Does chronotherapy for essential hypertension matter by class? A systematic review and meta-analysis

Hongyu Kuang[1], Yunlin Chen[1]

Department of Cardiology, Chongqing Medical Affiliated Second Hospital, Chongqing, China

Abstract

Objectives The study was performed to evaluate the efficacy and safety of chronotherapy of hypertension with different medications monotherapy or a combination compared with traditional regimens

Methods Three databases including PubMed, EMBASE and the Cochrane Library were searched, from the inception of each database to 10 April 2020. The Review Manager 5.4 was adopted for meta-analyses and subgroup analyses. The blood pressure delta (Δ) was used as mean of differences (MD) with 95% confidence intervals (CIs), and the estimated effect for events estimates the 95% CIs for frequency of events. The adults with essential hypertension were treated with chronotherapy and traditional regimens.

Results Twenty-eight RCTs, recruiting 1865 patients in bedtime/evening dosing and 1867 in awakening/morning dosing, were enrolled in this quantitative review. Meta-analysis showed no significant differences for overall drug-related AEs (RR=0.81, P=0.17; I^2=41%), but an obvious reduction of risk for overall withdrawals (RR=0.52, P=0.005; I^2=0.0%) with bedtime dosing. No statistically significant differences were noted for clinic BP and diurnal BP, but 24-hour (48-hour) BP,

nocturnal BP, morning BP, and non-dippers (%) showed obvious reductions, statistically. By class, there existed different efficacy between 2 administrations, with great decrease in nocturnal BP control and changes in circadian rhythm with RAAS blockers monotherapy, but an all-day control of BP for CCBs and diuretics. With regard to a combination, no significant differences in BP management were detected and the data about beta-receptor blockers were limited.

Conclusions The safety and efficacy of chronotherapy in antihypertensive drugs might be based on the classes.

Keywords: Essential hypertension; Blood pressure; Chronotherapy; Traditional; By class

Introduction

Hypertension (HTN) is one of the most common chronic diseases with high prevalence, which is the most important risk of cardiovascular diseases. It is well known that there is a strong linear relationship between blood pressure (BP) level and cardiovascular events[1-2]. Recently, BP characteristics, including BP pattern (dipping status), morning surge, nocturnal BP level and asleep/awake BP ratio have been identified as all independent risk factors for organ damages, cardiovascular morbidity and mortality than awake or 24-hour BP mean [3-7]. Hence, chronotherapy is defined as the purposeful timing of medications, to proportion serum and tissue concentrations in synchrony with known circadian rhythms in disease processes and symptoms as a means of

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enhancing beneficial outcomes and/or attenuating or averting adverse effects [8-10]. Since chronotherapy for HTN has been studied from 1980s[11], it has been identified of an increase beneficial effect and/or minimized adverse medication effects across the day and night for the tailored timing matches the body's natural circadian rhythm and behavioral patterns [12]. Zhao et al. [13] have reviewed BP management of 21 RCTs in 1993 patients only focusing on 24-hour BP and morning BP, lacking outcomes such as nocturnal BP, awake and asleep ratio and dipping patterns. Lately, clinical registries indicated a clinical meaning in hypertension, with a viewpoint that at least 1 hypertension medications at bedtime, compared with a traditional ingestion, could significantly reduce sleep-time relative BP decline towards the more normal dipper profiles and cardiovascular toxin [14-16]. Nonetheless, there is currently a lack of proofs about comparison of different antihypertensive agents or formulations monotherapy or a combined medication, between awakening and bedtime schedules, respectively. In this review, we collected data from randomized trials with an evaluation of the reduction of BP level and change of BP characteristics in patients with essential hypertension (EH) after chronotherapy, and subgroup analysis has distinguished these findings when different agents when administered for the first-time.

Methods

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This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions [17-18].

Data sources and literature searches

We searched the following electronic databases for randomized controlled trials (RCTs) in 3 databases, including *The Cochrane Central Register of Controlled Trials (CENTRAL)* on Ovid, Ovid MEDLINE, and EMBASE. And the search strategy was displayed as **Supplementary 1**. Additional manually retrieval, mainly the cited reference lists of relevant citations, and no restrictions of language were imposed.

Inclusion and exclusion criteria

Two investigators independently screened articles at title, abstract, and full text level. We included all randomized trials performed on adults with EH sharing the lifestyle is active during daytime, and taking a rest during nighttime, that compared outcomes from group with evening dosing to that assigned to morning dosing, once-daily drug regimen. Antihypertensive drugs included ACEIs, ARBs, diuretics, CCBs, beta-receptor blockers, as monotherapy or a combined administration. We excluded review articles, letters, case reports or series, and animal experimental studies. Trials recruiting subjects with unclear

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therapeutic regimens or without undergoing washout period after a long-term antihypertensive drug were excluded. With a consideration that prevalence of non-dipper and riser patterns is very high in certain cohorts, studies focusing on patients with type 2 diabetes, chronic kidney failure, chronic heart failure, and coronary heart disease would be excluded in this meta-analysis to reduce the bias.

Outcomes

Primary outcomes: 1) All-cause mortality; 2) Cardiovascular mortality; 3) Event (stroke, myocardial infarction, coronary heart disease, congestive heart failure, aortic aneurysm)-free survivals; 4) Nocturnal BP mean. ***Secondary outcomes:*** 1) Change in clinic systolic BP (SBP) and diastolic BP (DBP) from baseline; 2) Change in 24-hour mean SBP and DBP from baseline; 3) Change in morning SBP and DBP from baseline; 3) Awake/asleep BP ratio; 4) Non-dipper status; 5) Overall adverse events and serious adverse events; 6) Withdrawals.

Data extraction and quality assessment

Data were extracted by two reviewers independently according to a standard Cochrane protocol with items including: the first author, year of publication, age, drug administrations (dosage, time, duration), SBP/DBP at baseline, and type of study design, and then the relevant data were cross-checked. The

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corresponding author confirmed all numeric calculations and graphic interpolations, and two reviewers have assessed with the standard Cochrane Collaboration's risk-of-bias tool, including 6 domains.

Data synthesis and analysis

The statistical software Review Manager 5.4 was adopted for meta-analyses and subgroup analyses. The blood pressure delta (Δ) was used as mean of differences (MD) with their 95% confidence intervals (CIs). In addition to the outcomes mentioned above, the cardiovascular events were recorded when described in an article, and the estimated effect (ES) for events estimates the corresponding 95% CI was calculated. Then, the software SPSS 23.0 was applied to detect the correlation between nocturnal SBP decrease with bedtime dosing and initial characteristics (age, proportion of male, proportion of non-dippers, glucose, cholesterol, triglycerides, BMI, creatinine, uric acid, clinic SBP and clinic DBP), in order to find potential factors impacting nocturnal SBP management. A P-value of less than 0.05 was considered as a statistical significance.

