN; BMI 24 ± 2 men, 21 ± 3 women; 100% non-dipper[b]; 100% Caucasian; sedentary occupation; non-smokers; no other comorbidity; no other regular medication (prescribed or illicit); no cardiologic complains; normal sleep quality; and clinically free of any sleep-related disorder ($n = 164$, group 1, $n = 41$)	Office SBP ≥160 mmHg, DBP ≥100 mmHg, and confirmed by 2 4-h ABPM with mean SBP/DBP >130/80 mmHg and diurnal mean >135/85 mmHg or nocturnal mean >120/80 mmHg untreated	~0.5	Group 1: None. Group 2: Split-dose of long-acting ACEI at 8 AM OR split-dose of long-acting ARB at 8 AM	Group1: Complete dose of long-acting ACEI OR long-acting ARB at 8 PM. Group 2: Split-dose of long-acting ACEI at 8 PM OR split-dose of long-acting ARB at 8 PM	24-h ABPM-SBP/DBP mean, hypertensive time index (proportion of timing BP values are above normal), diurnal index (difference between day-time and night-time BP), hyperbaric impact/pressure load: in mmHg × h	N/A	Mean BP, percent of time elevation index, and the hyperbaric impact ↓ in all groups. Diurnal index (i.e., reducing number of non-dippers) ↑ with group 2 (either drug) compared to group 1
Ushijima et al. 2015 [93]	Japan	Multicenter, open-label, RCT; parallel group; comparison of morning valsartan ARB vs. evening of valsartan ARB (group 1), morning olmesartan ARB (group 2) and evening olmesartan ARB (group 3), no blinding	65% male; aged 65 ± 9; 5% T2D; 100% non-dipper[b] ($n = 40$; group 1, $n = 12$; group 2, $n = 13$; group 3, $n = 15$; 88% completed study—results not presented in an intention to treat format)	Office SBP ≥ 140 mmHg, DBP ≥90 mmHg; controlled BP: office BP <140/90 mmHg in non-diabetic patients and <130/80 mmHg in diabetic patients	4	All groups—valsartan ARB at randomization. Group 2: Switched to olmesartan ARB. Group 3: None	Group 1: Switched to valsartan ARB. Group 2: None. Group 3: Switched to olmesartan ARB	24-h ABPM-SBP reduction at night, SBP/DBP during waking hours, during sleep, and average 24 h	Renal function: serum creatinine, eGFR	Compared to baseline SBP ↓during sleep and ↑during waking hours in group 1, SBP ↓during sleep and waking hours for group 2 and 3. Percent reduction in SBP at night compared to SBP at waking ↑in all dosing groups compared to valsartan AM. Serum creatinine ↓in groups 2 and 3; ↑ eGFR in group 2
Zappe et al. 2015 [94••]	Germany, Spain, France, Italy, and the Netherlands	Multicenter, randomized, double-blind, double-dummy, active-controlled, parallel group; morning administration of long-acting ACEI (group 1) vs. ARB administered in the morning (group 2) or evening (group 3)	56% male; aged 62 ± 11; BMI 29 ± 4; 55% non-dipper[b], 27% controlled T2D; 12% metabolic syndrome; 4% MI/PTCA/CABS/stroke (group 1, $n = 359$; group 2, $n = 367$; group 3, $n = 356$)	24-h ABMP > 130/80 mmHg + 1 additional CV risk factor; BP did not exceed 160/95 mmHg	6.5	Group 1: ACEI. Group 2: ARB + possible addition of diuretic if BP not controlled following 12 weeks of treatment. Group 3: None	Group 1: None. Group 2: None. Group 3: ARB + possible addition of diuretic if BP not controlled following 12 weeks of treatment	BP control rate (24-h ABPM average <130/80 mmHg) and change from baseline to week 12 mean 24-h ABPM-before addition of diuretic; office BP (sitting mean of 3 measures), daytime BP, nighttime BP; daytime/nighttime BP ratio,	N/A	Mean 24-h ABPM similar between groups

Table 1 (continued)

Reference	Country	Study design	Participant details	HTN definition	Follow-up (month)	Morning antihypertensive medications	Evening antihypertensive medications	Measures of BP	Ancillary measures	Results
						Meta-analysis		early-morning BP, morning BP surge, BP variability		Evening dosing ↓risk of coronary artery disease and stroke vs. usual dosing
Roush et al. 2014 [95••]		Meta-analysis of randomized trials using evening dosing or usual dosing of antihypertensives to reduce cardiovascular events	5 evening dosing trials: 33–73% male; mean age 63–77 years, (evening dosing, n = 35,075; usual dosing, n = 312,057).	Varied	24–64	3 studies had a morning dosing arm using ACEI	4 studies used CCB, 1 used ACEI	Office BP	Coronary artery disease, CV events, stroke	

Inclusive of original studies reviewed from January 2013 to December 2017. [a] Mean number of medications taken in total. [b] Non-dipping BP defined as average nocturnal SBP reduction compared to average awake SBP (measured using ABPM) ≥ 0% but < 10%; extreme dipper nocturnal SBP reduction ≥ 20%; and riser or reverse dipper when reduction < 0%. *ABPM*, ambulatory blood pressure monitoring; *ACEI*, angiotensin-converting enzyme inhibitors; *AF*, atrial fibrillation; *ARB*, angiotensin II receptor blocker; *BP*, blood pressure; *CABS*, coronary artery bypass surgery; *CCB*, calcium channel blockers; *CKD*, chronic kidney disease; *CVD*, cardiovascular disease; *DBP*, diastolic blood pressure; *HF*, heart failure; *HTN*, hypertension; *ICPC-2*, International Classification of Primary Care second edition; *MI*, myocardial infarction; *OSA*, obstructive sleep apnea; *PTCA*, percutaneous transluminal coronary angioplasty; *RCT*, randomized controlled trial; *SBP*, systolic blood pressure; *sCr*, serum creatinine; *T2D*, type 2 diabetes mellitus; *y*, years

morning surge of SBP as compared to baseline [86]. In patients with HTN and atrial fibrillation, combined therapy of an ARB and a CCB reduced 24-h BP, nighttime BP, pre-awake BP, morning BP, and nighttime BP variability regardless of dose timing [87]. Similarly, a non-inferiority clinical trial that compared the effect of morning and bedtime administration of an ARB and CCB combination reported that morning dosing reduced nocturnal brachial and central SBP and DBP whereas bedtime dosing only reduced nocturnal central DBP [84]. This was the first chronotherapy study to report central aortic BP, which the research group estimated from brachial pulse wave non-invasively using an oscillometric ABPM. Consistent findings of equivalent effects on nocturnal brachial BP reduction with ARB and CCB combination therapy may reflect the long-acting properties of these medications when taken concomitantly [116, 117].

