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Chronotherapy for hypertension

N.P. Bowles[*], **S.S. Thosar**, **M.X. Herzig**, and **S.A. Shea**

Oregon Institute of Occupational Health Sciences, Oregon Health and Sciences University, Portland, OR 97239

Abstract

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. 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. 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

[*]Corresponding author: bowlesn@ohsu.edu, 3181 S.W. Sam Jackson Park Rd. L606, Portland, OR 97239, Tel: 503-494-2541.

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 demonstrate 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.

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 1980's. 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 anti-hypertensive 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: 1) The 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 versus 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 the 1987 to 2012 are briefly discussed immediately below, whereas this review will focus on research published in the 5-year period from 2013–2017. 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/or 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), HTN with a specific comorbid conditions (OSA, chronic kidney disease, diabetes) (n=13), meta-analysis or systematic review (n=5), or chronopharmocolgy (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 ≥3 antihypertensive medications) have improved ambulatory BP control, a lower incidence of CV events, and reduced mortality over a five to six-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, and improves 24-h BP control (82–84). A smaller RCT of ARB, found no significant effects of treatment timings on morning home BP or office BP based (85). However, this study did not include overnight or sleep measures of BP and included use of various other medications concurrently. Furthermore, there was a non-significant (p=0.052) difference in baseline office SBP (mean difference of 5 mmHg), 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 (86).

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 twelve studies (including nine RCTs) that described outcomes of BP (87, 88). In general, studies which 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 which examined populations with treated HTN or with established CVD had no improvements on ABPM regardless of aspirin timing (89–91). However, bedtime administration was correlated with lower morning platelet reactivity (89) 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 (92). 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, 93). 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 (1–2) antihypertensive medications at bedtime compared to the morning resulted in improved 24-h BP control (94). 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 morning surge of SBP as compared to baseline (95). 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 (96). Similarly, a noninferiority clinical trial, which 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 (97). This was the first chronotherapy study to report central aortic BP, which the research group estimated from brachial pulse wave noninvasively 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(98, 99).

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 compliance (80). Yet, despite the long terminal half-life of, for example, the ARB telmisartan (~24-h (100)), 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, 100). In contrast, Ushijima et al. (101), 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 6–9 hours) is taken at bedtime compared to the morning (100, 101). 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 (102). 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 (103). The latter study suggests that for some drug classes in order to obtain ideal pharmacological profiles twice-daily dosing may be required.

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 the morning (104). Thus, regardless of the complexities of the varied studies, the different sizes, study designs and patient groups in the studies, the different degrees of HTN and of non-dipping HTN, it seems possible to make the general conclusion that evening dosing of anti-hypertensive 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 (105). 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 (105, 106). 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 a comorbid conditions may greatly alter (attenuate or enhance) the effects of anti-hypertensive medications (107). Adding the dimension of timed medication therefore increases complexity but, with 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, and sex and obesity status (77, 108–111). Prospective epidemiological studies have demonstrated a robust dose-dependent association between OSA at baseline and the prevalence and incidence of HTN (112–114). Continuous positive airway pressure (CPAP) therapy can lower the risk of HTN (115). 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 (116–118) - levels not sufficient to bring HTN under control nor large enough to reduce risk of stroke or coronary heart disease (119). Treatment with antihypertensive drugs yields larger long-lasting

reductions in BP in populations with OSA who do not use CPAP (120–122), but, these drugs fail to generate the reductions obtained in HTN patients without OSA (123). Moreover, standard antihypertensive treatment does not bring BP under control in people with severe OSA (124) and requires the addition of CPAP to achieve reductions in both daytime and nocturnal SBP (125). Of further concern, non-dipping BP occurs in 48–84% of patients with OSA (126–129), possibly related to the associated hypoxia and hypercapnia induced sympathetic activity and subsequent vasoconstriction (130). 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 (131). These maladaptations may actually account for improved efficacy of β−1 adrenergic blockers in older hypertensive OSA patients (132).

Nocturnal medication dosing may improve BP control in the absence of CPAP compliance in patients with nocturnal HTN (133), non-dipping BP (134–136), 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 (137). 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 (138). 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 (139). 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 (140) 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 cross-over study comparing the effect of nighttime dosing of a CCB versus a non-selective β1/2-adrenergic receptor blocker (141). 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 (142). 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 results 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 (143). 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 (144–147). CKD is often classified into five stages using thresholds of serum creatinine, eGFR and/or evidence of structural renal changes such as proteinuria (148). 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 3–5, 10.6% (149). HTN is the most common comorbidity in patients with CKD with the prevalence of HTN increasing with declining renal function (150, 151). Although elevated BP can occur as a result of CKD, increased BP is also a risk factor for severe CKD (152). Therefore, control of HTN is a medical priority in the management of CKD and offers an opportunity to slow further loss of kidney function (153, 154). Additionally, optimal HTN control in CKD helps prevent end organ damage, notably in the heart and brain (153, 155, 156). ABPM in patients with CKD often reveals elevated nocturnal BP (157, 158) with non-dipping increasing risk of total mortality or end stage renal disease (159). 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 (160, 161), reduce non-dipping (161), and prevent adverse CV events and mortality (160). Table 2 summarizes 4 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 (162). Thus, the prevalence of non-dipping 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 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; (163). 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 (164). 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. We note that various regulators of renal function exhibit circadian fluctuations including glomerular filtration rate in humans (165) as well as sodium excretion and renal blood flood in rodent models (166). 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 (167–169). 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 anti-hypertensive 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 (170). The study found only modest nonsignificant 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 HTN. 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 (151, 171–173).

Diabetes—Hypertension is often a comorbid condition with both type 1 and type 2 diabetes (174). 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 (174, 175). Patients with type 2 diabetes usually exhibit overt HTN upon initial detection of microalbuminuria (176). 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 (177). 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 dipping with type 1 diabetes and microalbuminuria could be the result of a lack of sympathetic withdrawal during sleep (177–182). Prospectively it has been demonstrated that an increase of nocturnal SBP over the course of five or more years can precede the development of microalbuminuria (183). 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 (174)) with each disease state possibly exacerbating the other. For instance, hyperinsulinemia increases sympathetic activity, and hyperglycemia activates the renin-angiotensin system (174), which itself may be a mechanism for increased risk of diabetes in HTN (184, 185). Further, individuals with type 2 diabetes are more likely to exhibit a non-dipping BP or reverse dipping BP phenotype (186, 187). Thus, chonotherapeutic 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 (188). 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 (189). 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 (190). 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 participants of 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 (191). 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 2007–2015, 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 (192).

Discussion

Research conducted from 2013–2017 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 agonist have been shown to decrease both SBP and DBP (193), 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 United States. 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 (194–202). The racial differences in HTN control 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 (195, 203–206). Furthermore, Black Americans have an increased burden of end-stage renal disease despite the larger prevalence of CKD among White Americans (151, 171–173). 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 (207–209). 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 (210). Similarly, women have generally been underrepresented in relation to their burden of disease in RCTs of CVD prevention (211, 212). 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 (213). Women may have different endogenous circadian rhythms compared to men (214, 215). 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 United Kingdom (216, 217). The trial is expected to run for five 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 (217). 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 promising to 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 (218).

Given that BP and its primary regulators exhibit robust endogenous circadian rhythms (219–222) it follows that antihypertensive medications display a time-dependent chronopharmacokinetic and chronopharmacodynamic profile (223). 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 (224). 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 (224). 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 (225–228).

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 (229). 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 (230). 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 (231). The same combination also reduced proteinurea more than either drug alone (232). Mechanistically, this reduction is likely because the addition of ARB related to reduction in angiotensin II which is not achieved by ACEI alone (232), 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 (233). 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 (234). Therefore, one could speculate that a CCB would be more effective as a morning dose to reduce the day time 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 (235).

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 (236), 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Literature cited:

1. Singh BN. Effects of food on clinical pharmacokinetics. Clinical pharmacokinetics. 1999;37(3): 213–55. [PubMed: 10511919]
2. Lemmer B Temporal aspects in the effects of cardiovascular active drugs in man. Chronopharmacology—Cellular and Biochemical Interactions. 1989:525–42.
3. Rumble RH, Roberts MS, Denton MJ. Effects of posture and sleep on the pharmacokinetics of paracetamol (acetaminophen) and its metabolites. Clinical pharmacokinetics. 1991;20(2):167–73. [PubMed: 2029807]
4. Baraldo M The influence of circadian rhythms on the kinetics of drugs in humans. Expert Opin Drug Metab Toxicol. 2008;4(2):175–92. [PubMed: 18248311]
5. Thosar SS, Butler MP, Shea SA. Role of the circadian system in cardiovascular disease. The Journal of Clinical Investigation. 2018;128(6):2157–67. [PubMed: 29856365]
6. Natesh R, Schwager SL, Evans HR, Sturrock ED, Acharya KR. Structural details on the binding of antihypertensive drugs captopril and enalaprilat to human testicular angiotensin I-converting enzyme. Biochemistry. 2004;43(27):8718–24. [PubMed: 15236580]
7. Morris CJ, Purvis TE, Mistretta J, Hu K, Scheer FA. Circadian misalignment increases C-reactive protein and blood pressure in chronic shift workers. Journal of biological rhythms. 2017;32(2):154–64. [PubMed: 28347188]
8. Zhang R, Lahens NF, Ballance HI, Hughes ME, Hogenesch JB. A circadian gene expression atlas in mammals: implications for biology and medicine. Proc Natl Acad Sci U S A. 2014;111(45):16219–24. [PubMed: 25349387]
9. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. Executive Summary: Heart Disease and Stroke Statistics—2014 Update A Report From the American Heart Association. Circulation. 2014;129(3):399–410. [PubMed: 24446411]
10. Degaute J-P, Van De Borne P, Linkowski P, Van Cauter E. Quantitative analysis of the 24-hour blood pressure and heart rate patterns in young men. Hypertension. 1991;18(2):199–210. [PubMed: 1885228]
11. Muller JE, Ludmer PL, Willich SN, Tofler GH, Aylmer G, Klangos I, et al. Circadian variation in the frequency of sudden cardiac death. Circulation. 1987;75(1):131–8. [PubMed: 3791599]
12. Whelton PK, Carey RM, Aronow WS, Casey DE Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017.
13. Burgess HJ, Trinder J, Kim Y, Luke D. Sleep and circadian influences on cardiac autonomic nervous system activity. Am J Physiol. 1997;273(4 Pt 2):H1761–8. [PubMed: 9362241]
14. Dodt C, Breckling U, Derad I, Fehm HL, Born J. Plasma epinephrine and norepinephrine concentrations of healthy humans associated with nighttime sleep and morning arousal. Hypertension. 1997;30(1 Pt 1):71–6. [PubMed: 9231823]
15. Brotman DJ, Davidson MB, Boumitri M, Vidt DG. Impaired diurnal blood pressure variation and all-cause mortality. American journal of hypertension. 2008;21(1):92–7. [PubMed: 18091750]
16. Grimaldi D, Provini F, Calandra-Buonaura G, Barletta G, Cecere A, Pierangeli G, et al. Cardiovascular-sleep interaction in drug-naive patients with essential grade I hypertension. Chronobiol Int. 2013;30(1–2):31–42. [PubMed: 23072288]
17. O'Brien E, Sheridan J, O'Malley K. Dippers and non-dippers. The Lancet. 1988;332(8607):397.
18. Kario K, Shimada K. Risers and extreme-dippers of nocturnal blood pressure in hypertension: antihypertensive strategy for nocturnal blood pressure. Clin Exp Hypertens. 2004;26(2):177–89. [PubMed: 15038628]
19. Birkenhager AM, van den Meiracker AH. Causes and consequences of a non-dipping blood pressure profile. Neth J Med. 2007;65(4):127–31. [PubMed: 17452760]
20. Fagard RH, Thijs L, Staessen JA, Clement DL, De Buyzere ML, De Bacquer DA. Night-day blood pressure ratio and dipping pattern as predictors of death and cardiovascular events in hypertension. J Hum Hypertens. 2009;23(10):645–53. [PubMed: 19225527]