Dealing with missing data

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If there were missing data, in general, the corresponding or first author could be contacted *via* e-mail. In cases where missing information was ultimately not available, the best estimate was included based on information in the article. Suppose a study is not available to the mean (standard deviation, SD) of change BP level from baseline to endpoint (mean (*Change)*, and SD (*Change*)), we used an imputed correlation coefficient of 0.5 (r=0.5), and mean (*Change*)=mean (*Final*)-mean (*Baseline*), associated with SD (*change*)=sqrt (SD (*Baseline*)^2+SD (*Final*)^2-(2*r*SD (*Baseline*)*SD (*Final*))). The similar outcomes were obtained for the interventional and controlled group.

Results

Study selection and characteristics

Overall, the electronic searches identified 1127 references, and after a screening at the title and abstract levels,1096 articles were excluded. The remaining 41 articles for detailed assessments where 11 literature [19-29] were excluded for the reason that hypertensive drugs had been administered at either morning or evening without washout periods. Additionally, 4 studies [30-33] from previous reviews were eligible for further assessments, where full text of a study could not be obtained [31]. The trial conducted by Smolensly et al. [32] and Hermida et al. [33] have been excluded for a lack of washout periods. Eventually, 31 RCTs meeting the inclusion criteria, and after an exclusion of 3 large-sample RCTs [14-16] recruiting hypertensive patients treated with at least 1 drug, 28 studies

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describing the efficacy and safety of detailed agents for hypertension are enrolled in this study-level meta-analysis that provided data on 1867 individuals in awakening/morning dosing, and 1865 individuals in bedtime/evening dosing [30, 34-60]. And **Fig.1** is the flowchart of literature screening and details of pooled RCTs are described in the **Table 1** (**Included studies**). Twenty-one trials reported monotherapy of anti-hypertensive drugs, and 7 studies about the combined regimens.

Bias in enrolled studies

For the overall assessment of the risk of bias in included studies were shown in **Fig 2.1** and **Fig 2.2**. Although all the included trials were randomized, the quality was downgraded due to lack of allocation concealment and selective reporting as major risks of bias. Publication bias were calculated, indicating no obvious bias in funnel plots (**Fig 2.3** and **Fig 2.4**).

Profiles of safety

With regard to the safe profiles, only 2 RCTs of ARBs [43, 45] reported on all-cause mortality, comparing 3.6% in the morning regimen versus 1.9% in the bedtime regimen, and 0.5% in the morning versus 0.0% before bedtime, respectively. There was no statistically significant difference for overall drug-related AEs (RR=0.81, 95%CI [0.60, 1.10], P=0.17; I^2=41%), but an obvious reduction of risk for overall withdrawals (RR=0.52, 95%CI [0.33, 0.82], P=0.005;

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I^2=0.0%) with bedtime dosing. The majority of AEs were mild to moderate intensity, and the most frequently reported events were mild cough in ACEIs, gastric syndromes in ARBs, abdominal pain and diarrhea in diuretics, edema, headache and skin rash in CCBs. Two of the trials [45, 55] reported serious adverse drug responses occurred, showing a nonobvious difference, RR=0.66 with 95%CI from 0.23 to 1.90. This study has given the details of subgroup analysis, displaying no significant differences in risk ratio between two kinds of administrations, even CCBs ingested at bedtime may lead to an low risk of overall drug-related AEs (Chi^2=1.75, RR=0.32, P=0.0007) (**Table 2 Meta-analyses and subgroup analyses for safety profiles comparing morning dosing versus bedtime dosing**). Data mentioned that one patient had congestive failure and a second patient had palpitation with morning dosing, one patient had palpitation with bedtime dosing monotherapy. And cardiovascular mortality was not reported in enrolled trials.

Control of blood pressure

Comparison of clinic BP reduction between bedtime dosing and awakening dosing

Overall, 21 RCTs [30, 35-50, 54-56, 58] have provided data on the change of clinic SBP/DBP. Outcomes indicated that the bedtime (evening) regimen reduced clinic SBP/DBP by -1.04 mmHg (95%CI from -2.38 to 0.31, P=0.13; I^2=41%) and -0.13 mmHg (95%CI from -2.01 to 1.76, P=0.89; I^2=84%) than the morning regimen, lacking an obviously statistical difference, and the random-effect model was then applied.

Comparison of ambulatory 24-hour or 48-hour BP reduction between bedtime dosing and awakening dosing

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Ayala et al. [14] and Hermida et al. [16] have monitored 48-hour SBP/DBP, showing evening dosing greatly reduced the ambulatory SBP and DBP by another 1.68 mmHg (P<0.0001) and 1.24 mmHg (P<0.0001). The analysis of ambulatory SBP in 23 RCTs[30,36-42, 44, 46-51, 53-60]in verified that the evening regimen significantly reduced 24-hour or 48-hour blood pressure with statistical differences, MD=-2.26mmHg, 95%CI -3.24 to -1.28, P<0.0001(**Fig 3.1**). And there reported a similar trend toward DBP reduction comparing evening with conventional dosing regimen (MD=-2.03 mmHg, 95%CI -3.15 to -0.91; P=0.0004, I^2=68.0%) (**Fig 3.2**).

Comparison of morning BP reduction between bedtime dosing and awakening dosing

Morning BP is defined as average BP during the first 2 hours after wake-up time, and previous studies have demonstrated cardiovascular events occur in the morning most frequently, hinting an important role of the morning BP plays in hypertension. The analysis of mean difference in morning SBP/DBP based on very limited data, and meta-analysis of 4 RCTs [37, 43, 45, 50] found that there was a statistical difference in monotherapy with evening dosing versus morning dosing regimen, -4.51 mmHg in SBP (95%CI -6.28 to -2.74, I^2=46%; P<0.0001) and -3.06 mmHg in DBP(95%CI -4.15 to -1.96, I^2=74%; P<0.0001). Not a study reported the change in morning blood pressure with the combined regimens.