Most patients treated for HTN receive once-daily regimens (monotherapy or combination therapy) as a result of the therapeutics' 24-h efficacy or in an effort to increase treatment adherence [80]. Yet despite the long terminal half-life of, for example, the ARB telmisartan (~ 24 h [118]), Hermida et al. report additional benefits of taking the drug at night including increased nighttime sleep decline of BP [53]. The group has presented similar findings related to olmesartan (ARB) which has a terminal half-life of ~ 13 h [52, 118]. In contrast, Ushijima et al. [93] report no additional benefit of taking olmesartan in the evening compared to the morning. Moreover, the study confirms decreased BP during sleep when valsartan (ARB with terminal half-life of 6 to 9 h) is taken at bedtime compared to the morning [93, 118]. Thus, it is surprising that Zappe et al. conclude that once-daily administration of valsartan resulted in similar 24-h BP control regardless of dosing time and when compared to administration of a long-acting ACEI taken in the morning [94••]. In contrast, Szauder et al. report that twice-daily administration of an ACEI or an ARB was more effective in converting non-dippers to dippers compared to once-daily dosing of either medication in the evening [92]. The latter study suggests that for some drug classes, twice-daily dosing may be required to obtain ideal BP control.

Finally, the meta-analysis shown at the end of Table 1 compared five clinical trials that administered antihypertensive medications in the evening compared to 170 clinical trials with dosing in the morning, and reported a significant 48% reduction in relative risk of adverse CV events in patients ingesting their medications in the evening compared to that in the morning [95••]. Thus, regardless of the complexities of the varied studies, the different sizes, study designs, and patient groups in the studies, and the different degrees of HTN and of non-dipping BP, it seems possible to make the general conclusion that evening dosing of antihypertensive medication is not harmful and yet may be highly beneficial to important clinical outcomes in the general population with HTN.

More studies are needed to determine the specific mechanisms and the specific medications that provide this benefit. The next section examines the same question, but in populations with HTN and other specific comorbidities.

Chronotherapy in Comorbid Populations

Comorbid conditions are more common in people with HTN compared to those who are normotensive [119]. It has been recommended that management of any comorbidity should be directed at both the underlying condition as well as lowering BP, with awareness for possible drug interactions and adverse side effects [77]. However, current treatment regimens successfully control BP levels in fewer than half of comorbid HTN participants, which likely contributes to the increased incidence of CVD and stroke in patients with HTN and comorbidity [119, 120]. Furthermore, the study of therapy for HTN in the presence of additional disease is important because medications rarely have simple linear additive effects, such that interactions between treatment for comorbid conditions may greatly alter (attenuate or enhance) the effects of antihypertensive medications [121]. Adding the dimension of timed medication therefore increases complexity but more understanding of the extent and direction of such interactions could reveal opportunities for even better therapy both for HTN and any underlying comorbidity.

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) can be a secondary cause of HTN independent of age, sex and obesity status [77, 122–125]. Prospective epidemiological studies have demonstrated a robust dose-dependent association between OSA at baseline and the prevalence and incidence of HTN [126–128]. Continuous positive airway pressure (CPAP) therapy can lower the risk of HTN [129]. However, due in part to low long-term adherence to CPAP therapy, meta-analyses indicate that CPAP therapy for OSA results in only small (1–2 mmHg) average reductions in BP [130–132]—levels not sufficient to bring HTN under control nor large enough to reduce risk of stroke or coronary heart disease [133]. Treatment with antihypertensive drugs yields larger long-lasting reductions in BP in populations with OSA who do not use CPAP [134–136], but these drugs fail to generate the reductions obtained in HTN patients without OSA [137]. Moreover, standard antihypertensive treatment does not bring BP under control in people with severe OSA [138] and requires the addition of CPAP to achieve reductions in both daytime and nocturnal SBP [139]. Of further concern, non-dipping BP occurs in 48–84% of patients with OSA [28, 140–142], possibly related to the associated hypoxia- and hypercapnia-induced sympathetic activity and subsequent vasoconstriction [143]. Arousal ends the upper airway obstruction and with this arousal and upon

resumption of breathing, cardiac output increases in conjunction with constricted peripheral vasculature resulting in increased BP. This can happen hundreds of times per night. Recurrent activation of this pathway can lead to daytime persistence of HTN [144]. These maladaptations may actually account for improved efficacy of β1-adrenergic blockers in older hypertensive OSA patients [145].

Nocturnal medication dosing may improve BP control in the absence of CPAP adherence in patients with nocturnal HTN [146], non-dipping BP [147–149], or resistant HTN, as discussed below. Table 2 summarizes five original studies and one meta-analysis of the effects of time-dependent dosing for treatment of HTN in patients with HTN and OSA. Generally, these studies demonstrate that nighttime dosing of an antihypertensive medication improves BP control in OSA. Specifically, a prospective study comparing administration of an ARB alone or combination of an ARB and CCB demonstrated a greater reduction of both nighttime SBP and DBP and increased dipping BP as a result of evening compared to morning dosing irrespective of CPAP use [98•]. A retrospective analysis of an observational study also revealed that add-on nocturnal treatment with a CCB among patients with OSA resulted in a distinct reduction of both mean nighttime SBP and DBP and an increased dipping BP pattern independent of CPAP treatment [96]. Finally, in a case study, bedtime dosing of an α1-blocker suppressed exaggerated hypoxia-triggered nocturnal SBP surges, as well as the early-morning SBP surge [100]. This report was unique in its use of a trigger sleep BP (TSP) monitoring system that takes a BP measurement when a patient's oxygen desaturation falls below a set threshold that is monitored continuously by pulse oximetry. This method allows researchers to assess the BP surge associated with an apnea/arousal cycle [150], and may be a useful addition to any study of the effectiveness of antihypertensive medication in OSA. The TSP monitoring method was also employed in a crossover study comparing the effect of nighttime dosing of a CCB vs. a non-selective β1/2-adrenergic receptor blocker [97••]. This prospective study demonstrated that a nighttime single-dose administration of both medications resulted in a pronounced reduction of the mean sleep SBP and the hypoxia-related peak sleep SBP in HTN patients with OSA. Unfortunately, the latter study did not compare these effects to morning dosing.