21. Salles GF, Reboldi G, Fagard RH, Cardoso CR, Pierdomenico SD, Verdecchia P, et al. Prognostic Effect of the Nocturnal Blood Pressure Fall in Hypertensive Patients: The Ambulatory Blood Pressure Collaboration in Patients With Hypertension (ABC-H) Meta-Analysis. Hypertension. 2016;67(4):693–700. [PubMed: 26902495]
22. Ermiş N, Otlu YÖ, Afşin A, Hidayet Ş, Açıkgöz N, Cansel M, et al. Comparison of left atrial volume and function in non-dipper versus dipper hypertensives: A real-time three-dimensional echocardiography study. Anatolian journal of cardiology. 2016;16(6):428. [PubMed: 27182617]
23. Acar G, Bulut M, Arslan K, Alizade E, Ozkan B, Alici G, et al. Comparison of left atrial mechanical function in nondipper versus dipper hypertensive patients: a speckle tracking study. Echocardiography. 2013;30(2):164–70. [PubMed: 23167459]
24. Tadic M, Cuspidi C, Pencic B, Ivanovic B, Scepanovic R, Marjanovic T, et al. Circadian blood pressure pattern and right ventricular and right atrial mechanics: A two- and three-dimensional echocardiographic study. J Am Soc Hypertens. 2014;8(1):45–53. [PubMed: 24016835]
25. Liu M, Takahashi H, Morita Y, Maruyama S, Mizuno M, Yuzawa Y, et al. Non-dipping is a potent predictor of cardiovascular mortality and is associated with autonomic dysfunction in haemodialysis patients. Nephrology Dialysis Transplantation. 2003;18(3):563–9.
26. Timio M, Venanzi S, Lolli S, Lippi G, Verdura C, Monarca C, et al. " Non-dipper" hypertensive patients and progressive renal insufficiency: a 3-year longitudinal study. Clinical nephrology. 1995;43(6):382–7. [PubMed: 7554522]
27. Ukkola O, Vasunta R-L, Kesäniemi YA. Non-dipping pattern in ambulatory blood pressure monitoring is associated with metabolic abnormalities in a random sample of middle-aged subjects. Hypertension Research. 2009;32(11):1022–7. [PubMed: 19730439]
28. Suzuki M, Guilleminault C, Otsuka K, Shiomi T. Blood pressure" dipping" and" non-dipping" in obstructive sleep apnea syndrome patients. Sleep. 1996;19(5):382–7. [PubMed: 8843529]
29. Wang C, Zhang J, Liu X, Li C, Ye Z, Peng H, et al. Reversed dipper blood-pressure pattern is closely related to severe renal and cardiovascular damage in patients with chronic kidney disease. PLoS One. 2013;8(2):e55419. [PubMed: 23393577]
30. Yan B, Peng L, Han D, Sun L, Dong Q, Yang P, et al. Blood pressure reverse-dipping is associated with early formation of carotid plaque in senior hypertensive patients. Medicine (Baltimore). 2015;94(10):e604. [PubMed: 25761180]
31. Yan B, Peng L, Dong Q, Zheng F, Yang P, Sun L, et al. Reverse-dipper pattern of blood pressure may predict lacunar infarction in patients with essential hypertension. Eur J Neurol. 2015;22(6): 1022–5. [PubMed: 25614275]
32. Huang Y, Mai W, Hu Y, Wu Y, Song Y, Qiu R, et al. Poor sleep quality, stress status, and sympathetic nervous system activation in nondipping hypertension. Blood pressure monitoring. 2011;16(3):117–23. [PubMed: 21562453]
33. Schillaci G, Verdecchia P, Borgioni C, Ciucci A, Gattobigio R, Sacchi N, et al. Predictors of diurnal blood pressure changes in 2042 subjects with essential hypertension. J Hypertens. 1996;14(10):1167–73. [PubMed: 8906514]
34. Pedulla M, Silvestri R, Lasco A, Mento G, Lanuzza B, Sofia L, et al. Sleep structure in essential hypertensive patients: differences between dippers and non-dippers. Blood Press. 1995;4(4):232–7. [PubMed: 7496562]
35. Huang Y, Mai W, Cai X, Hu Y, Song Y, Qiu R, et al. The effect of zolpidem on sleep quality, stress status, and nondipping hypertension. Sleep Med. 2012;13(3):263–8. [PubMed: 22153779]
36. Smolensky MH, Hermida RC, Ayala DE, Tiseo R, Portaluppi F. Administration-time-dependent effects of blood pressure-lowering medications: basis for the chronotherapy of hypertension. Blood Press Monit. 2010;15(4):173–80. [PubMed: 20571367]
37. Pickering TG, Levenstein M, Walmsley P. Nighttime dosing of doxazosin has peak effect on morning ambulatory blood pressure. Results of the HALT Study. Hypertension and Lipid Trial Study Group. Am J Hypertens. 1994;7(9 Pt 1):844–7. [PubMed: 7811444]
38. Lemmer B, Nold G, Behne S, Kaiser R. Chronopharmacokinetics and cardiovascular effects of nifedipine. Chronobiol Int. 1991;8(6):485–94. [PubMed: 1799930]

39. Hermida RC, Calvo C, Ayala DE, Dominguez MJ, Covelo M, Fernandez JR, et al. Administration-time-dependent effects of doxazosin GITS on ambulatory blood pressure of hypertensive subjects. Chronobiol Int. 2004;21(2):277–96. [PubMed: 15332347]
40. Langner B, Lemmer B. Circadian changes in the pharmacokinetics and cardiovascular effects of oral propranolol in healthy subjects. Eur J Clin Pharmacol. 1988;33(6):619–24. [PubMed: 3366165]
41. Palatini P, Mos L, Motolese M, Mormino P, Del Torre M, Varotto L, et al. Effect of evening versus morning benazepril on 24-hour blood pressure: a comparative study with continuous intraarterial monitoring. Int J Clin Pharmacol Ther Toxicol. 1993;31(6):295–300. [PubMed: 8335427]
42. Witte K, Weisser K, Neubeck M, Mutschler E, Lehmann K, Hopf R, et al. Cardiovascular effects, pharmacokinetics, and converting enzyme inhibition of enalapril after morning versus evening administration. Clin Pharmacol Ther. 1993;54(2):177–86. [PubMed: 8394796]
43. Morgan T, Anderson A, Jones E. The effect on 24 h blood pressure control of an angiotensin converting enzyme inhibitor (perindopril) administered in the morning or at night. J Hypertens. 1997;15(2):205–11. [PubMed: 9469797]
44. Palatini P Can an angiotensin-converting enzyme inhibitor with a short half-life effectively lower blood pressure for 24 hours? Am Heart J. 1992;123(5):1421–5. [PubMed: 1575169]
45. Palatini P, Racioppa A, Raule G, Zaninotto M, Penzo M, Pessina AC. Effect of timing of administration on the plasma ACE inhibitory activity and the antihypertensive effect of quinapril. Clin Pharmacol Ther. 1992;52(4):378–83. [PubMed: 1330398]
46. Myburgh DP, Verho M, Botes JH, Erasmus TP, Luus HG. 24-hour blood pressure control with ramipril: comparison of once-daily morning and evening administration. Current therapeutic research. 1995;56(12):1298–306.
47. Kuroda T, Kario K, Hoshide S, Hashimoto T, Nomura Y, Saito Y, et al. Effects of bedtime vs. morning administration of the long-acting lipophilic angiotensin-converting enzyme inhibitor trandolapril on morning blood pressure in hypertensive patients. Hypertens Res. 2004;27(1):15–20. [PubMed: 15055251]
48. Middeke M, Kluglich M, Holzgreve H. Chronopharmacology of captopril plus hydrochlorothiazide in hypertension: morning versus evening dosing. Chronobiol Int. 1991;8(6):506–10. [PubMed: 1799931]
49. Kohno I, Ijiri H, Takusagawa M, Yin D, Sano S, Ishihara T, et al. Effect of imidapril in dipper and nondipper hypertensive patients: comparison between morning and evening administration. Chronobiology international. 2000;17(2):209–19. [PubMed: 10757465]
50. Hermida RC, Calvo C, Ayala DE, Dominguez MJ, Covelo M, Fernandez JR, et al. Administration time-dependent effects of valsartan on ambulatory blood pressure in hypertensive subjects. Hypertension. 2003;42(3):283–90. [PubMed: 12874091]
51. Hermida RC, Calvo C, Ayala DE, Mojon A, Rodriguez M, Chayan L, et al. Administration time-dependent effects of valsartan on ambulatory blood pressure in elderly hypertensive subjects. Chronobiol Int. 2005;22(4):755–76. [PubMed: 16147905]
52. Hermida RC, Ayala DE, Chayan L, Mojon A, Fernandez JR. Administration-time-dependent effects of olmesartan on the ambulatory blood pressure of essential hypertension patients. Chronobiol Int. 2009;26(1):61–79. [PubMed: 19142758]
53. Hermida RC, Ayala DE, Fernandez JR, Calvo C. Comparison of the efficacy of morning versus evening administration of telmisartan in essential hypertension. Hypertension. 2007;50(4):715–22. [PubMed: 17635851]
54. Hermida RC, Calvo C, Ayala DE, Fernandez JR, Covelo M, Mojon A, et al. Treatment of non-dipper hypertension with bedtime administration of valsartan. J Hypertens. 2005;23(10):1913–22. [PubMed: 16148616]
55. Hermida RC, Ayala DE, Mojon A, Chayan L, Dominguez MJ, Fontao MJ, et al. Comparison of the effects on ambulatory blood pressure of awakening versus bedtime administration of torasemide in essential hypertension. Chronobiol Int. 2008;25(6):950–70. [PubMed: 19005898]
56. Okeahialam BN, Ohihoin EN, Ajuluchukwu JN. Diuretic drugs benefit patients with hypertension more with night-time dosing. Ther Adv Drug Saf. 2012;3(6):273–8. [PubMed: 25083241]