Comparison of circadian rhythm between bedtime dosing and awakening dosing

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Nocturnal and diurnal mean BP were monitored in 20 studies, including 14 studies [30, 33, 36-37, 39-42, 46-51] about monotherapy and 6 studies [54-59] about a combined medication. Meta-analysis indicated that nocturnal BP regulation was significantly better achieved at bedtime as compared with morning administration (i.e., MD=-5.21mmHg, 95%CI from -6.70 to -3.72, P<0.0001 in SBP, and MD=-2.92 mmHg, 95% from -4.31 to -1.54, P<0.0001), using a random-model effect. And no obvious changes were found in diurnal BP control after chronotherapy, with MD of -1.40/-0.54mmHg (95%CI from -2.80 to 0.0 in SBP and from -1.40 to 0.33 in DBP). In so-called awake: asleep blood pressure ratio, there remained a lower proportion with the upon-awakening regimens (i.e., MD=-1.80%, 95%CI -1.57% to -0.58 % in SBP and MD=-1.10%, 95%CI -1.69% to -0.51% in DBP) but significantly increased toward a more dipping pattern with the bedtime treatment schedule with a ratio, by 2.74 % (95%CI 1.33% to 1.33%, P=0.0001)/3.40% (95%CI 2.09% to 4.70%, P<0.0001) in BP. Accordingly, there was a significant decrease in the proportion of non-dipper patients only after treatment in the bedtime-dosing group (i.e., increased from 47.0% to 52.0% in the morning-dosing group and decreased from 49.0% to 18.0% in the bedtime-dosing group). Chronotherapy medications may benefit patients of dipping pattern of nocturnal BP, a reasonably large proportion after anti-hypertensive drugs, and the population of non-dippers decreased with bedtime dosing, associated with an increase with morning dosing, however (**Fig 3.3**).

Subgroup analysis of BP management

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Subgroup analysis indicated chronotherapy contributed to the efficacy of blood pressure level and characteristics in ACEIs (ramipril and spirapril), ARBs (valsartan, telmisartan, olmesentan, and candesartan), diuretics (torasemide), CCBs (nifedipine, amlodipine), BBs (propranolol, nebivolol), and a combination including ARBs/CCBs (valsartan/amlodipine, telmisartan/amlodipine), ARBs/diuretics (losartan/indapamide, valsartan/HCTZ) and CCBs/ diuretics (amlodipine/HCTZ) (**Supplementary 2**). The intents of subgroup analysis have demonstrated that ACEIs and ARBs monotherapy could not significantly decline clinic BP, 24-hour (48-hour) ABPM, diurnal (awakening) mean BP, while having more effects on nocturnal BP management and ratio of non-dippers, namely ACEIs administered at bedtime declined nocturnal (asleep) mean BP by -5.97 (95%CI from -8.89 mmHg to -3.06mmHg, P<0.0001)/-4.49 mmHg (95%CI from -7.37 to -1.60 mmHg, P=0.002), and by -6.63mmHg (95%CI from -9.07 to -4.19 mmHg, P<0.001)/-2.11mmHg (95% from -0.96 to 2.10 mmHg, P=0.22) in ARBs. Meanwhile, the ratio of non-dippers in ACEIs and ARBs were synthesized and analyzed with bedtime and awakening regimens, from baseline which verified that these agents blocking RAAS could significantly decrease the ratio when administered at bedtime (i.e., OR=0.42, 95%CI [0.24, 0.72], P=0.002 with ACEIs, and OR=0.31, 95%CI [0.22, 0.43], P<0.0001 with ARBs), but an opposite effect in the morning. While bedtime dosing of ACEIs and ARBs contributed to a significant increase in awake/asleep BP ratio, more focusing on nocturnal BP management. With regard to diuretics and CCBs monotherapy, evening dosing could contribute to a better management of BP all day, including ambulatory BP, nocturnal(asleep) mean BP, morning BP and diurnal mean BP, with significant differences. However, there existed changes with minor statistically difference in circadian rhythm after bedtime

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dosing from baseline, like awake/asleep BP ratio and odds ratio of non-dippers, which was 1.47 (95%CI= [0.72, 3.02], P=0.293) in diuretics and 0.69 (95%CI= [0.50, 0.94], P=0.019) in CCBs. Less loss in efficacy was found with a combination comparing bedtime with morning schedules, but 2 RCTs [58-59] have demonstrated that ARBs combined diuretics significantly decreased nocturnal mean SBP by -3.81 mmHg [95%CI=-6.55, -1.07], P=0.006, associated with a meaningful change of awake/asleep SBP and DBP ratio (SBP: increased 3.90% and DBP: increased 4.60%; P<0.0001). Zeng et al. found a decrease of 24-hour SBP by -4.0mmHg and DBP by -5.40mmHg in CCBs with diuretics evening versus conventional morning dosing [60].

Correlation analysis between nocturnal SBP control and event-free survivals according to treatment-time regimen

Correlation between nocturnal SBP control and event-free survival was investigated, hinting a good correlation between nocturnal SBP delta (Δ) and event-free survivals with bedtime dosing regimens (P=0.013). Person's analysis (Bivariate) detected the potential factors impacting nocturnal SBP reduction, showing a linear dependence between Δ and age (P=0.027), and non-dippers (%, P=0.001) in monotherapy. And in a combination, the factor, glucose level (P=0.020), was displayed significantly.

Discussion

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In general, drugs for HTN have been significantly improved in the last decades, and many pharmacological data found that long-acting anti-hypertensive drugs, with long half-life, have made it possible once daily with sufficient compliance [62]. Though, these hypertensive agents have been traditionally administered either monotherapy or in combinations upon awakening, more recent studies indicate greater reductions of asleep BP mean and restores of dipping in non-dippers when ingested at bedtime than upon awakening, hinting a better choice of chronotherapy whereby a drug is given according to physiologic requirements [63-64]. Knowledge of the circadian rhythm of BP is as the culmination of the interrelationship of many 24-hour biological, behavioral, and environmental determinants [65]. Advances in ambulatory BP monitoring showed that not only a higher asleep BP mean or nocturnal hypertension, but also a non-dipper BP pattern are all good risk predictors of cardiovascular events, and it is reviewed that previous findings pointing that non-dipper pattern is indeed associated with increased morbidity of target organ damages [66]. Especially, Verdecchia et al. [67] reported, after a follow-up period of 3.2 years, non-dippers suffered from nearly 3 times as many cardiovascular events as dippers. In order to improve hypertension management and decreases the occurrence of cardiovascular events, chronotherapy for high BP is as the practice of adjusting medication administration time to elicit a preferred effect conforming to their pharmacokinetics and pharmacodynamics [68]. More recent evidence from clinical trials, like the Hygia Chronotherapy Trial, provided data assessing prospectively in a large cohort of hypertensive persons diagnosed by ABP criteria, resulting in considerably enhanced reduction in BP level than ingestion of medications in the morning upon awakening. Meanwhile, it appears that bedtime administration of antihypertensive drugs is superior in terms of improvement

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in cardiovascular outcomes compared with morning administration [69-70]. Based on the above-mentioned studies, there still lacks proofs about the chronotherapy of different drug treatment strategies leading to BP control and regulation of the circadian rhythm, by class. Thus, there is a clear unmet need for new strategies to treat HTN and improve the quality of life.