In contrast to the above studies, a RCT in patients with moderate to severe OSA and HTN showed that an ACEI taken at night did not further reduce nocturnal SBP compared with morning dosing (− 6.9 mmHg, − 8.0 mmHg, respectively), regardless of the addition of CPAP, which similarly lowered sleep SBP both with morning and evening dosing [99]. Morning compared to evening administration of the ACEI was also superior at reducing daytime SBP. Neither morning nor evening ingestion improved the rates of non-dipping BP.

Finally, the meta-analysis shown at the end of the OSA section in Table 2 presents the combined result of 3582 patients and revealed that evening compared to morning antihypertensive medications in OSA result in significantly reduced nocturnal SBP and DBP, as well as reduced non-dipping BP profiles. These results are therefore similar to the results in the general population (Table 1), but conflicting results between the prospective RCT and smaller mixed designed studies emphasize the need for additional rigorously run studies among a diverse population of OSA patients.

Chronic Kidney Disease

Chronic kidney disease (CKD) is considered an accelerator of CVD and an independent risk factor for adverse CV events [151]. CV risk increases inversely to the estimated glomerular filtration rate (eGFR) and all stages of CKD are associated with increased risks of CV morbidity, premature mortality, and/or decreased quality of life [152–155]. CKD is often classified into five stages using thresholds of serum creatinine, eGFR, and/or evidence of structural renal changes such as proteinuria [156]. A systematic review and meta-analysis in 2016 estimated the global CKD prevalence to be 11–13% with prevalence by severity: CKD stages 1 to 5, 13.4%; and stages 3 to 5, 10.6% [157]. HTN is the most common comorbidity in patients with CKD with the prevalence of HTN increasing with declining renal function [158, 159]. Although elevated BP can occur as a result of CKD, increased BP is also a risk factor for severe CKD [160]. Therefore, control of HTN is a medical priority in the management of CKD and offers an opportunity to slow further loss of kidney function [161, 162]. Additionally, optimal HTN control in CKD helps prevent end-organ damage, notably in the heart and brain [161, 163, 164]. ABPM in patients with CKD often reveals elevated nocturnal BP [165, 166] with non-dipping increasing risk of total mortality or end-stage renal disease [167]. However, to date, studies that consider chronotherapy in CKD patients are limited and with mixed effects. Two systematic reviews conducted between 2013 and 2017 suggest that administration of antihypertensive medications in the evening should be considered for CKD patients with HTN to lower nighttime SBP and/or DBP [109••, 168], reduce non-dipping BP [109••], and prevent adverse CV events and mortality [168]. Table 2 summarizes four original studies of the effects of time-dependent dosing for treatment of HTN in patients with HTN and CKD. A cross-sectional study (also included in the systematic reviews mentioned above) demonstrated that ingestion of one or more antihypertensive medications at night in participants with mild HTN and CKD was associated with lower asleep SBP and DBP [101]. Thus, the prevalence of non-dipping BP was attenuated when at least one antihypertensive medication was taken at night, and was further decreased when all medications were ingested at night. In a pilot RCT, participants

Table 2 Effects of time-dependent dosing for treatment of HTN: reviewed studies (2013–2017) of populations with specific comorbid conditions (obstructive sleep apnea, chronic kidney disease, or diabetes)