57. Nold G, Strobel G, Lemmer B. Morning versus evening amlodipine treatment: effect on circadian blood pressure profile in essential hypertensive patients. Blood Press Monit. 1998;3(1):17–25. [PubMed: 10212327]
58. Qiu YG, Chen JZ, Zhu JH, Yao XY. Differential effects of morning or evening dosing of amlodipine on circadian blood pressure and heart rate. Cardiovasc Drugs Ther. 2003;17(4):335–41. [PubMed: 14618095]
59. Kitahara Y, Saito F, Akao M, Fujita H, Takahashi A, Taguchi H, et al. Effect of morning and bedtime dosing with cilnidipine on blood pressure, heart rate, and sympathetic nervous activity in essential hypertensive patients. J Cardiovasc Pharmacol. 2004;43(1):68–73. [PubMed: 14668570]
60. Kohno I, Iwasaki H, Okutani M, Mochizuki Y, Sano S, Satoh Y, et al. Administration-time-dependent effects of diltiazem on the 24-hour blood pressure profile of essential hypertension patients. Chronobiol Int. 1997;14(1):71–84. [PubMed: 9042553]
61. Fogari R, Malacco E, Tettamanti F, Gnemmi AE, Milani M. Evening vs morning isradipine sustained release in essential hypertension: a double-blind study with 24 h ambulatory monitoring. Br J Clin Pharmacol. 1993;35(1):51–4. [PubMed: 8448068]
62. Portaluppi F, Vergnani L, Manfredini R, degli Uberti EC, Fersini C. Time-dependent effect of isradipine on the nocturnal hypertension in chronic renal failure. Am J Hypertens. 1995;8(7):719–26. [PubMed: 7546498]
63. Greminger P, Suter PM, Holm D, Kobelt R, Vetter W. Morning versus evening administration of nifedipine gastrointestinal therapeutic system in the management of essential hypertension. Clin Investig. 1994;72(11):864–9.
64. White WB, Mansoor GA, Pickering TG, Vidt DG, Hutchinson HG, Johnson RB, et al. Differential effects of morning and evening dosing of nisoldipine ER on circadian blood pressure and heart rate. Am J Hypertens. 1999;12(8 Pt 1):806–14. [PubMed: 10480474]
65. Umeda T, Naomi S, Iwaoka T, Inoue J, Sasaki M, Ideguchi Y, et al. Timing for administration of an antihypertensive drug in the treatment of essential hypertension. Hypertension. 1994;23(1 Suppl):I211–4. [PubMed: 8282361]
66. Hermida RC, Calvo C, Ayala DE, Lopez JE, Rodriguez M, Chayan L, et al. Dose- and administration time-dependent effects of nifedipine gits on ambulatory blood pressure in hypertensive subjects. Chronobiol Int. 2007;24(3):471–93. [PubMed: 17612946]
67. Meilhac B, Mallion JM, Carre A, Chanudet X, Poggi L, Gosse P, et al. Study of the influence of the time of administration on the antihypertensive effect and nitrendipine tolerance in mild to moderate essential hypertensive patients. Value of ambulatory recording of blood pressure on 24 hours. Therapie. 1992;47(3):205–10. [PubMed: 1295122]
68. Hermida RC, Ayala DE, Mojon A, Alonso I, Fernandez JR. Reduction of morning blood pressure surge after treatment with nifedipine GITS at bedtime, but not upon awakening, in essential hypertension. Blood pressure monitoring. 2009;14(4):152–9. [PubMed: 19543080]
69. Trialists'Collaboration A. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. Bmj. 2002;324(7329):71–86. [PubMed: 11786451]
70. Hermida RC, Ayala DE, Calvo C, López JE. Aspirin administered at bedtime, but not on awakening, has an effect on ambulatory blood pressure in hypertensive patients. Journal of the American College of Cardiology. 2005;46(6):975–83. [PubMed: 16168278]
71. Ayala DE, Hermida RC. Sex differences in the administration-time-dependent effects of low-dose aspirin on ambulatory blood pressure in hypertensive subjects. Chronobiol Int. 2010;27(2):345–62. [PubMed: 20370474]
72. Hermida RC, Ayala DE, Mojon A, Fernandez JR. Ambulatory blood pressure control with bedtime aspirin administration in subjects with prehypertension. Am J Hypertens. 2009;22(8):896–903. [PubMed: 19407805]
73. Hermida RC, Ayala DE, Mojon A, Fernandez JR. Influence of circadian time of hypertension treatment on cardiovascular risk: results of the MAPEC study. Chronobiol Int. 2010;27(8):1629–51. [PubMed: 20854139]

74. Hermida RC, Ayala DE, Mojon A, Fernandez JR. Influence of time of day of blood pressure-lowering treatment on cardiovascular risk in hypertensive patients with type 2 diabetes. Diabetes Care. 2011;34(6):1270–6. [PubMed: 21617110]

75. Hermida RC, Ayala DE, Fernandez JR, Calvo C. Chronotherapy improves blood pressure control and reverts the nondipper pattern in patients with resistant hypertension. Hypertension. 2008;51(1):69–76. [PubMed: 17968001]

76. Neldam S, Dahlof B, Oigman W, Schumacher H. Early combination therapy with telmisartan plus amlodipine for rapid achievement of blood pressure goals. Int J Clin Pract. 2013;67(9):843–52. [PubMed: 23952464]

77. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr., et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42(6):1206–52. [PubMed: 14656957]

78. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2007;25(6):1105–87. [PubMed: 17563527]

79. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. BMJ. 2003;326(7404):1427. [PubMed: 12829555]

80. Saini SD, Schoenfeld P, Kaulback K, Dubinsky MC. Effect of medication dosing frequency on adherence in chronic diseases. Am J Manag Care. 2009;15(6):e22–33. [PubMed: 19514806]

81. Ayala DE, Hermida RC, Mojon A, Fernandez JR. Cardiovascular risk of resistant hypertension: dependence on treatment-time regimen of blood pressure-lowering medications. Chronobiol Int. 2013;30(1–2):340–52. [PubMed: 23077973]

82. Hermida RC, Rios MT, Crespo JJ, Moya A, Dominguez-Sardina M, Otero A, et al. Treatment-time regimen of hypertension medications significantly affects ambulatory blood pressure and clinical characteristics of patients with resistant hypertension. Chronobiol Int. 2013;30(1–2):192–206. [PubMed: 23098160]

83. Hermida RC, Ayala DE, Crespo JJ, Mojon A, Chayan L, Fontao MJ, et al. Influence of age and hypertension treatment-time on ambulatory blood pressure in hypertensive patients. Chronobiol Int. 2013;30(1–2):176–91. [PubMed: 23077974]

84. Santiago LM, Pereira C, Botas P, Simoes AR, Carvalho R, Pimenta G, et al. Hypertensive patients in a general practice setting: comparative analysis between controlled and uncontrolled hypertension. Rev Port Cardiol. 2014;33(7–8):419–24. [PubMed: 25062612]

85. Mori H, Yamamoto H, Ukai H, Yuasa S, Nakajima K, Mikawa T, et al. Comparison of effects of angiotensin II receptor blocker on morning home blood pressure and cardiorenal protection between morning administration and evening administration in hypertensive patients: the COMPATIBLE study. Hypertens Res. 2013;36(3):202–7. [PubMed: 23013888]

86. Smolensky MH, Hermida RC, Portaluppi F. Comparison of the efficacy of morning versus evening administration of olmesartan in uncomplicated essential hypertension. Chronobiology international. 2007;24(1):171–81. [PubMed: 17364587]

87. Bem D, Dretzke J, Stevens S, Lordkipanidze M, Hodgkinson J, Bayliss S, et al. Investigating the effectiveness of different aspirin dosing regimens and the timing of aspirin intake in primary and secondary prevention of cardiovascular disease: protocol for a systematic review. Syst Rev. 2015;4:88. [PubMed: 26088608]

88. Bem D, Lordkipanidze M, Hodgkinson J, Stevens S, Bayliss S, Moore D, et al. The Effects of Different Aspirin Dosing Frequencies and the Timing of Aspirin Intake in Primary and Secondary Prevention of Cardiovascular Disease: A Systematic Review. Clin Pharmacol Ther. 2016;100(5):500–12. [PubMed: 27449968]