In this study-level meta-analysis of RCTs comparing bedtime dosing with the conventional administration of antihypertensive drugs for EH, it has been focused on both blood pressure management and safety. The chronotherapy of hypertension specially entails significant attenuation of the accelerated morning rise of SBP and DBP and this may be achieved through the use of special drug-delivery technology or by changing the dosing time of conventional BP-lowering medications. Meanwhile, the pooled studies evaluated the routine drugs for hypertension once daily in both monotherapy and combination regimens. Data supporting bedtime administration for specific antihypertensive agents is limited, and from the data available, it can be concluded that bedtime administration of many antihypertensive agents has demonstrated safety and efficacy compared with morning administration. Analysis and synthesis of all above-mentioned studies appears that bedtime dosing is superior in terms of improvement in ambulatory SBP/DBP, morning blood pressure, and circadian rhythm characteristics compared with morning administration, with no increased risk of AEs, serious AEs, withdrawals, cardiovascular morbidity and all-cause mortality [71-72]. It indicated a good correlation between nocturnal SBP decrease and event-free survivals comparing the two administrations.

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Furthermore, it was found that when treated with agent monotherapy in a bedtime dosing, the factors including age (P=.027) and non-dippers (%, P=.001) might significantly influence the nocturnal SBP change, while glucose level (P=.020) in a combined regimen. Subgroup analysis of BP control displayed that similar efficacy was detected for a combined regimen evening dosing versus morning dosing, with different outcomes with monotherapy by class. For blockers of RAAS (ACEIs and ARBs), although minor differences were found in clinic BP, diurnal mean BP, even 24-hour or 48-hour ambulatory BP change, these agents actually contribute to chronotherapeutic reduction in nocturnal SBP/DBP mean and enhancement of the asleep/awake relative SBP and DBP decline. Additionally, these drugs contribute to a significant decline of morning SBP (ACEI: MD=-7.20mmHg, P=0.0002; ARBs: MD=-1.70mmHg, P=0.01) and DBP (ACEI: MD=-6.50mmHg, P<0.0001; ARBs: MD=-2.40mmHg, P=0.05), as an essential factor for cardiovascular risk [73], where it hinted a possible larger difference in ACEIs than ARBs monotherapy when compared two regimens. Besides BP control, it documented outcomes towards the less non-dipper profiles with bedtime dosing, showing an OR of 0.42 (P=0.002) in ACEIs and OR=0.31 (P<0.0001) in ARBs from baseline. Even though different pharmacokinetic characteristics exist in ACEIs and ARBs, these data verified the hypothesis that drugs targeting RAAS with bedtime administration may be most effective rather than morning administration, possibly for the reason that sympathetic activity decreases during asleep periods, resulting in asleep-BP relying more heavily on the renin system [9, 74]. Clinical trials documented significant reductions in all-day blood pressure profiles with CCBs at bedtime than upon awakening, with few changes in proportion of non-dippers, however. This may, in part, be explained by long time-to-peak concentrations and half-lives,

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even contributing to a more reduction in morning surge [68, 75]. Furthermore, bedtime administration of nifedipine GITS contributed to fewer side effects, suggesting a safer option than morning administration [46, 77]. Meta-analysis of 2 RCTs about the loop diuretic torsemide indicated similar BP control to CCBs, greatly decreasing 24-hour ambulatory BP, nocturnal(asleep) mean BP, morning BP and diurnal mean BP, when conventionally formulated agents are ingested at bedtime than awakening [47-48]. Though limited data have provided the compared efficacy and safety in BBs with different administrations, Neutel et al. [53] conducted a 4-week prospective trial as a comparison of a chronotherapeutically administered propranolol versus a traditionally administered, leading to reductions in mean 24-hour blood pressure (-9.0/-6.9 mmHg dosed at 8 a.m. and -10.4/7.7 mmHg dosed at 10 p.m.). While a trial of nebivolol indicated a similar efficacy in 24-hour BP control between two administrations [54].

Conclusions and Implications

Hence, data supporting bedtime administration is a safe option, leading to less events than traditional administration. All BP measurements were not significantly different between two administrations with combined hypertensive medications, where use of ARBs and diuretics in the bedtime regimens showed an obvious reduction of nocturnal mean SBP (P=0.006), with similar trend of awake/asleep SBP and DBP ratio. Changes in proportion of non-dippers were rarely detected in the combined medications, and Zeng et al. found that bedtime dosing of CCBs combined with diuretics could not ameliorate non-

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dipping status, obviously [61]. For antihypertensive medications monotherapy, if decreasing asleep-BP to achieve dipper status is the goal, most evidence is in support of evening dosing for ACEIs and ARBs. If there is a requirement to achieve the optimal 24-hour BP mean, it is a better choice of evening dosing for CCBs and diuretics than morning dosing.

Study limitations

Limited data about cardiovascular outcomes were provided. Most trials have been conducted by the Team with a leader Hermida RC. Randomized controlled trials enrolled in this systematic review and meta-analysis included medications ACEIs and ARBs about 50%. Hence, prospective clinical studies about CCBs, diuretics and BBs should be noticed in the future.