Reference	Country	Study design	Participant details	HTN definition	Follow-up (month)	Morning antihypertensive medications	Evening antihypertensive medications	Measures of BP	Ancillary measures	Results
Obstructive sleep apnea										
Crippa et al. 2016 [96]	Italy	Post hoc analysis of observational study; current drug regimen (baseline [group 1]) vs. addition of bedtime antihypertensive medication to current drug regimen (group 2); no blinding	56% male; aged 69 ± 17 y; 100% untreated moderate-to-severe OSA; 78% non-dippers; 22% reverse-dippers[b] (n = 41)	Mean daytime ABPM > 135/85 mmHg and mean nighttime ABPM > 120/70 mmHg	3	Group 1 and 2: ACEI, ARB, β-blockers, early distal tubule diuretics	Group 1: None. Group 2: Addition of 10 mg CCB at 10–11 PM	24-h ABPM	Adverse effects	Group 2 compared to group 1 ↓ in daytime and nighttime BP; dipping BP was normalized in 78% of participants; 3 developed mild symptomatic diurnal hypotension; and 6 showed mild-to-moderate leg edema
Kario et al. 2014 [97••]	Japan	Prospective, parallel group, Crossover, RCT; comparison of nighttime single-dose administration of a CCB vs. β-blocker on sleep BP in OSA patients. Analysis blinded to treatment group	73% male; aged 65 ± 13 y; 100% AHI ≥ 15; untreated by CPAP; no prior bedtime hypertensive drugs, renal failure, or severe liver dysfunction (n = 11)	Sleep BP (measured by ABPM) ≥ 120/70 mmHg	0.03	3 ± 1[a] including 54% CCB, 18% ACEI, 73% ARB, and 36% diuretics	CCB or β-blocker administered at 6 PM	Sleep SBP surge (hypoxia-peak SBP), mean sleep BP, morning BP	Polysomnography parameters (i.e., AHI/h)	CCB and β-blocker ↓mean sleep and morning SBP and DBP compared to baseline; CCB had more extensive lowering effect than β-blocker. β-blocker ↓ sleep BP surge and pulse rates
Kasiakogias et al. 2015 [98•]	Greece	Prospective, open-label, fixed-dose, crossover study; morning vs. bedtime dosing, BP measures taken by physician blinded to study protocol	78% male; aged 52 ± 9 y; BMI 34 ± 6 kg/m², AHI mean 31 (21–45) events/h; 61% severe OSA (AHI ≥ 30 events/h); 49% treated with CPAP; without daytime somnolence, ESS 6 ± 3. Patients were without secondary HTN; diabetes; established CVD; CKD or pulmonary disease (n = 41)	Office SBP/DBP ≥ 140/90 mmHg recorded following 5 min of rest in quiet place, average of 2nd and 3rd readings taken in 2-min intervals and confirmed by mean 24-h ABPM > 130/80 mmHg	2	ARB or fixed combination of ARB/CCB in a single dose before breakfast; 8–9 AM	Same as morning (crossover design); 2 h before bedtime	Office BP (measured 8–9 AM before morning pill) and 24-h ABPM	N/A	Morning and evening dosing ↓office and 24-h ABPM SBP/DBP compared to baseline; evening dosing ↓ office and nighttime SBP/DBP compared to morning dosing. Prevalence of nighttime dippers ↑from 24% at baseline to 34% with morning dosing and 61% with bedtime dosing. No interaction with CPAP treatment
Serinel et al. 2016 [99]	Australia	Double-blind, placebo-controlled, crossover RCT followed by open label in final study phase; effects of morning vs. evening antihypertensive administration with placebo at opposite time points; treatment sequence performed by independent company by block design with results stored in sealed envelopes	81% male, aged 52 ± 9 y; BMI, 34 ± 7 y; 48 ± 23 AHI, events/h; 9% T2D, 1% stroke, 7% heart disease; on <3 antihypertensive medications not including ACEI or ARB at randomization (49% on 0; 42% on 1; and 8% on 2 antihypertensive medications); participants were free from serve OSA (minimum oxygen saturation ≤ 65% or respiratory disturbance	Office SBP 140–179 mmHg and/or DBP 90–109 mmHg AND 24-h ABPM with awake SBP ≥ 135 and/or DBP ≥ 85 mmHg OR asleep SBP ≥ 120 and/or DBP ≥ 70 mmHg; excluded if office SBP ≥ 180 and/or DBP ≥ 110 mmHg	1.5 dosing; 2 dosing + CPAP	9 AM administration of ACEI +9 PM placebo + previously prescribed medication regimen; final 8 weeks addition of CPAP	Same drug dosing (crossover study) at 9 PM + 9 AM placebo; final 8 weeks addition of CPAP	24-h ABPM—sleep and 24-h BP, BP dipping ratios, and office BP	Sleep and wake times (actigraphy, sleep diary); adverse events	Sleep SBP and DBP ↓from baseline with both evening and morning dosing of ACEI, no difference between dosing groups; wake SBP and DBP ↓more with morning than evening dosing. CPAP ↓sleep SBP and DBP with morning and evening dosing, no difference between dosing time

Table 2 (continued)

Reference	Country	Study design	Participant details	HTN definition	Follow-up (month)	Morning antihypertensive medications	Evening antihypertensive medications	Measures of BP	Ancillary measures	Results
		index >80), excessive sleepiness, and CKD (at randomization n=85; 92% completed study—results not presented in an intention to treat format)								↓In hypoxia-triggered nocturnal SBP surge and early-morning BP
Yoshida et al. 2017 [100]	Japan	Case report; use of bedtime antihypertensive dosing to improve hypoxia-triggered nocturnal SBP surge and early-morning BP	Young adult male with severe OSA with BP surge during sleep measured by TSP followed by sleep onset stroke 3×, CPAP intolerance	N/A	24	N/A	Bedtime dosing of selective α-1 blocker (time not specified)	Overnight TSP	N/A	
Reference	Country	Study design	Participant details	HTN definition	Follow-up (month)	Morning antihypertensive medications	Evening antihypertensive medications	Measures of BP	Ancillary measures	Results
Chronic kidney disease										
Crespo et al. 2013 [101]	Spain	Cross-sectional study; all medications upon awakening (group 1), ≥1 medications at bedtime (group 2) in hypertensive patients with CKD	60% male; aged 65±13 y; 100% CKD with eGFR <60 mL/min/1.73 m² and/or albuminuria (n=2659; group 1, n=1446)	Uncontrolled HTN: awake SBP/DBP mean ≥135/85 mmHg and/or asleep SBP/DBP mean ≥120/70 mmHg	N/A	Group 1: 3[†]±1 including 74% ARB, 21% ACEI, 72% CCB, 41% α-blocker, 30% β-blocker, and 69% diuretics. Group 2: Varied	Group 1: None. Group 2: 2[†]±1 including 59% ARB, 13% ACEI, 33% CCB, 13% α-blocker, 11% β-blocker, and 23% diuretics	48 h ABPM, office BP (2× seated BP after 10-min rest)	Clinical laboratory test including fasting glucose, serum creatinine, uric acid, cholesterol, triglycerides, and eGFR	Group 2 significantly ↓mean sleep SBP/DBP, prevalence of non-dipping[b] pattern, total cholesterol, LDL, vs. group 1. Prevalence of non-dipping and glucose, creatinine, and uric acid further ↓with all medications taken at bedtime. Riser BP significantly ↑with morning medication, than ≥1 medications at bedtime, or than all medications at bedtime with significant difference between all groups
Sakai et al. 2013 [102]	Japan	Observational; comparison of twice-daily ARB (morning and evening) vs. once-daily (morning only) ARB	58% male; aged 70±12 y; 100% CKD; mean eGFR 49±18 mL/min/1.73 m² (n=39)	N/A	2	Pre-study: 20 mg ARB. Study dose: 40 mg ARB	Pre-study: 20 mg ARB. Study dose: None	Average of 2× office and morning at-home BPs after 5-min rest	Renal function/proteinuria: eGFR, urinary albumin-to-creatinine ratio	No significant change in BP. ↑ eGFR with morning-only dose
Rahman et al. 2013 [103]	USA	Open-label, multicenter, 3-period, crossover, RCT; standard morning medication regimen vs. ≥1 medication moved to bedtime, OR an additional medication added to drug regimen at bedtime; no blinding	64% male; aged 65±10 y; 100% African American; 60% BMI >30 kg/m²; HTN mean 30 years; 45% non-dipper; 29% reverse dipper[b]. Participants had not suffered a MI or cerebrovascular accident within 3 months prior to	Office BP ≤140/90 mmHg based on 2 BP values measured >1 week apart and currently prescribed 1 antihypertensive medication taken 1× daily, 2 antihypertensive medications with >1 taken 1× daily, or ≥3	1.5	All participants—all medications 4[a].	In 49% of participants 1 antihypertensive medication moved to bedtime (72.5% ACEI; 15% ARB; and 12.5% CCB). In 48% of participants >2 antihypertensive medication moved to bedtime.	Nocturnal SBP; 24-h ABPM, office BP	N/A	Nocturnal, 24 h, nor daytime SBP significantly differed by treatment timing