89. Bonten TN, Snoep JD, Assendelft WJ, Zwaginga JJ, Eikenboom J, Huisman MV, et al. Time-dependent effects of aspirin on blood pressure and morning platelet reactivity: a randomized cross-over trial. Hypertension. 2015;65(4):743–50. [PubMed: 25691622]

90. Lafeber M, Grobbee DE, Schrover IM, Thom S, Webster R, Rodgers A, et al. Comparison of a morning polypill, evening polypill and individual pills on LDL-cholesterol, ambulatory blood

pressure and adherence in high-risk patients; a randomized crossover trial. Int J Cardiol. 2015;181:193–9. [PubMed: 25528311]

91. Suomela I, Varis J, Kantola I. The Antihypertensive Effect of ASA Lasts Less than 24 Hours? World Journal of Cardiovascular Diseases. 2015;5(03):62.
92. Ridker PM, Manson JE, Buring JE, Muller JE, Hennekens CH. Circadian variation of acute myocardial infarction and the effect of low-dose aspirin in a randomized trial of physicians. Circulation. 1990;82(3):897–902. [PubMed: 2203556]
93. Krousel-Wood M, Thomas S, Muntner P, Morisky D. Medication adherence: a key factor in achieving blood pressure control and good clinical outcomes in hypertensive patients. Curr Opin Cardiol. 2004;19(4):357–62. [PubMed: 15218396]
94. Farah R, Makhoul N, Arraf Z, Khamisy-Farah R. Switching therapy to bedtime for uncontrolled hypertension with a nondipping pattern: a prospective randomized-controlled study. Blood Press Monit. 2013;18(4):227–31. [PubMed: 23660686]
95. Huangfu W, Duan P, Xiang D, Gao R. Administration time-dependent effects of combination therapy on ambulatory blood pressure in hypertensive subjects. Int J Clin Exp Med. 2015;8(10): 19156–61. [PubMed: 26770548]
96. Kario K, Hoshide S, Uchiyama K, Yoshida T, Okazaki O, Noshiro T, et al. Dose Timing of an Angiotensin II Receptor Blocker/Calcium Channel Blocker Combination in Hypertensive Patients With Paroxysmal Atrial Fibrillation. J Clin Hypertens (Greenwich). 2016;18(10):1036–44. [PubMed: 26989846]
97. Fujiwara T, Hoshide S, Yano Y, Kanegae H, Kario K. Comparison of morning vs bedtime administration of the combination of valsartan/amlodipine on nocturnal brachial and central blood pressure in patients with hypertension. J Clin Hypertens (Greenwich). 2017.
98. Weycker D, Keskinaslan A, Levy DG, Edelsberg J, Kartashov A, Oster G. Effectiveness of add-on therapy with amlodipine in hypertensive patients receiving valsartan. Blood pressure. 2008;17(sup2):5–12. [PubMed: 18568686]
99. Allemann Y, Fraile B, Lambert M, Barbier M, Ferber P, Izzo JL. Efficacy of the combination of amlodipine and valsartan in patients with hypertension uncontrolled with previous monotherapy: The Exforge in Failure after Single Therapy (EX-FAST) study. The Journal of Clinical Hypertension. 2008;10(3):185–94. [PubMed: 18326958]
100. Oparil S Newly emerging pharmacologic differences in angiotensin II receptor blockers. Am J Hypertens. 2000;13(1 Pt 2):18S–24S. [PubMed: 10678284]
101. Ushijima K, Nakashima H, Shiga T, Harada K, Ishikawa S, Ioka T, et al. Different chronotherapeutic effects of valsartan and olmesartan in non-dipper hypertensive patients during valsartan treatment at morning. J Pharmacol Sci. 2015;127(1):62–8. [PubMed: 25704020]
102. Zappe DH, Crikelair N, Kandra A, Palatini P. Time of administration important? Morning versus evening dosing of valsartan. J Hypertens. 2015;33(2):385–92. [PubMed: 25259546]
103. Szauder I, Csajagi E, Major Z, Pavlik G, Ujhelyi G. Treatment of Hypertension: Favourable Effect of the Twice-Daily Compared to the Once-Daily (Evening) Administration of Perindopril and Losartan. Kidney Blood Press Res. 2015;40(4):374–85. [PubMed: 26160625]
104. Roush GC, Fapohunda J, Kostis JB. Evening dosing of antihypertensive therapy to reduce cardiovascular events: a third type of evidence based on a systematic review and meta-analysis of randomized trials. J Clin Hypertens (Greenwich). 2014;16(8):561–8. [PubMed: 25039609]
105. Wong ND, Lopez VA, L'Italien G, Chen R, Kline SE, Franklin SS. Inadequate control of hypertension in US adults with cardiovascular disease comorbidities in 2003–2004. Arch Intern Med. 2007;167(22):2431–6. [PubMed: 18071164]
106. Johnson ML, Pietz K, Battleman DS, Beyth RJ. Prevalence of comorbid hypertension and dyslipidemia and associated cardiovascular disease. Am J Manag Care. 2004;10(12):926–32. [PubMed: 15617368]
107. Elliott WJ. Drug interactions and drugs that affect blood pressure. The Journal of Clinical Hypertension. 2006;8(10):731–7. [PubMed: 17028488]
108. Lavie P, Herer P, Hoffstein V. Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study. BMJ. 2000;320(7233):479–82. [PubMed: 10678860]

109. Strollo PJ Jr., Rogers RM. Obstructive sleep apnea. The New England journal of medicine. 1996;334(2):99–104. [PubMed: 8531966]
110. Hla KM, Young TB, Bidwell T, Palta M, Skatrud JB, Dempsey J. Sleep apnea and hypertension. A population-based study. Ann Intern Med. 1994;120(5):382–8. [PubMed: 8304655]
111. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA. 2000;283(14):1829–36. [PubMed: 10770144]
112. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. The New England journal of medicine. 2000;342(19): 1378–84. [PubMed: 10805822]
113. Marin JM, Agusti A, Villar I, Forner M, Nieto D, Carrizo SJ, et al. Association between treated and untreated obstructive sleep apnea and risk of hypertension. JAMA. 2012;307(20):2169–76. [PubMed: 22618924]
114. Barbe F, Duran-Cantolla J, Sanchez-de-la-Torre M, Martinez-Alonso M, Carmona C, Barcelo A, et al. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. JAMA. 2012;307(20):2161–8. [PubMed: 22618923]
115. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. Proc Am Thorac Soc. 2008;5(2):173–8. [PubMed: 18250209]
116. Guo J, Sun Y, Xue LJ, Huang ZY, Wang YS, Zhang L, et al. Effect of CPAP therapy on cardiovascular events and mortality in patients with obstructive sleep apnea: a meta-analysis. Sleep Breath. 2016;20(3):965–74. [PubMed: 26873722]
117. Hu X, Fan J, Chen S, Yin Y, Zrenner B. The role of continuous positive airway pressure in blood pressure control for patients with obstructive sleep apnea and hypertension: a meta-analysis of randomized controlled trials. J Clin Hypertens (Greenwich). 2015;17(3):215–22. [PubMed: 25582849]
118. Schein AS, Kerkhoff AC, Coronel CC, Plentz RD, Sbruzzi G. Continuous positive airway pressure reduces blood pressure in patients with obstructive sleep apnea; a systematic review and meta-analysis with 1000 patients. J Hypertens. 2014;32(9):1762–73. [PubMed: 24979300]
119. Lawes CM, Rodgers A, Bennett DA, Parag V, Suh I, Ueshima H, et al. Blood pressure and cardiovascular disease in the Asia Pacific region. J Hypertens. 2003;21(4):707–16. [PubMed: 12658016]
120. Diogo LN, Monteiro EC. The efficacy of antihypertensive drugs in chronic intermittent hypoxia conditions. Front Physiol. 2014;5:361. [PubMed: 25295010]
121. Pepin JL, Tamisier R, Barone-Rochette G, Launois SH, Levy P, Baguet JP. Comparison of continuous positive airway pressure and valsartan in hypertensive patients with sleep apnea. Am J Respir Crit Care Med. 2010;182(7):954–60. [PubMed: 20522795]
122. Kasai T, Bradley TD, Friedman O, Logan AG. Effect of intensified diuretic therapy on overnight rostral fluid shift and obstructive sleep apnoea in patients with uncontrolled hypertension. J Hypertens. 2014;32(3):673–80. [PubMed: 24284499]
123. Thunstrom E, Manhem K, Rosengren A, Peker Y. Blood Pressure Response to Losartan and Continuous Positive Airway Pressure in Hypertension and Obstructive Sleep Apnea. Am J Respir Crit Care Med. 2016;193(3):310–20. [PubMed: 26414380]
124. Walia HK, Li H, Rueschman M, Bhatt DL, Patel SR, Quan SF, et al. Association of severe obstructive sleep apnea and elevated blood pressure despite antihypertensive medication use. J Clin Sleep Med. 2014;10(8):835–43. [PubMed: 25126027]
125. Varounis C, Katsi V, Kallikazaros IE, Tousoulis D, Stefanadis C, Parissis J, et al. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: a systematic review and meta-analysis. Int J Cardiol. 2014;175(1):195–8. [PubMed: 24841834]
126. Nabe B, Lies A, Pankow W, Kohl FV, Lohmann FW. Determinants of circadian blood pressure rhythm and blood pressure variability in obstructive sleep apnoea. J Sleep Res. 1995;4(S1):97–101. [PubMed: 10607183]
127. Suzuki M, Guilleminault C, Otsuka K, Shiomi T. Blood pressure “dipping” and “non-dipping” in obstructive sleep apnea syndrome patients. Sleep. 1996;19(5):382–7. [PubMed: 8843529]

128. Lavie P, Yoffe N, Berger I, Peled R. The relationship between the severity of sleep apnea syndrome and 24-h blood pressure values in patients with obstructive sleep apnea. Chest. 1993;103(3):717–21. [PubMed: 8449057]