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Figure and the legends:

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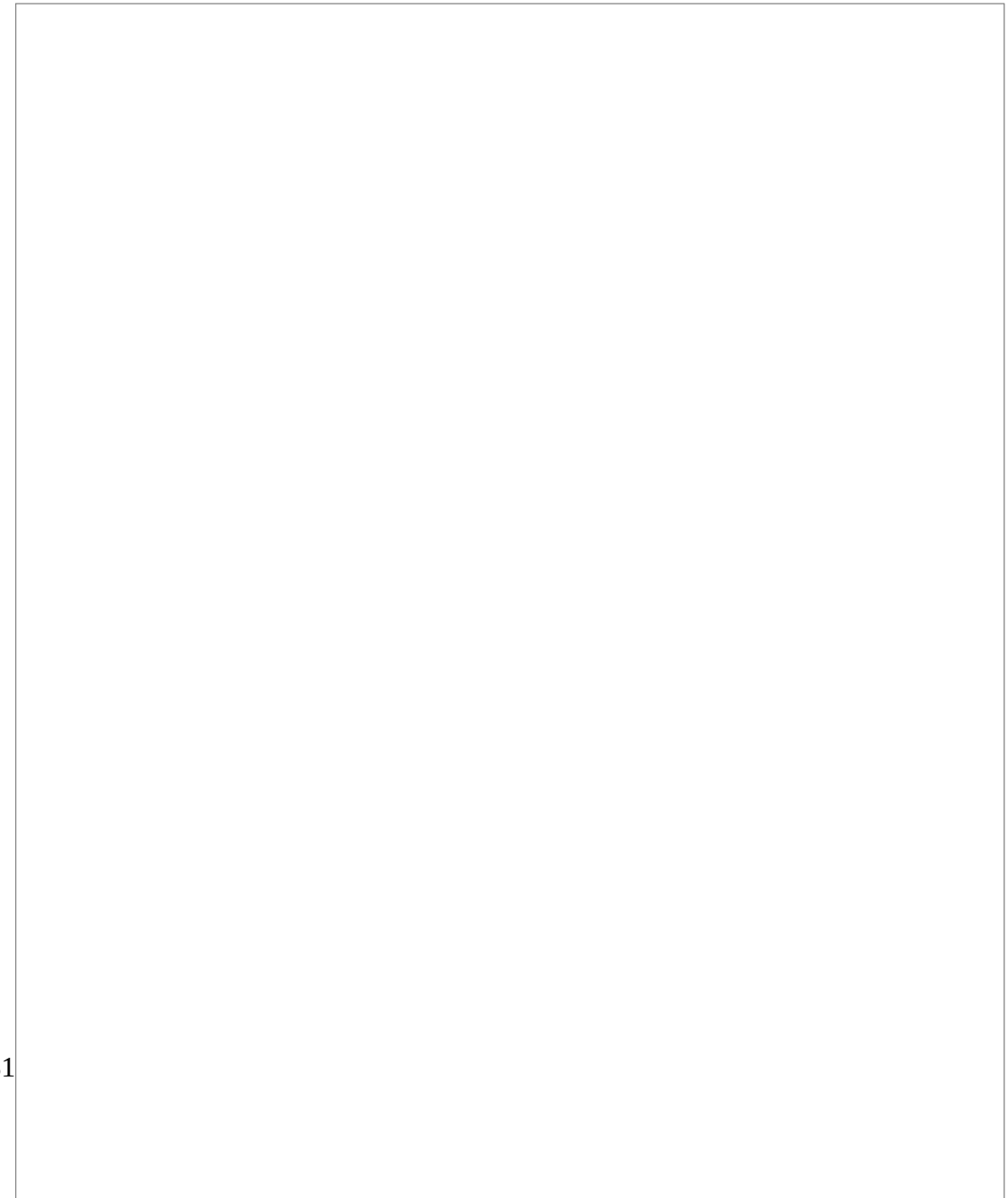

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Fig.1 Flowchart of literature screening.

Fig.2.1 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

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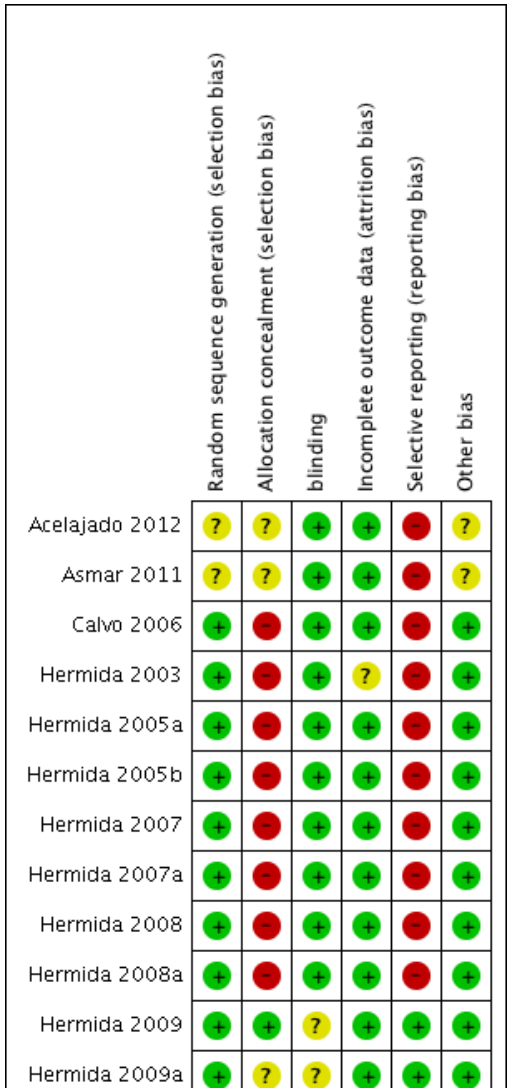
Random sequence generation (selection bias)
Allocation concealment (selection bias)
blinding
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Acelajado 2012
Asmar 2011
Calvo 2006
Hermida 2003
Hermida 2005a
Hermida 2005b
Hermida 2007
Hermida 2007a
Hermida 2008
Hermida 2008a
Hermida 2009
Hermida 2009a

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Fig. 2.2 Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