Table 2 (continued)

Reference	Country	Study design	Participant details	HTN definition	Follow-up (month)	Morning antihypertensive medications	Evening antihypertensive medications	Measures of BP	Ancillary measures	Results
			study enrollment and had an EF >40% (n = 147)	antihypertensive medications with > 2 taken 1× daily			For add-on schedule, 49.5% received hydralazine; 18.1% diltiazem; 7.6% ramipril; and 24.8% received another medication			
Wang et al. 2013 [104]	China	Prospective, RCT; comparison of awakening dose in dipping (group 1) vs. non-dipping BP (group 2), or bedtime dose in non-dipping BP (group 3) of an ARB; no blinding	67% male; aged 36 ± 9 y; 100% CKD[b] and free from CV disorders	Standard ABPM dipping criteria[b]	3	Group 1: ARB BP dippers. Group 2: ARB BP non-dippers. Group 3: None	Groups 1/2: None. Group 3: ARB non-dippers	24-h ABPM	Cardiac ultrasound; urinary protein, creatinine, and sodium excretion	Group 3 ↓ nocturnal SBP ↑renal protection (slower decline in eGFR) and target organ protection, and ↓proteinuria, vs. group 2
Reference	Country	Study design	Participant details	HTN definition	Follow-up (month)	Morning antihypertensive medications	Evening antihypertensive medications	Measures of BP	Ancillary measures	Results
Diabetes										
Ciobanu et al. 2015 [105]	Romania	Cross-sectional; no medication (group 1) vs. ≥1 antihypertensive medications at morning (group 2) or ≥1 antihypertensive medications at bedtime (group 3)	44% male; T2D: no unstable CV conditions, severe infections, malignancies, or eGFR <30 mL/min/1.73m³ (n = 144; bedtime, n = 60; morning, n = 56; no medications, n = 28)	SBP and DBP were measured at least 2× after 10 min of sitting rest, measures were obtained and averaged from both arms	N/A	Medications included ACEI, ARB, β-blocker, diuretic, and CCB	ACEI (n = 38); ARB (n = 17); β-blocker (n = 45); Diuretic (n = 39); CCB (n = 25); α-antagonist (n = 4)	24-h ABPM, dipping index	HTN duration, CVD, T2DM duration	↑Dipping BP in group 3 compared to group 1 or 2. Bedtime medication use (group 3) associated with ↑ presence of CVD
Hermida et al. 2016 [106**]	Spain	Prospective, open-label, blinded end point, single-center RCT; replacement of one antihypertensive medication with a new one ingested upon awakening (group 1) vs. at bedtime (group 2)	48% male; aged 52 ± 13 y; no diabetes at baseline; no secondary HTN or CVD. Groups had similar distributions of OSA (8–9%); metabolic syndrome (47–50%); obesity (38–39%); previous CV events (6–7%); and non-dipping BP[b] (44–45%) (total participants, n = 2012; group 1, n = 1029)	Awake SBP/DBP mean ≥ 135/85 mm-Hg or asleep SBP/DBP mean ≥ 120/70 mm-Hg	70.8 (12–107)	Group 1: All medications (n = 2 ± 1): 62% ARB, 21% ACEI; 35% CCB; 21% alpha-blocker; 20% beta-blocker; 36% diuretic. Group 2: Varied	Group 1: None Group 2: ≥1 medications (n = 2 ± 1): 60% ARB, 19% ACEI; 37% CCB; 22% alpha-blocker; 22% beta-blocker; 36% diuretic. Unspecified which drugs were taken at bedtime	48-h ABPM recorded annually (or quarterly if treatment was adjusted)	New-onset diabetes	Bedtime medication (group 2) ↓mean sleep SBP/DBP and HR of new-onset diabetes; ↑ dipping and ABPM control vs. morning medication group. Ingesting ACEIs, β-blocker, or ARB at bedtime compared to morning ↓ risk of new-onset diabetes; non-significance with other drug classes, but may be due to limited sample size of individual treatment class
Hjortkjaer et al. 2016 [107**]	Denmark	Placebo-controlled, double-blind, two-way crossover, RCT; comparison between morning and bedtime	42% male; aged 60 ± 7 y; BMI 25 ± 4 kg/m²; diabetes duration 36 ± 11 y; 71% prescribed	N/A	3	ACEI + placebo at bedtime + previously prescribed medication regimen	Same as morning (crossover design) with placebo in the morning	24-h ABPM, nighttime SBP/DBP, BP-dipping[b]	Left ventricular function	Bedtime dose ↑ SBP dipping compared to morning dose. No changes in daytime BP or left ventricular function

Table 2 (continued)