129. Portaluppi F, Provini F, Cortelli P, Plazzi G, Bertozzi N, Manfredini R, et al. Undiagnosed sleep-disordered breathing among male nondippers with essential hypertension. J Hypertens. 1997;15(11):1227–33. [PubMed: 9383171]

130. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest. 1995;96(4):1897–904. [PubMed: 7560081]

131. Brooks D, Horner RL, Kozar LF, Render-Teixeira CL, Phillipson EA. Obstructive sleep apnea as a cause of systemic hypertension. Evidence from a canine model. The Journal of clinical investigation. 1997;99(1):106–9. [PubMed: 9011563]

132. Ziegler MG, Milic M, Sun P. Antihypertensive therapy for patients with obstructive sleep apnea. Curr Opin Nephrol Hypertens. 2011;20(1):50–5. [PubMed: 21326007]

133. Baguet JP, Hammer L, Levy P, Pierre H, Rossini E, Mouret S, et al. Night-time and diastolic hypertension are common and underestimated conditions in newly diagnosed apnoeic patients. J Hypertens. 2005;23(3):521–7. [PubMed: 15716692]

134. Pankow W, Nabe B, Lies A, Becker H, Kohler U, Kohl FV, et al. Influence of sleep apnea on 24-hour blood pressure. Chest. 1997;112(5):1253–8. [PubMed: 9367465]

135. Hla KM, Young T, Finn L, Peppard PE, Szklo-Coxe M, Stubbs M. Longitudinal association of sleep-disordered breathing and nondipping of nocturnal blood pressure in the Wisconsin Sleep Cohort Study. Sleep. 2008;31(6):795–800. [PubMed: 18548823]

136. Mokhlesi B, Hagen EW, Finn LA, Hla KM, Carter JR, Peppard PE. Obstructive sleep apnoea during REM sleep and incident non-dipping of nocturnal blood pressure: a longitudinal analysis of the Wisconsin Sleep Cohort. Thorax. 2015;70(11):1062–9. [PubMed: 26307037]

137. Kasiakogias A, Tsioufis C, Thomopoulos C, Andrikou I, Aragiannis D, Dimitriadis K, et al. Evening versus morning dosing of antihypertensive drugs in hypertensive patients with sleep apnoea: a cross-over study. J Hypertens. 2015;33(2):393–400. [PubMed: 25318654]

138. Crippa G, Zabzuni D, Cassi A, Bravi E. Effect of bedtime dosing of barnidipine hydrochloride in non-dipper hypertensive patients with obstructive sleep apnoea not treated with continuous positive airway pressure. Eur Rev Med Pharmacol Sci. 2016;20(2):339–44. [PubMed: 26875906]

139. Yoshida T, Kuwabara M, Hoshide S, Kario K. The effect of the bedtime-dosing doxazosin on nocturnal hypoxia-triggered blood pressure surge in a young adult man with severe obstructive sleep apnea syndrome and a history of three recurrent sleep-onset strokes. Blood Press Monit. 2017;22(3):173–4. [PubMed: 28459764]

140. Shirasaki O, Yamashita S, Kawara S, Tagami K, Ishikawa J, Shimada K, et al. A new technique for detecting sleep apnea-related “midnight” surge of blood pressure. Hypertens Res. 2006;29(9): 695–702. [PubMed: 17249525]

141. Kario K, Kuwabara M, Hoshide S, Nagai M, Shimpo M. Effects of nighttime single-dose administration of vasodilating vs sympatholytic antihypertensive agents on sleep blood pressure in hypertensive patients with sleep apnea syndrome. J Clin Hypertens (Greenwich). 2014;16(6): 459–66. [PubMed: 24798657]

142. Serinel Y, Yee BJ, Grunstein RR, Wong KH, Cistulli PA, Arima H, et al. Chronotherapy for hypertension in obstructive sleep apnoea (CHOSA): a randomised, double-blind, placebo-controlled crossover trial. Thorax. 2017;72(6):550–8. [PubMed: 27974526]

143. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. The New England journal of medicine. 2004;351(13):1296–305. [PubMed: 15385656]

144. Chronic Kidney Disease Prognosis C, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375(9731):2073–81. [PubMed: 20483451]

145. Abramson JL, Jurkovitz CT, Vaccarino V, Weintraub WS, McClellan W. Chronic kidney disease, anemia, and incident stroke in a middle-aged, community-based population: the ARIC Study. Kidney Int. 2003;64(2):610–5. [PubMed: 12846757]

146. Van Biesen W, De Bacquer D, Verbeke F, Delanghe J, Lameire N, Vanholder R. The glomerular filtration rate in an apparently healthy population and its relation with cardiovascular mortality during 10 years. Eur Heart J. 2007;28(4):478–83. [PubMed: 17223665]

147. Perlman RL, Finkelstein FO, Liu L, Roys E, Kiser M, Eisele G, et al. Quality of life in chronic kidney disease (CKD): a cross-sectional analysis in the Renal Research Institute-CKD study. Am J Kidney Dis. 2005;45(4):658–66. [PubMed: 15806468]

148. National Kidney F K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39(2 Suppl 1):S1–266. [PubMed: 11904577]

149. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. PLoS One. 2016;11(7):e0158765. [PubMed: 27383068]

150. Torbjornsdotter TB, Jaremko GA, Berg UB. Nondipping and its relation to glomerulopathy and hyperfiltration in adolescents with type 1 diabetes. Diabetes Care. 2004;27(2):510–6. [PubMed: 14747237]

151. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al. Prevalence of chronic kidney disease in the United States. JAMA. 2007;298(17):2038–47. [PubMed: 17986697]

152. Hsu C-y, McCulloch CE, Darbinian J, Go AS, Iribarren C. Elevated blood pressure and risk of end-stage renal disease in subjects without baseline kidney disease. Archives of internal medicine. 2005;165(8):923–8. [PubMed: 15851645]

153. Bakris GL, Williams M, Dworkin L, Elliott WJ, Epstein M, Toto R, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Am J Kidney Dis. 2000;36(3):646–61. [PubMed: 10977801]

154. Palmer BF. Hypertension management in patients with chronic kidney disease. Curr Hypertens Rep. 2008;10(5):367–73. [PubMed: 18775113]

155. Etgen T, Chonchol M, Forstl H, Sander D. Chronic kidney disease and cognitive impairment: a systematic review and meta-analysis. Am J Nephrol. 2012;35(5):474–82. [PubMed: 22555151]

156. Smith GL, Lichtman JH, Bracken MB, Shlipak MG, Phillips CO, DiCapua P, et al. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. J Am Coll Cardiol. 2006;47(10):1987–96. [PubMed: 16697315]

157. Fedecostante M, Spannella F, Cola G, Espinosa E, Dessì-Fulgheri P, Sarzani R. Chronic kidney disease is characterized by "double trouble" higher pulse pressure plus night-time systolic blood pressure and more severe cardiac damage. PloS one. 2014;9(1):e86155. [PubMed: 24465931]

158. Portaluppi F, Montanari L, Massari M, Di Chiara V, Capanna M. Loss of nocturnal decline of blood pressure in hypertension due to chronic renal failure. Am J Hypertens. 1991;4(1 Pt 1):20–6. [PubMed: 2006993]

159. Agarwal R, Andersen MJ. Prognostic importance of ambulatory blood pressure recordings in patients with chronic kidney disease. Kidney Int. 2006;69(7):1175–80. [PubMed: 16467785]

160. Liu X, Liu X, Huang W, Leo S, Li Y, Liu M, et al. Evening -versus morning- dosing drug therapy for chronic kidney disease patients with hypertension: a systematic review. Kidney Blood Press Res. 2014;39(5):427–40. [PubMed: 25471279]

161. Wang C, Ye Y, Liu C, Zhou Y, Lv L, Cheng C, et al. Evening versus morning dosing regimen drug therapy for chronic kidney disease patients with hypertension in blood pressure patterns: a systematic review and meta-analysis. Intern Med J. 2017;47(8):900–6. [PubMed: 28544243]

162. Crespo JJ, Piñeiro L, Otero A, Castiñeira C, Ríos MT, Regueiro A, et al. Administration-time-dependent effects of hypertension treatment on ambulatory blood pressure in patients with chronic kidney disease. Chronobiology international. 2013;30(1–2):159–75. [PubMed: 23098134]

163. Wang C, Zhang J, Liu X, Li CC, Ye ZC, Peng H, et al. Effect of valsartan with bedtime dosing on chronic kidney disease patients with nondipping blood pressure pattern. J Clin Hypertens (Greenwich). 2013;15(1):48–54. [PubMed: 23282124]