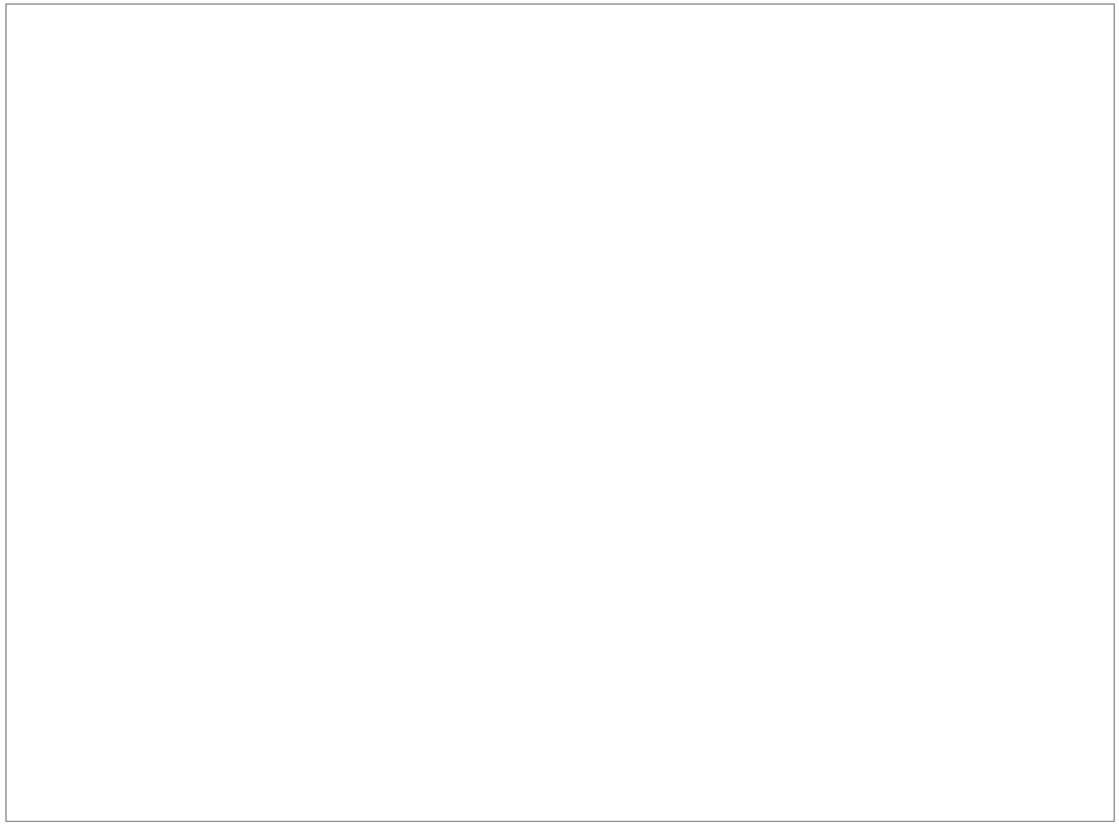

Fig. 2.3 Funnel plot of comparison: evening versus morning dosing regimen, outcome: nocturnal mean systolic blood pressure.

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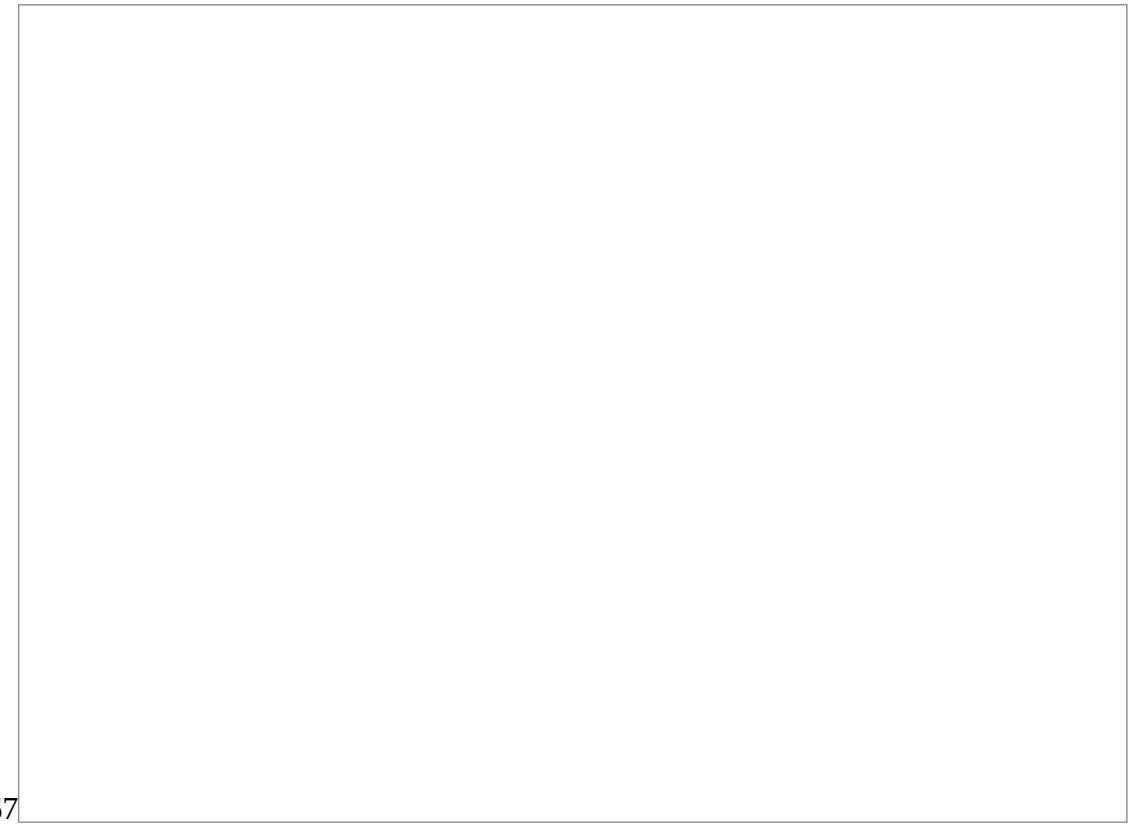

Fig 2.4 Funnel plot of comparison: evening versus morning dosing regimen, outcome: nocturnal mean diastolic blood pressure.

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370**Fig 3.1 Forest plot of comparison: evening versus morning dosing regimen, outcome: 24-hour or 48-hour ambulatory systolic blood pressure.**

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372**Fig 3.2 Forest plot of comparison: evening versus morning dosing regimen, outcome: 24-hour or 48-hour ambulatory diastolic blood pressure.**

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374**Fig 3.3 Odds ratio of non-dipper ratio (%) comparing morning/bedtime dosing from baseline.** (A, morning dosing versus baseline; B, bedtime dosing versus baseline)**.**

375

Table 1 Included studies (by class)