Reference	Country	Study design	Participant details	HTN definition	Follow-up (month)	Morning antihypertensive medications	Evening antihypertensive medications	Measures of BP	Ancillary measures	Results
		dosing of an ACEI in patients with type 1 diabetes and with cardiac autonomic neuropathy. Double blinded	antihypertensive treatment (n = 24)							
Rossen et al. 2014 [108•]	Denmark	Open-label crossover study, RCT; morning vs. bedtime administration of participants' 1× daily medication; unclear blinding	73% male; aged 65 (54–75) y; 100% T2D; no presence of MI, AF, or known HF with EF <45% (n = 41)	Nighttime SBP ≥120 mmHg *and* daytime SBP: (1) ≤130 mmHg and minimum 1 antihypertensive drug; (2) 131–135 mmHg and minimum 2 antihypertensive drugs; (3) 136–140 mmHg and minimum 3 antihypertensive drugs; *or* (4) 141–150 mmHg and minimum 4 antihypertensive drugs. Office BP measured 4 times, reported average of the latter 3	2	Median number of once-daily antihypertensive drugs, 3 (1–6); median number twice-daily antihypertensive drugs 3 (1–6). Drugs by class included ACEIs, ARBs, β-blockers, CCBs, and thiazide. All once-daily drugs included a RASI	Same as morning (crossover design)	24-h ABPM, office BP, pre-awakening morning BP surge; sleep-through morning BP surge; nadir-average	Arterial stiffness, autonomic dysfunction, creatinine, HbA1c, cholesterol, parameters of RAAS, markers of endothelial dysfunction, markers of inflammation, arginine vasopressin, atrial natriuretic peptide, sleep duration, time of drug intake, nighttime bathroom, and adverse events	Bedtime administration of antihypertensive drugs ↓nighttime and 24-h SBP. Urinary sodium/creatine and potassium/creatine ↓, urinary osmolality ↑, and C-reactive protein (inflammation marker) ↓with bedtime administration
Meta-analysis										
Wang et al. 2017 [109••]		Meta-analysis comparing evening vs. morning dosing regimen of antihypertensive drugs on BP patterns of CKD patients with HTN	5 RCTs and 1 comparative study: 40–64% male; mean age 36–70 y (n = 3582)	SBP and/or DBP ≥140 and/or ≥90 mmHg	1–70					Evening dosing regimen drug therapy ↓percentage of non-dipper BP patterns, nocturnal SBP and DBP

Inclusive of original studies reviewed from January 2013 to December 2017. [a] Mean number of medications taken in total. [b] Non-dipping BP defined as average nocturnal SBP reduction compared to average awake SBP (measured using ABPM) ≥0% but <10%; extreme dipper nocturnal SBP reduction ≥20%; and riser or reverse dipper when reduction <0%. *ABPM*, ambulatory blood pressure monitoring; *ACEI*, angiotensin-converting enzyme inhibitors; *AF*, atrial fibrillation; *ARB*, angiotensin II receptor blocker; *BP*, blood pressure; *CCB*, calcium channel blockers; *CKD*, chronic kidney disease; *CVD*, cardiovascular disease; *DBP*, diastolic blood pressure; *EF*, ejection fraction; *ESS*, Epworth sleepiness scale; *HTN*, hypertension; *MI*, myocardial infarction; *OSA*, obstructive sleep apnea; *RAAS*, renin-angiotensin aldosterone system; *RASI*, renin-angiotensin system inhibitor; *RCT*, randomized controlled trial; *SBP*, systolic blood pressure; *T2D*, type 2 diabetes mellitus; *TSP*, trigger sleep BP; *y*, years

with non-dipping BP and CKD who received an ARB at bedtime, demonstrated not only decreased nighttime BP but also improved renal and CV protection (i.e., slower decline in eGFR, decreased proteinuria, and better target organ protection [107]). A smaller observational study suggested that morning and evening administration compared to morning dosing alone resulted in similar effects on office BP and morning home BP [105]. However, the study did not measure BP across the night and was therefore unable to account for potential benefits related to the prevalence of non-dipping BP. We note that various regulators of renal function exhibit circadian fluctuations including glomerular filtration rate in humans [169], as well as sodium excretion and renal blood flood in rodent models [170]. Thus, the kidney is highly relevant to daily fluctuations in pharmacodynamics and potential responsiveness to medications. For instance, the kidneys are vital sources and targets of hormones that regulate BP including angiotensin II, aldosterone, vasopressin, angiotensin-converting enzymes, and plasma renin activity all of which exhibit circadian rhythms in rodent models [171–173]. Thus, by considering these factors, there ought to be great potential for the use of chronotherapy to take advantage of rhythm peaks and troughs that could lead to superior BP control and reduced side effects in patients with CKD. However, overall, the results in CKD are somewhat similar to the results in the general population (Table 1) showing some benefit in terms of increasing dipping profile by reducing nocturnal BP more than daytime BP, but there are fewer studies and so far no hard CV outcomes such as incidence of serious adverse CV events in the specific trials of timed antihypertensive medications in CKD. This therefore remains an important area for further research. Moreover, also included in Wang and colleague's meta-analysis of CKD and HTN is the only study to our knowledge that has specifically studied individuals of African descent [103••]. The study found only modest non-significant reductions in nocturnal BP with either evening schedule compared to morning dosing. This all-Black study population took on average four antihypertensive medications and ~ 75% had non-dipping or reverse dipping BP. Thus, there appears to be an interaction between race/ethnicity and time of medication to control HTN in CKD. Therefore, there is an urgent need for additional prospective randomized studies that focus on minority populations that are at increased risk for end-stage kidney disease [159, 174–176].

Diabetes

Hypertension is often a comorbid condition with both type 1 and type 2 diabetes [177]. Microvascular and macrovascular dysfunction (retinopathy, neuropathy, nephropathy, increased predisposition to atherosclerosis, etc.) and ultimately an adverse CV event or death are more prevalent in people with diabetes who also have HTN than in those without HTN [177, 178]. Patients with type 2 diabetes usually exhibit overt HTN upon initial detection of microalbuminuria [179]. Patients with type 1 diabetes often do not present with elevated office BP even in the presence of microalbuminuria which is an early indicator of nephropathy [180]. However, ABPM reveals that individuals with type 1 diabetes and microalbuminuria have higher nocturnal BP and an increased prevalence of non-dipping BP compared to those with type 1 diabetes and a normal urinary albumin excretion, and this lack of BP dipping with type 1 diabetes and microalbuminuria could be the result of a lack of sympathetic withdrawal during sleep [180–185]. Prospectively, it has been demonstrated that an increase of nocturnal SBP over the course of 5 or more years can precede the development of microalbuminuria [186]. Taken together, these findings highlight the necessity for use of ABPM to avoid the underdiagnosis of HTN in type 1 diabetes, and the logical potential for chronotherapy for HTN in individuals with type 1 diabetes. Type 2 diabetes and HTN increase CV risk by common physiological pathways (i.e., obesity, insulin resistance, hyperglycemia, decreased nitric oxide [177]) with each disease state possibly exacerbating the other. For instance, hyperinsulinemia increases sympathetic activity, and hyperglycemia activates the renin-angiotensin system [177], which in itself may be a mechanism for increased risk of diabetes in HTN [187, 188]. Further, individuals with type 2 diabetes are more likely to exhibit a non-dipping BP or reverse dipping BP phenotype [189, 190]. Thus, chronotherapeutic treatment strategies that target nighttime BP among people with type 1 or type 2 diabetes ought to be seriously considered.