164. Sakai Y, Suzuki A, Mugishima K, Sumi Y, Otsuka Y, Otsuka T, et al. Comparison of once daily versus twice daily olmesartan in patients with chronic kidney disease. Int J Nephrol Renovasc Dis. 2013;6:223–7. [PubMed: 24143121]
165. Koopman MG, Koomen GC, Krediet RT, de Moor EA, Hoek FJ, Arisz L. Circadian rhythm of glomerular filtration rate in normal individuals. Clin Sci (Lond). 1989;77(1):105–11. [PubMed: 2667855]
166. Pons M, Forpomes O, Espagnet S, Cambar J. Relationship between circadian changes in renal hemodynamics and circadian changes in urinary glycosaminoglycan excretion in normal rats. Chronobiol Int. 1996;13(5):349–58. [PubMed: 8957586]
167. Hilfenhaus M Circadian rhythm of the renin-angiotensin-aldosterone system in the rat. Arch Toxicol. 1976;36(3–4):305–16. [PubMed: 1036902]
168. Morawska-Barszczewska J, Guzek JW, Kaczorowska-Skora J. Cholecystokinin octapeptide and the daily rhythm of vasopressin and oxytocin release. Exp Clin Endocrinol Diabetes. 1996;104(2):164–71. [PubMed: 8740941]
169. Stepien M, Witte K, Lemmer B. Chronobiologic evaluation of angiotensin-converting enzyme activity in serum and lung tissue from normotensive and spontaneously hypertensive rats. Chronobiol Int. 1993;10(5):331–7. [PubMed: 8261532]
170. Rahman M, Greene T, Phillips RA, Agodoa LY, Bakris GL, Charleston J, et al. A trial of 2 strategies to reduce nocturnal blood pressure in blacks with chronic kidney disease. Hypertension. 2013;61(1):82–8. [PubMed: 23172931]
171. Hsu CY, Lin F, Vittinghoff E, Shlipak MG. Racial differences in the progression from chronic renal insufficiency to end-stage renal disease in the United States. J Am Soc Nephrol. 2003;14(11):2902–7. [PubMed: 14569100]
172. Martins D, Tareen N, Norris KC. The epidemiology of end-stage renal disease among African Americans. Am J Med Sci. 2002;323(2):65–71. [PubMed: 11863081]
173. Zhang QL, Rothenbacher D. Prevalence of chronic kidney disease in population-based studies: systematic review. BMC Public Health. 2008;8:117. [PubMed: 18405348]
174. Ferrannini E, Cushman WC. Diabetes and hypertension: the bad companions. Lancet. 2012;380(9841):601–10. [PubMed: 22883509]
175. Eguchi K, Pickering TG, Hoshide S, Ishikawa J, Ishikawa S, Schwartz JE, et al. Ambulatory blood pressure is a better marker than clinic blood pressure in predicting cardiovascular events in patients with/without type 2 diabetes. Am J Hypertens. 2008;21(4):443–50. [PubMed: 18292756]
176. Ritz E, Orth SR. Nephropathy in patients with type 2 diabetes mellitus. The New England journal of medicine. 1999;341(15):1127–33. [PubMed: 10511612]
177. Lurbe A, Redon J, Pascual JM, Tacons J, Alvarez V, Batlle DC. Altered blood pressure during sleep in normotensive subjects with type I diabetes. Hypertension. 1993;21(2):227–35. [PubMed: 8428785]
178. Poulsen PL, Ebbehoj E, Hansen KW, Mogensen CE. 24-h blood pressure and autonomic function is related to albumin excretion within the normoalbuminuric range in IDDM patients. Diabetologia. 1997;40(6):718–25. [PubMed: 9222653]
179. Voros P, Lengyel Z, Nagy V, Nemeth C, Rosivall L, Kammerer L. Diurnal blood pressure variation and albuminuria in normotensive patients with insulin-dependent diabetes mellitus. Nephrol Dial Transplant. 1998;13(9):2257–60. [PubMed: 9761505]
180. Hansen HP, Rossing P, Tarnow L, Nielsen FS, Jensen BR, Parving HH. Circadian rhythm of arterial blood pressure and albuminuria in diabetic nephropathy. Kidney Int. 1996;50(2):579–85. [PubMed: 8840289]
181. Moore WV, Donaldson DL, Chonko AM, Ideus P, Wiegmann TB. Ambulatory blood pressure in type I diabetes mellitus. Comparison to presence of incipient nephropathy in adolescents and young adults. Diabetes. 1992;41(9):1035–41. [PubMed: 1499855]
182. Pecis M, Azevedo MJ, Moraes RS, Ferlin EL, Gross JL. Autonomic dysfunction and urinary albumin excretion rate are associated with an abnormal blood pressure pattern in normotensive normoalbuminuric type 1 diabetic patients. Diabetes Care. 2000;23(7):989–93. [PubMed: 10895852]

183. Lurbe E, Redon J, Kesani A, Pascual JM, Tacons J, Alvarez V, et al. Increase in nocturnal blood pressure and progression to microalbuminuria in type 1 diabetes. The New England journal of medicine. 2002;347(11):797–805. [PubMed: 12226150]

184. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. Lancet. 2007;369(9557):201–7. [PubMed: 17240286]

185. Emdin CA, Anderson SG, Woodward M, Rahimi K. Usual Blood Pressure and Risk of New-Onset Diabetes: Evidence From 4.1 Million Adults and a Meta-Analysis of Prospective Studies. J Am Coll Cardiol. 2015;66(14):1552–62. [PubMed: 26429079]

186. Ayala DE, Moya A, Crespo JJ, Castineira C, Dominguez-Sardina M, Gomara S, et al. Circadian pattern of ambulatory blood pressure in hypertensive patients with and without type 2 diabetes. Chronobiol Int. 2013;30(1–2):99–115. [PubMed: 23098178]

187. Sun L, Yan B, Gao Y, Su D, Peng L, Jiao Y, et al. Relationship between blood pressure reverse dipping and type 2 diabetes in hypertensive patients. Sci Rep. 2016;6:25053. [PubMed: 27109832]

188. Hjortkjaer HO, Jensen T, Kofoed KF, Mogensen UM, Sigvardsen PE, Kober L, et al. Nocturnal antihypertensive treatment in patients with type 1 diabetes with autonomic neuropathy and non-dipping: a randomised, placebo-controlled, double-blind cross-over trial. BMJ Open. 2016;6(12):e012307.

189. Ciobanu D, Veresiu I, Bala C, Roman G, Mircea P, editors. Benefits of bedtime hypertension medication in type 2 diabetes demonstrated on ambulatory blood pressure monitoring. Proceedings of the 49th Annual Scientific Meeting of the European Society for Clinical Investigation Edited by Dumitrascu DL, Portincasa P Medimond, Italy; 2015.

190. Rossen NB, Knudsen ST, Fleischer J, Hvas AM, Ebbehoj E, Poulsen PL, et al. Targeting nocturnal hypertension in type 2 diabetes mellitus. Hypertension. 2014;64(5):1080–7. [PubMed: 25259747]

191. Hermida RC, Ayala DE, Mojon A, Fernandez JR. Bedtime ingestion of hypertension medications reduces the risk of new-onset type 2 diabetes: a randomised controlled trial. Diabetologia. 2016;59(2):255–65. [PubMed: 26399404]

192. Hermida RC. Sleep-time ambulatory blood pressure as a prognostic marker of vascular and other risks and therapeutic target for prevention by hypertension chronotherapy: Rationale and design of the Hygia Project. Chronobiol Int. 2016;33(7):906–36. [PubMed: 27221952]

193. Hinnen D Glucagon-Like Peptide 1 Receptor Agonists for Type 2 Diabetes. Diabetes Spectr. 2017;30(3):202–10. [PubMed: 28848315]

194. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics-2013 update. Circulation. 2013;127(1).

195. Hertz RP, Unger AN, Cornell JA, Saunders E. Racial disparities in hypertension prevalence, awareness, and management. Arch Intern Med. 2005;165(18):2098–104. [PubMed: 16216999]

196. Muntner P, He J, Cutler JA, Wildman RP, Whelton PK. Trends in blood pressure among children and adolescents. Jama. 2004;291(17):2107–13. [PubMed: 15126439]

197. Lackland DT. Racial disparities in hypertension. J Clin Hypertens (Greenwich). 2005;7(9):500–2. [PubMed: 16227768]

198. Bosworth HB, Powers B, Grubber JM, Thorpe CT, Olsen MK, Orr M, et al. Racial differences in blood pressure control: potential explanatory factors. J Gen Intern Med. 2008;23(5):692–8. [PubMed: 18288540]

199. Gretler DD, Fumo MT, Nelson KS, Murphy MB. Ethnic differences in circadian hemodynamic profile. Am J Hypertens. 1994;7(1):7–14. [PubMed: 8136114]

200. Muntner P, Lewis CE, Diaz KM, Carson AP, Kim Y, Calhoun D, et al. Racial differences in abnormal ambulatory blood pressure monitoring measures: Results from the Coronary Artery Risk Development in Young Adults (CARDIA) study. Am J Hypertens. 2015;28(5):640–8. [PubMed: 25376639]

201. Thomas SJ, Booth JN 3rd, Bromfield SG, Seals SR, Spruill TM, Ogedegbe G, et al. Clinic and ambulatory blood pressure in a population-based sample of African Americans: the Jackson Heart Study. J Am Soc Hypertens. 2017.

202. Agyemang C, Bhopal R, Bruijnzeels M, Redekop WK. Does nocturnal blood pressure fall in people of African and South Asian descent differ from that in European white populations? A systematic review and meta-analysis. J Hypertens. 2005;23(5):913–20. [PubMed: 15834272]

203. Bosworth HB, Dudley T, Olsen MK, Voils CI, Powers B, Goldstein MK, et al. Racial differences in blood pressure control: potential explanatory factors. Am J Med. 2006;119(1):70 e9–15.

204. Lackland DT, Keil JE. Epidemiology of hypertension in African Americans. Semin Nephrol. 1996;16(2):63–70. [PubMed: 8668862]

205. Howard G, Prineas R, Moy C, Cushman M, Kellum M, Temple E, et al. Racial and geographic differences in awareness, treatment, and control of hypertension: the REasons for Geographic And Racial Differences in Stroke study. Stroke. 2006;37(5):1171–8. [PubMed: 16556884]

206. Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988–2000. JAMA. 2003;290(2):199–206. [PubMed: 12851274]

207. Brancati FL, Kao WH, Folsom AR, Watson RL, Szklo M. Incident type 2 diabetes mellitus in African American and white adults: the Atherosclerosis Risk in Communities Study. JAMA. 2000;283(17):2253–9. [PubMed: 10807384]

208. Gaskin DJ, Thorpe RJ Jr., McGinty EE, Bower K, Rohde C, Young JH, et al. Disparities in diabetes: the nexus of race, poverty, and place. Am J Public Health. 2014;104(11):2147–55. [PubMed: 24228660]

209. Freedman BI, Tuttle AB, Spray BJ. Familial predisposition to nephropathy in African-Americans with non-insulin-dependent diabetes mellitus. Am J Kidney Dis. 1995;25(5):710–3. [PubMed: 7747724]

210. Carnethon MR, Pu J, Howard G, Albert MA, Anderson CA, Bertoni AG, et al. Cardiovascular health in african americans: a scientific statement from the american heart association. Circulation. 2017;136(21):e393–e423. [PubMed: 29061565]

211. Sardar MR, Badri M, Prince CT, Seltzer J, Kowey PR. Underrepresentation of women, elderly patients, and racial minorities in the randomized trials used for cardiovascular guidelines. JAMA Intern Med. 2014;174(11):1868–70. [PubMed: 25264856]

212. Melloni C, Berger JS, Wang TY, Gunes F, Stebbins A, Pieper KS, et al. Representation of women in randomized clinical trials of cardiovascular disease prevention. Circ Cardiovasc Qual Outcomes. 2010;3(2):135–42. [PubMed: 20160159]

213. Tamargo J, Rosano G, Walther T, Duarte J, Niessner A, Kaski JC, et al. Gender differences in the effects of cardiovascular drugs. Eur Heart J Cardiovasc Pharmacother. 2017;3(3):163–82. [PubMed: 28329228]

214. Duffy JF, Cain SW, Chang A-M, Phillips AJ, Münch MY, Gronfier C, et al. Sex difference in the near-24-hour intrinsic period of the human circadian timing system. Proceedings of the National Academy of Sciences. 2011;108(Supplement 3):15602–8.