Study	Year	Groups (N)	Dosage (daily)	Time of administration	Duration	Age* Mean (SD) (yrs)	Baseline (O)* SBP/DBP (mmHg)	Inclusion criteria	Study design
ACEIs									
Witte	1993	Enalapril (10)	10mg	Morning (07:00)	3 wks	NR	NR	Mild-to-moderate EH	RCOT; washout period: 1 week
		Enalapril (10)	10mg	Bedtime (19:00)	3 wks				
Macchiarulo	1999	Lisinopril (40)	20mg	Morning (08:00)	2 mths	45.0 (10.0)**	160.1/100.7 **	Mild-to-moderate EH	RCOT; washout period: 1 week
		Lisinopril (40)	20mg	Bedtime (10:00)	2 mths				
Kuroda	2004	Trandolapril (16)	1-2mg	Morning (NR)	8 wks	68.0 (9.0)	158.0/93.0	Mild-to-moderate EH	Multicenter, open-label, RCT
		Trandolapril (14)	1-2mg	Bedtime (NR)	8 wks	66.0 (13.0)	161.0/92.0		
Hermide	2009	Ramipril (60)	5mg	Awakening (NR)	6 wks	46.9(12.3)	150.0/91.2	Grade 1-2 EH	Multicenter, parallel-group
		Ramipril (60)	5mg	Bedtime (NR)	6 wks	46.5(10.2)	147.6/92.0		PROBE trial
Hermida	2009a	Spirapril (83)	6mg	Awaking (NR)	12 wks	42.4 (12.9)	144.6/86.6	Grade 1-2 EH	Open-label, parallel-group,
		Spirapril (82)	6mg	Bedtime (NR)	12 wks	42.6 (14.8)	146.8/85.8		blinded-endpoint trial
ARBs									
Hermida	2003	Valsartan (46)	160mg	Morning (NR)	3 mths	49.3 (12.3)	157.0/92.0	Grade 1-2 EH	Randomized, open-label trial
		Valsartan (44)	160mg	Bedtime (NR)	3 mths	48.7 (16.2)	158.3/91.6		
Hermida	2005a	Valsartan (72)	160mg	Awakening (NR)	3 mths	53.1 (12.1)	160.7/92.1	Grade 1-2 EH	PROBE trial
		Valsartan (76)	160mg	Bedtime (NR)	3 mths	52.9 (13.0)	160.0/92.1		
Hermida	2005b	Valsartan (50)	160mg	Awakening (NR)	3 mths	68.3 (4.7)	161.1/87.4	Grade 1-2 EH	PROBE trial

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		Valsartan (50)	160mg	Bedtime (NR)	3 mths	68.1 (5.3)	161.3/87.1		
Hermida	2007	Telmisartan(107)	80mg	Morning (NR)	12 wks	46.4(11.5)	151.8/90.9	Grade 1-2 EH	PROBE trial
		Telmisartan(108)	80mg	Bedtime (NR)	12 wks	46.5(12.6)	153.5/91.6		
Hermida	2009b	Olmesartan (73)	20mg	Awakening (NR)	3 mths	45.5(11.9)	151.8/89.9	Untreated grade 1-2 UEH	PROBE trial
		Olmesartan (71)	20mg	Bedtime (NR)	3 mths	47.6 (12.7)	150.4/88.4		
Mori	2013	Olmesartan (110)	NR	Morning (NR)	6 mths	62.1 (13.6)	161.2/91.0*	Siting SBP/DBP≥140/90	RCT
		Olmesartan (108)	NR	Evening (NR)	6 mths	60.8 (9.4)	156.2/89.6*	mmHg	
Ushijima	2015	Olmesartan (11)	20mg	Morning (NR)	4 mths	64.3 (13.0)	143.8/86.3	NR	Multicenter, open-label,
		Olmesartan (12)	20mg	Evening (NR)	4 mths	66.2 (7.0)	140.2/12.9	NR	randomized, parallel trial
Kario	2009	Candesartan(221)	NR	Awakening (NR)	24 wks	66.6 (13.3)	NR	NR	RCT
		Candesartan(229)	NR	Bedtime (NR)	24 wks	66.6 (12.6)	NR	NR	
Duretics									
Calvo	2006	Torasemide (30)	5mg	Morning (NR)	NR	NR	NR	Grade 1-2 EH	RCT
		Torasemide (28)	5mg	Bedtime (NR)	NR	NR	NR		
Hermida	2008	Torasemide (61)	5mg	Morning (NR)	6 wks	53.3 (10.8)	154.1/86.6	Grade 1-2 EH	PROBE trial
		Torasemide (60)	5mg	Bedtime (NR)	6 wks	49.7 (10.1)	153.1/88.2		
CCBs									
Hermida	2007a	Nifedipine (39)	30mg	Morning (NR)	8 wks	51.5 (11.1)	155.4/92.1	Grade 1-2 EH	RCT
		Nifedipine (41)	30mg	Bedtime (NR)	8 wks	52.6 (10.3)	157.3/92.8		
Hermida	2008a	Nifedipine (88)	30mg	Morning (NR)	8 wks	52.1 (11.2)	157.0/94.0	Untreated grade 1-2 EH	PROBE trial
		Nifedipine (92)	30mg	Bedtime (NR)	8 wks	52.8 (10.2)	158.0/93.0		
Hermida	2009c	Nifedipine (118)	30mg	Awaking (NR)	8 wks	53.5 (11.8)	159.1/94.8	Untreated grade 1-2 UEH	PROBE trial
		Nifedipine (120)	30mg	Bedtime (NR)	8 wks	53.1 (11.1)	160.8/93.2		
Nold	1998	Amlodipine (12)	5mg	Morning (08:00)	3 wks	46.9 (13.8) **	NA	Mild to moderate EH	Open, two-period, RCOT;