Table 2 summarizes four recent original studies of the effects of time-dependent dosing for treatment of HTN in patients with diabetes. At present, there is only one published study investigating morning compared to evening dosing of antihypertensive medications in individuals with type 1 diabetes. This report suggests that bedtime dosing of an ACEI in patients with CV autonomic neuropathy increased nighttime BP dipping [107••]. A cross-sectional study in participants with type 2 diabetes reported bedtime medication administration was a positive predictor for a normal dipping BP pattern and that CCBs and β-blockers were more likely to be administered at bedtime than in the morning [105]. In a prospective open-label trial of participants with type 2 diabetes and high nocturnal BP, bedtime compared to morning dosing reduced both nighttime and 24-h SBP and DBP [108•]. However, bedtime dosing in this population did not decrease daytime SBP and DBP and the morning SBP surge did not differ between morning and bedtime dosing. Similar results were published from post hoc analysis of individuals with type 2 diabetes in the prospective MAPEC study [74]. Additional analysis of the MAPEC cohort demonstrated that dosing of at least one antihypertensive medication at bedtime, particularly those acting to regulate angiotensin II signaling, resulted in not only

improved ABPM control, but also a reduced risk of new-onset diabetes [106••]. Evidence available thus far suggests that nocturnal dosing of medications helps in reduction of nocturnal BP and controlling morning surge in BP and is at least as good as daytime medication for CV outcomes. Studying the antihypertensive effects of medications prescribed at different times of the day holds promise and should be followed through by conducting prospective randomized controlled blinded clinical trials with solid morbidity and mortality outcomes. Such a trial, the Hygia Project—a multicenter study in Spain conducted from 2007 to 2015—aims to extend the current body of knowledge to investigate if treatment-induced changes to ABPM reduce risk of CVD events, stroke, new-onset diabetes, and/or CKD in a primary care setting [191•].

Discussion

Research conducted from 2013 to 2017 generally demonstrates improved 24-h BP profiles, and more dipping BP profiles, with at least one medication taken in the evening. In most cases, these findings persist regardless of medication class or disease comorbidity. The incorporation of nocturnal BP averages as either study inclusion criteria or as a study outcome points to the increased recognition for the need to improve nocturnal BP dipping rather than simply avoiding diurnal BP surges. Among studies that report no difference between morning and evening dosing of antihypertensive medications, none report significant increases of nocturnal hypotension, unwanted side effects, or increased non-adherence to medication schedule. Thus overall, these results suggest that taking medication in the evening should be endorsed in most cases. This decision can be made because of the potential for benefit (especially for nocturnal BP and improved dipping status, and in some cases overall 24-h BP, and in some cases hard clinical CV outcomes), and without increase in harm. However, beyond this general recommendation, it should be noted that in addition to receiving an antihypertensive medication at bedtime, many of the participants in studies that reported improved benefit with nocturnal dosing also continued to receive morning medications. For example, in the MAPEC trial, participants moved one or more drugs to the evening, but continued to take the remainder of their medications in the morning [73]. Additionally, although less transparent, participants in HTN studies with a comorbid disease are likely taking additional non-antihypertensive medications in the morning such as glucagon-like peptide 1 (GLP-1) receptor agonists for the treatment of type 2 diabetes. GLP-1 receptor agonists have been shown to decrease both SBP and DBP [192], thereby potentially impacting BP control independently or synergistically with antihypertensive medications as further discussed below. Therefore, a refined recommendation and simplified general rule may be to split

medication dosing between the evening and morning. Moving forward, chronotherapy as it pertains to HTN could be further advanced by improving study design and developing a clearer understanding of the physiological mechanism(s) that contribute to the cause and effect of altered BP dipping profiles. Both concepts are discussed below.

RCT Study Design

Many of the reviewed studies used small sample sizes despite also applying complicated study designs. As a result, studies may lack sufficient power for firm conclusions and perhaps more importantly are unable to generalize their findings. The latter is particularly the case in terms of racial, ethnic, and gender diversity. This may be a particular concern for Americans, yet of the reviewed studies, only one was conducted in the USA. To that extent, Black compared to White Americans have an earlier incidence of CVD, more difficulty in controlling their HTN, and an increased prevalence of non-dipping BP [193–201]. The racial differences in HTN cannot be attributed to differences in awareness or treatment—reported to be increased among Blacks compared to Whites, nor the use of non-pharmacological therapy, lack of health-insurance, economic barriers, or access to healthcare [194, 202–205]. Furthermore, Black Americans have an increased burden of end-stage renal disease despite the larger prevalence of CKD among White Americans [159, 174–176]. Middle-aged Black compared to White Americans are also at a greater risk of developing type 2 diabetes and have higher BP prior to the development to diabetes [206–208]. The increased prevalence of these traditional CV risk factors in Blacks likely require additional strategies to promote equitable CV outcomes as noted in a 2017 American Heart Association Scientific Statement [209••]. Similarly, women have generally been underrepresented in relation to their burden of disease in RCTs of CVD prevention [210, 211]. As highlighted in a review by Tamargo et al., women present differences in body composition, physiology, pharmacokinetics, and pharmacodynamics that may impact their response to antihypertensive medications [212••]. Women may have different endogenous circadian rhythms compared to men [213, 214]. Although it remains unclear how these differences between genders in circadian rhythms may impact regulators of BP, these differences highlight the need for increased inclusion of women in RCTs in order to better inform evidence-based treatment regimens. In light of these differences, RCTs examining the time of day that antihypertensive medications are administered could benefit from improved study design with clear statements on a priori power calculations and study populations with distributions that more accurately represent their disease prevalence.