215. Cain SW, Dennison CF, Zeitzer JM, Guzik AM, Khalsa SBS, Santhi N, et al. Sex differences in phase angle of entrainment and melatonin amplitude in humans. Journal of biological rhythms. 2010;25(4):288–96. [PubMed: 20679498]

216. Rorie DA, Rogers A, Mackenzie IS, Ford I, Webb DJ, Willams B, et al. Methods of a large prospective, randomised, open-label, blinded end-point study comparing morning versus evening dosing in hypertensive patients: the Treatment In Morning versus Evening (TIME) study. BMJ Open. 2016;6(2):e010313.

217. Rorie DA, Flynn RWV, Mackenzie IS, MacDonald TM, Rogers A. The Treatment In Morning versus Evening (TIME) study: analysis of recruitment, follow-up and retention rates post-recruitment. Trials. 2017;18(1):557. [PubMed: 29169373]

218. Wittmann M, Dinich J, Merrow M, Roenneberg T. Social jetlag: misalignment of biological and social time. Chronobiol Int. 2006;23(1–2):497–509. [PubMed: 16687322]

219. Shea SA, Hilton MF, Hu K, Scheer FA. Existence of an endogenous circadian blood pressure rhythm in humans that peaks in the evening. Circulation research. 2011;108(8):980–4. [PubMed: 21474818]

220. Scheer FA, Hu K, Evoniuk H, Kelly EE, Malhotra A, Hilton MF, et al. Impact of the human circadian system, exercise, and their interaction on cardiovascular function. Proc Natl Acad Sci U S A. 2010;107(47):20541–6. [PubMed: 21059915]

221. Scheer FA, Michelson AD, Frelinger AL 3rd, Evoniuk H, Kelly EE, McCarthy M, et al. The Human Endogenous Circadian System Causes Greatest Platelet Activation during the Biological Morning Independent of Behaviors. PLoS One. 2011;6(9):e24549. [PubMed: 21931750]

222. Hu K, Scheer FA, Laker M, Smales C, Shea SA. Endogenous circadian rhythm in vasovagal response to head-up tilt. Circulation. 2011;123(9):961–70. [PubMed: 21339480]

223. Lemmer B. Chronobiology and chronopharmacology of cardiovascular diseases. Wien Med Wochenschr. 1995;145(17–18):445–7. [PubMed: 8588361]

224. Khodadoustan S, Nasri Ashrafi I, Vanaja Satheesh K, Kumar C, Hs S, S C. Evaluation of the effect of time dependent dosing on pharmacokinetic and pharmacodynamics of amlodipine in normotensive and hypertensive human subjects. Clin Exp Hypertens. 2017;39(6):520–6. [PubMed: 28598202]

225. Luo D, Kim JH, Park C, Oh E, Park JB, Cui JH, et al. Design of fixed dose combination and physicochemical characterization of enteric-coated bilayer tablet with circadian rhythmic variations containing telmisartan and pravastatin sodium. Int J Pharm. 2017;523(1):343–56. [PubMed: 28330645]

226. Biswas N, Kuotsu K. Chronotherapeutically Modulated Pulsatile System of Valsartan Nanocrystals-an In Vitro and In Vivo Evaluation. AAPS PharmSciTech. 2017;18(2):349–57. [PubMed: 26961969]

227. Newton AM, Indana VL, Kumar J. Chronotherapeutic drug delivery of Tamarind gum, Chitosan and Okra gum controlled release colon targeted directly compressed Propranolol HCl matrix tablets and in-vitro evaluation. Int J Biol Macromol. 2015;79:290–9. [PubMed: 25936283]

228. Gangane P, Mahajan N, Danao K, Pawde G. Formulation and evaluation of chronomodulated pulsatile therapeutic system of early morning surge in blood pressure. International Journal of Pharmacy and Pharmaceutical Sciences. 2015;7(6):337–41.

229. Gradman AH, Basile JN, Carter BL, Bakris GL. Combination therapy in hypertension. Journal of the American Society of Hypertension. 2010;4(1):42–50. [PubMed: 20374950]

230. Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. The American journal of medicine. 2009;122(3):290–300. [PubMed: 19272490]

231. Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin–angiotensin system on proteinuria in renal disease. Annals of internal medicine. 2008;148(1):30–48. [PubMed: 17984482]

232. Ferrari P, Marti H-P, Pfister M, Frey FJ. Additive antiproteinuric effect of combined ACE inhibition and angiotensin II receptor blockade. Journal of hypertension. 2002;20(1):125–30. [PubMed: 11791035]

233. Villamil A, Chrysant SG, Calhoun D, Schober B, Hsu H, Matrisciano-Dimichino L, et al. Renin inhibition with aliskiren provides additive antihypertensive efficacy when used in combination with hydrochlorothiazide. Journal of hypertension. 2007;25(1):217–26. [PubMed: 17143194]

234. Fabia MJ, Abdilla N, Oltra R, Fernandez C, Redon J. Antihypertensive activity of angiotensin II AT1 receptor antagonists: a systematic review of studies with 24 h ambulatory blood pressure monitoring. Journal of hypertension. 2007;25(7):1327–36. [PubMed: 17563549]

235. Cooney D, Pascuzzi K. Polypharmacy in the elderly: focus on drug interactions and adherence in hypertension. Clinics in geriatric medicine. 2009;25(2):221–33. [PubMed: 19555869]

236. Association AD. Standards of medical care in diabetes—2014. Diabetes care. 2014;37(Supplement 1):S14–S80. [PubMed: 24357209]

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	Participants details	HTN definition	Follow up (month)	Morning anti-hypertensive medications	Evening anti-hypertensive medications	Measures of BP	Ancillary Measures	Results
Ayala et al. 2013 (81).	Spain.	Prospective, open-label, blinded endpoint, 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).	Resistant HTN: SBP/DBP awake mean ≥ 135/85 mmHg and/or asleep mean ≥120/70 mmHg (48h ABPM) *AND* compliant to 3 HTN medications (unspecified) *OR* treated with ≥4 HTN medications.	64.8 (6-102).	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 (89).	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).	Baseline BP ≥ 120/70 or ≥160/100 mm Hg (average of 6 BP measured 2 minutes apart after 10 minutes of rest).	3.	Aspirin within 1 hour of waking.	Same as morning (crossover design); 1 hour before bedtime.	24h ABPM.	Platelet reactivity.	No significant differences in ABPM between morning and bedtime aspirin administration. Bedtime administration ↓morning platelet reactivity.
Farah et al. 2013 (94).	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/m^2; no evidence of target organ damage or systemic	Uncontrolled HTN: Sitting SBP >140 mmHg, sitting DBP> 90 mmHg (mean of 3 outpatient visits); and	4.	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 24h SBP and DBP. Four participants with

Reference	Country	Study Design	Participants details	HTN definition	Follow up (month)	Morning anti-hypertensive medications	Evening anti-hypertensive medications	Measures of BP	Ancillary Measures	Results
			disease. (Total participants, n=60; group 1, n=30).	awake BP >135/85 mmHg or nocturnal BP > 120/70 mmHg (24h ABPM).						monotherapy were unresponsive to bedtime dosing, but their BP was controlled by the addition of a 2nd drug at bedtime.
Fujiwara et al. 2017 (97).	Japan.	Prospective, multicenter, open-label, crossover, noninferiority, 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).	Office SBP ≥140 mmHg or DBP ≥90 mmHg (mean of 2 consecutive BP measurements after ≥2 minutes of seated rest).	2.	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. Need to say something about adherence.
Hermida et al. 2013 (82).	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).	Awake SBP/DBP mean ≥135/85 mm Hg and/or asleep SBP/DBP mean ≥120/70 mmHg.	N/A	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.	48h 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.
Huangfu et al. 2015 (95).	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).	24h 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: none. Group 2: diuretic and ARB. Group 3: ARB. Group 4: diuretic.	24h ABPM.	N/A.	Group 2 ↓morning surge in BP from baseline. No significant changes in dipping[b] status or 24h mean BP.
Kario et al. 2016 (96).	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.	SBP ≥140 mm Hg (office) or SBP ≥135 mm Hg (home), and/or DBP ≥90 mm Hg (office) or DBP ≥85 mm Hg (home). Office BP: mean of 3 consecutive measures. Home BP:	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, group 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-

Reference	Country	Study Design	Participants details	HTN definition	Follow up (month)	Morning anti-hypertensive medications	Evening anti-hypertensive medications	Measures of BP	Ancillary Measures	Results
			(Total completing study, n=81; group 1, n=41; 91% completed study)	mean of morning or evening BP for 5 consecutive days.						terminal pro-brain natriuretic peptide, and the urinary albumin/creatinine ratio.
Lafeber et al. 2014 (90).	The Netherlands.	Open blinded end-point, three-period cross-over, 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 5-11AM. Period 1: Polypill (containing aspirin, statin, ACEI, and diuretic) Period 2: none Period 3: aspirin, ACEI, and diuretic.	Evening administration between 9PM-12AM. Period 1: none Period 2: Polypill4 Period 3: statin.	24h 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 (85).	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 minutes. 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 # 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 # of antihypertensive drugs 1.4 including ACEI, CCB, β-blockers, diuretics and spironolactone.	Office BP and morning home BP obtained after 2 minutes of sitting rest within 1h 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, group 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.
Santiago et al. 2014 (84).	Portugal.	Cross-sectional; observational study; random sampling with replacement;	52% male; 86% aged <65 y; 65% controlled HTN; n=201.	ICPC-2 classification of HTN based on the mean of the last 3	N/A.	N/A.	N/A.	Number and type of antihypertensive medications, time of day of	Age, gender, previous CV events, comorbidity.	↑Target organ damage and nighttime dosing of antihypertensive

Reference	Country	Study Design	Participants details	HTN definition	Follow up (month)	Morning anti-hypertensive medications	Evening anti-hypertensive medications	Measures of BP	Ancillary Measures	Results
		patients with controlled (group 1) vs. uncontrolled (group 2) HTN.		measurements over a minimum of 9 months.				medication ingestion, use of NSAIDs.		medications in group 1; ↑NSAIDs use in group 2.
Soumela et al. 2015 (237).	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 (103).	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 24 h ABPM with mean SBP/DBP >130/80 mmHg and diurnal mean >135/85 mm Hg 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 8PM 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 x h	N/A.	Mean BP, % time elevation index, and the hyperbaric impact ↓ in all groups. Diurnal index (i.e. reducing # of non-dippers) ↑ with group 2 (either drug) compared to group 1.
Ushijima et al. 2015 (101).	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 mm Hg 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.	24h 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. % Reduction in SBP at night compared to SBP at waking ↑in all dosing groups compared to valsartan AM. Serum creatinine ↓in

Reference	Country	Study Design	Participants details	HTN definition	Follow up (month)	Morning anti-hypertensive medications	Evening anti-hypertensive medications	Measures of BP	Ancillary Measures	Results
										groups 2 and 3; ↑ eGFR in group 2.
Zappe et al. 2015 (102).	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).	24h 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 (24h ABPM average <130/80 mmHg) and change from baseline to week 12 mean 24h ABPM- before addition of diuretic; office BP (sitting mean of 3 measures), daytime BP, nighttime BP, daytime/ nighttime BP ratio, early morning BP, morning BP surge, BP variability.	N/A.	Mean 24h ABPM similar between groups.
Meta-analysis										
Roush et al. 2014 (104).		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.	Evening dosing ↓risk of coronary artery disease and stroke versus usual dosing.

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.

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).

Obstructive Sleep Apnea										
Reference	**Country**	**Study Design**	**Participants details**	**HTN definition**	**Follow up (month)**	**Morning anti-hypertensive medications**	**Evening anti-hypertensive medications**	**Measures of BP**	**Ancillary Measures**	**Results**
Crippa et al. 2016 (138).	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 oedema.
Kario et al. 2014 (141).	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 mm Hg.	0.03.	3±1[a], including: 54% CCB, 18% ACEI, 73% ARB, and 36% diuretics.	CCB or β-blocker administered at 6PM.	Sleep SBP surge (hypoxia-peak SBP), mean sleep BP, morning BP.	Polysomnography parameters (i.e. AHI/hour)	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 (137).	Greece.	Prospective, open label, fixed-dose, cross-over study; morning vs. bedtime dosing, BP measures taken by physician blinded to study protocol.	78% male; aged 52 ± 9 y; BMI 34 ± 6 kg/m^2; AHI mean 31 (21-45) events/hour; 61% severe OSA (AHI ≥ 30 events/hour); 49% treated with CPAP; without daytime somnolence, ESS 6 ± 3. Patients were without secondary HTN; diabetes; established CVD;	Office SBP/DBP ≥140/90 mmHg recorded following 5 min of rest in quiet place, average of 2nd and 3rd readings taken in 2 minute 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 hours before bedtime.	Office BP (measured 8-9 AM before morning pill) and 24h 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

Obstructive Sleep Apnea										
Reference	**Country**	**Study Design**	**Participants details**	**HTN definition**	**Follow up (month)**	**Morning anti-hypertensive medications**	**Evening anti-hypertensive medications**	**Measures of BP**	**Ancillary Measures**	**Results**
			CKD or pulmonary disease. (n=41).							dippers ↑from 24% at baseline to 34% with morning dosing and 61% with bedtime dosing. No interaction with CPAP treatment.
Serinel et al. 2016 (142).	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 point; 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/hours; 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 index >80), excessive sleepiness, and CKD. (At randomization n=85; 92% completed study-results not presented in an intention to treat format).	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.	24h ABPM-sleep and 24h 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.
Yoshida et al. 2017 (139).	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 3x, CPAP intolerance.	N/A.	24.	N/A.	Bedtime dosing of selective α-1 blocker (time not specified).	Overnight TSP.	N/A.	↓In hypoxia-triggered nocturnal SBP surge and early-morning BP.
Chronic Kidney Disease										
Reference	**Country**	**Study Design**	**Participants details**	**HTN definition**	**Follow up (month)**	**Morning anti-hypertensive medications**	**Evening anti-hypertensive medications**	**Measures of BP**	**Ancillary Measures**	**Results**

Obstructive Sleep Apnea										
Reference	**Country**	**Study Design**	**Participants details**	**HTN definition**	**Follow up (month)**	**Morning anti-hypertensive medications**	**Evening anti-hypertensive medications**	**Measures of BP**	**Ancillary Measures**	**Results**
Crespo et al. 2013 (162).	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 m^2 and/or albuminuria. (n=2659; group 1, n=1446).	Uncontrolled HTN: awake SBP/DBP mean ≥135/85 mm Hg and/or asleep SBP/DBP mean ≥120/70 mm Hg.	N/A.	Group 1: $3^{\dagger}$±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: $2^{\dagger}$±1 including 59% ARB, 13% ACEI, 33% CCB, 13% α-blocker, 11% β-blocker, and 23% diuretics.	48h ABPM, office BP (2x 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 (238).	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 m^2. (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 2x office and morning at-home BPs after 5 min rest.	Renal function/ preoteinuria: eGFR, urinary albumin-to-creatinine ratio.	No significant change in BP. ↑ eGFR with morning-only dose.
Rahman et al. 2013 (170).	United States.	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	64% male; aged 65 ± 10 y; 100% African American; 60% BMI > 30 kg/m^2; 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 study enrollment and had an EF >40%. (n=147).	Office BP ≤140/90 mm Hg based on 2 BP values measured >1 week apart and currently prescribed 1 antihypertensive medication taken 1x daily, 2 antihypertensive medications with >1 taken 1x daily, or ≥3 antihypertensive medications	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. For add-on	Nocturnal SBP; 24h ABPM, office BP.	N/A.	Nocturnal, 24h, nor daytime SBP significantly differed by treatment timing.

Obstructive Sleep Apnea										
Reference	**Country**	**Study Design**	**Participants details**	**HTN definition**	**Follow up (month)**	**Morning anti-hypertensive medications**	**Evening anti-hypertensive medications**	**Measures of BP**	**Ancillary Measures**	**Results**
		bedtime; no blinding.		with >2 taken 1x daily.			schedule, 49.5% received hydralazine; 18.1% diltiazem; 7.6% ramipril; and 24.8% received another medication.			
Wang et al. 2013 (239).	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.	24h 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.
Diabetes										
Reference	**Country**	**Study Design**	**Participants details**	**HTN definition**	**Follow up (month)**	**Morning anti-hypertensive medications**	**Evening anti-hypertensive medications**	**Measures of BP**	**Ancillary Measures**	**Results**
Ciobanu et al. 2015 (189).	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 <30ml/min/ 1.73m^3. (n=144; bedtime, n=60; morning, n=56; no medications, n=28).	SBP and DBP were measured at least 2x after 10 minutes of sitting rest, measures were obtained and averaged from both arms.	N/A	Medications included ACEI, ARB, B-blocker, Diuretic, and CCB.	ACEI (n=38); ARB (n=17); β-blocker (n=45); Diuretic (n=39); CCB (n=25); α-antagonist (n=4).	24h 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 (191).	Spain.	Prospective, open-label, blinded endpoint, 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,	Awake SBP/DBP mean ≥135/85 mmHg or asleep SBP/DBP mean ≥120/70 mmHg.	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.	48h 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

Obstructive Sleep Apnea										
Reference	**Country**	**Study Design**	**Participants details**	**HTN definition**	**Follow up (month)**	**Morning anti-hypertensive medications**	**Evening anti-hypertensive medications**	**Measures of BP**	**Ancillary Measures**	**Results**
			n=2012; group 1, n=1029).							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 (188).	Denmark.	Placebo-controlled, double-blind, two-way cross-over, RCT; comparison between morning and bedtime dosing of an ACEI in patients type 1 diabetes and with cardiac autonomic neuropathy. Double blinded.	42% male; aged 60±7 y; BMI 25±4 kg/m^2; diabetes duration 36±11 y; 71% prescribed antihypertensive treatment. (n=24).	N/A.	3.	ACEI + placebo at bedtime + previously prescribed medication regimen.	Same as morning (crossover design) with placebo in the morning.	24h 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.
Rossen et al. 2014 (190).	Denmark.	Open-label crossover study, RCT; morning vs. bedtime administration of participants' 1x 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. Office BP measured 4 times, reported average of the latter 3.	2.	Median # number of once-daily antihypertensive drugs, 3(1-6); median # 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-trough 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 24h SBP. Urinary sodium/creatine and potassium/creatine ↑, urinary osmolality ↓, and C-reactive protein (inflammation marker) ↓with bedtime administration.
Meta-analysis										
Wang et al. 2017 (161).		Meta-analysis comparing evening vs.	5 RCTs and 1 comparative study: 40-64% male; mean	SBP and/or DBP ≥140 and/or ≥90 mmHg.	1-70.					Evening dosing regimen drug therapy

Obstructive Sleep Apnea										
Reference	**Country**	**Study Design**	**Participants details**	**HTN definition**	**Follow up (month)**	**Morning anti-hypertensive medications**	**Evening anti-hypertensive medications**	**Measures of BP**	**Ancillary Measures**	**Results**
		morning dosing regimen of antihypertensive drugs on BP patterns of CKD patients with HTN.	age 36-70 y. (n=3582).							↓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; HF, heart failure; 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.