Before endorsing the routine administration of antihypertensive medications at night there is also a need for additional RCTs with long-term study outcomes. The largest

prospective, RCT, open-label study outside of the MAPEC trial, the Treatment In Morning versus Evening (TIME) study is currently underway in the UK [215, 216]. The trial is expected to run for 5 years with a primary end point of hospitalization for a non-fatal myocardial infarction, non-fatal stroke, or any vascular death determined by record-linkage. The TIME study (unlike the MAPEC study) has been prospectively powered and complete details of the study's randomization process have been published [216]. Unfortunately, this British-led study may continue to lack the study diversity necessary to generalize global dosing guidelines.

Physiology and Mechanisms of BP Dipping

Despite being a clear target for recent RCTs, the mechanism(s) that contribute to altered BP dipping profiles remain elusive and provide a continual challenge for developing an ideal medication schedule. A clearer understanding of the mechanisms driving the daily rhythms of BP, and ultimately matching classes of medications to the rhythms of their drug target, may result in improved BP control. More precisely, it would seem a promising endeavor to regulate BP to a pattern that not only falls within a specific threshold, but one that mimics the daily variation in BP in healthy subjects. This increased understanding of the interactions between behavior (e.g., sleep-wake cycles, feeding) and circadian rhythms that influence BP regulation and medication bioavailability could ultimately lead to RCTs tailored to underlying circadian physiology rather than just the sleep-wake cycle. The latter is particularly important for HTN patients who work a shift schedule or among patients who experience jetlag or social jetlag [217].

Given that BP and its primary regulators exhibit robust endogenous circadian rhythms [218–221], it follows that antihypertensive medications display a time-dependent chronopharmacokinetic and chronopharmacodynamic profile [222]. Recent developments in the field of chronopharmology are beginning to take these factors into consideration. Analysis of amlodipine, a CCB, revealed daily variations in the pharmacokinetic profile of oral amlodipine with a shorter time to maximum plasma concentration (T_{max}) and greater mean peak plasma concentration (C_{max}) after evening than morning dosing [223]. Both hypertensive and normotensive subjects demonstrated this pattern indicating increased absorption when dosed at night. Additionally, amlodipine had a longer half-life with night compared to morning ingestion. This pharmacokinetic profile correlated with reductions in SBP and heart rate following nighttime dosing, demonstrating a circadian time-dependent pharmacokinetic-pharmacodynamic relationship [223]. Based on the concept that delivery of medications should be synchronized in time to the chronobiology of targeted tissues, several groups have published strategies to engineer new drug delivery systems to appropriately time compound release to match circadian rhythms [224, 225•, 226•, 227].

The etiology of HTN is usually multifactorial because BP regulation is under the control of multiple mechanisms, such that multiple drug therapies are sometimes needed [228]. A meta-analysis consisting of 11,000 patients and 42 clinical trials concluded that BP reduction from combination therapy is approximately five times greater than simply increasing the dose of one drug [229]. This is an important consideration for chronotherapy because the additive effects of medications need to be considered to optimally reduce BP and reduce side effects. Combination therapy in HTN is also beneficial for other comorbid disease outcomes. For instance, ARBs and ACEIs prevent the progression of CKD to a similar degree, but, a combination of the two is significantly more effective at usual doses [230]. The same combination also reduced proteinuria more than either drug alone [231]. Mechanistically, this reduction is likely because of the addition of ARB related to reduction in angiotensin II which is not achieved by ACEI alone [231], suggesting an important synergy between medications. There are also instances where two drugs can help nullify an adverse effect of one drug taken alone. For example, when a combination of aliskiren (renin inhibitor) and hydrochlorothiazide (HCTZ) is used to treat HTN, aliskiren neutralizes the compensatory increase in plasma renin activity induced by HCTZ [232]. Another important consideration is the magnitude and duration of antihypertensive activity with different drugs. For instance, amlodipine (CCB) reduces the BP in a magnitude that is more dependent on the dose; in contrast, an ARB influences the duration, rather than magnitude of antihypertensive activity [233]. Therefore, one could speculate that a CCB would be more effective as a morning dose to reduce the daytime increases in BP induced by physical activity, whereas an ARB might be more effective as an evening medication as it would provide better control over nighttime BP and the morning BP surge. The above mentioned factors and drug interactions are perhaps most relevant in elderly patients with HTN who may be taking multiple medications due to increased comorbid states associated with aging [234].

Conclusions and Future Directions

In the last few years, the area of chronotherapy in HTN has exploded. In general, nighttime administration of antihypertensives improved overall 24-h BP profiles regardless of disease comorbidity and did not cause increased risk, and therefore ought to be seriously considered for management of HTN in the general population as well as in HTN with certain comorbidities. Yet, only the American Diabetic Association has made such a recommendation [235], potentially reflecting further need to conduct prospective randomized studies in large and diverse populations with preexisting comorbidities

allowing for adequate statistical power to perform subgroup analyses. In addition, preclinical studies to ascertain mechanisms by which chronotherapy is beneficial could aid antihypertensive drug design and guidelines for timed administration. The field may further progress by focusing on the mechanistic basis of bedtime medication use rather than simply moving a drug from morning to bedtime dosing. For instance, the mechanisms underlying the increased CV risk due to non-dipping BP are yet unclear. Furthermore, these mechanisms, which may be related to the timing of meal intake, sleep patterns, or endogenous circadian rhythms, may affect BP regulators (e.g., heart, kidney, or vasculature) differentially. The latter may require personalized medicine for individuals, such as shift workers, who often follow atypical sleep and eating patterns or the engineering of medications that optimize bioavailability and the naturalistic rhythms of drug targets.

Compliance with Ethical Standards

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•• Of major importance

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