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		Amlodipine (12)	5mg	Bedtime (20:00)					washout period: 1 week
BBs									
Neutel	2005	Propranolol (23)	120mg	Morning (08:00)	4 wks	54.1 (8.61)	151.7/100.4	Stage 1-2 EH	Multicenter, double-blind, double-dummy, randomized blind endpoint, crossover trial
		Propranolol (21)	120mg	Bedtime (22:00)	4 wks	52.6 (8.44)	151.4/99.5		
Acelajado	2012	Nebivolol (38)	5-10mg	Morning (NR)	3 wks	52.0 (12.0)**	152.4/92.8**	Mild to moderate EH	Single center, double-blind RCOT; washout period: 2 weeks
		Nebivolol (38)	5-10mg	Bedtime (NR)	3 wks				
Combination									
Hermida	2010	Valsartan/amlodipine (50)	160/5mg	Morning (NR)	12 wks	54.0 (12.3)	162.9/95.4	Untreated uncomplicated EH	PROBE trial
		Valsartan/amlodipine (52)	160/5mg	Bedtime (NR)	12 wks	59.7 (9.3)	161.0/92.3		
Asmar	2011	Valsartan/amlodipine (278)	160/5mg	Morning (06-10:00)	8 wks	56.0 (10.0)	144.0/86.0	Untreated EH	PROBE trial
		Valsartan/amlodipine (268)	160/5mg	Evening(18:00-22:00)	8 wks	56.0 (10.0)	144.0/86.0		
Kario	2016	Telmisartan/Amlodipine (41)	5/40mg	Morning(NR)	12 wks	NR	NR	HTN with paroxysmal AF†	Multicentered, PRO trial
		Telmisartan/Amlodipine (40)	5/40mg	Bedtime(NR)	12 wks	NR	NR		
Peng	2013	Telmisartan/Amlodipine (26)	5/80mg	Morning (6:00-08:00)	8 wks	58.3 (10.7)	158.1/93.3	> stage 2 EH	Single-blinded, randomized, parallel-controlled trial
		Telmisartan/Amlodipine (28)	5/80mg	Bedtime(19:00-21:00)	8 wks	57.1 (10.5)	157.2/95.4		
Hermida	2011	Valsartan/HCTZ (104)	160/12.5mg	Morning (NR)	12 wks	49.1 (10.7)	158.0/94.3	Untreated uncomplicated EH	PROBE trial
		Valsartan/HCTZ (100)	160/12.5mg	Bedtime (NR)	12 wks	50.4 (11.4)	156.7/92.4		
Huangfu	2015	Losartan/ Indapamide(20)	2.5/50mg	Morning (06-08:00)	12 wks	NR	NR	Stage 2-3 EH	Single-blinded, randomized, parallel-controlled trial
		Losartan/ Indapamide(21)	2.5/50mg	Bedtime (19-21:00)	12 wks	NR	NR		
Zeng	2011	Amlodipine/HCTZ (40)	5/25mg	Morning (08:00)	12 wks	66.9 (9.3)	158.5/92.4	Stage 1 to 2 EH	Multicenter, open-label, RCT (participants: blinded)
		Amlodipine/HCTZ (40)	5/25mg	Bedtime (22:00)	12 wks	68.5(10.0)	155.6/92.2		

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376*Data of patients who completed the trial in each study; ** The relevant data about all patients completing the trial; † Enrolled subjects were hypertensive individuals
377with paroxysmal AF;
378ACEI=angiotensin converting enzyme inhibitor; N.=number; SD=standard deviation; O=office; wks=weeks; yrs=years; DBP=dilated blood pressure;
379RCOT=randomized crossover trial; PROBE=prospective, randomized, open-label, blinded endpoint; PRO=prospective, randomized, open-label; ARB=angiotensin II
380receptor blocker; EH=essential hypertension; UEH=uncomplicated essential hypertension; HTN=hypertension; AF=atrial fibrillation; CCBs=calcium channel
381blockers; BBs=beta-adrenergic receptor blockers; ABs=alpha-adrenergic receptor blockers; NR=not reported
382

383**Table.2 Meta-analyses and subgroup analyses for safety profiles comparing morning dosing versus bedtime dosing**

Variable	No. of Trials	No. of subjects (M/E)	Heterogeneity (I^2)	RR	95%CI	P-value
Overall drug-related AEs						
Total	**14**	**1146/1147**	**Chi^2=18.70, I^2=41.0%**	**0.81**	**(0.60, 1.10)**	**P=0.17**
ACEIs	5	209/213	Chi^2=0.34, I^2=0.0%	0.35	(0.09, 1.40)	P=0.14
ARBs	2	300/294	Chi^2=2.55, I^2=61.0%	1.28	(0.32, 5.22)	P=0.73
Diuretics	2	88/91	Chi^2=0.17, I^2=0.0%	1.67	(0.57, 4.88)	P=0.35
CCBs	3	253/245	Chi^2=1.75, I^2=0.0%	0.32	(0.17, 0.62)	P=0.0007

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ARBs+CCBs	2	296/304	Chi^2=0.83, I^2=0.0%	1.20	(0.80, 1.82)	P=0.38
Overall withdrawals						
Total	**13**	**876/872**	**Chi^2=4.69, I^2=0.0%**	**0.58**	**(0.36, 0.93)**	**P=0.02**
ACEIs	3	67/70	Chi^2=0.85, I^2=0.0%	0.68	(0.20, 2.31)	P=0.54
ARBs	3	408/404	Chi^2=0.37, I^2=0.0%	0.64	(0.36, 1.13)	P=0.13
Diuretics*	2	88/91	NA	NA	-	-
CCBs	2	133/127	Chi^2=2.71, I^2=63%	0.29	(0.04, 1.95)	P=0.20
Combination*	3	180/180	NA	NA	-	-
Serious AEs						
Total	**2**	**497/499**	**Chi^2=1.60, I^2=37.0%**	**0.66**	**(0.23, 1.90)**	**P=0.44**
ARBs	1	229/221	NA	0.14	(0.01, 2.65)	P=0.19

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ARBs+CCBs	1	268/278	NA	1.04	(0.30, 3.54)	P=0.95

*The data in this row could not available;

AEs=adverse events; ACEIs= angiotensin converting enzyme inhibitor; ARB=angiotensin II receptor blockers; CCBs=calcium channel blockers; No. of trials=number of trials; No. of subjects=number of subjects; M/E=morning/evening; RR=risk ratio; CI=confidence interval; NA=not available.

Supp.1 Search Strategy

Ovid Medline 1946 to Present with Daily Update (Search date: 10 April, 2020)

No.	Query	Results
#1	Exp essential hypertension/	2233
#2	(essential adj hypertens*). mp.	24151
#3	(primary adj hypertens*).mp.	2114

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#4	**or/1-3**	**25896**
#5	exp Chronotherapy/	975
#6	(chronophrm* or chronomodulat* or chronotherapy*).mp	1675
#7	**5 or 6**	**1675**
#8	(morning or daytime or day or diurnal* or awak* or am).mp.	1209142
#9	(evening or bedtime or night* or nocturnal* or pm).mp.	178930
#10	**8 and 9**	**68740**
#11	**7 or 10**	**69983**
#12	randomized controlled trial. pt.	503644
#13	controlled clinical trial. pt.	93611
#14	randomized. ab.	475606
#15	placebo. ab.	206694

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#16	randomly. ab.	330775
#17	trial. ab.	501000
#18	groups. ab.	2031658
#19	**or/12-18**	**2930062**
#20	(animal* not (human* and animal*)).mp.	4479471
#21	19 not 20	2503917
#22	**4 and 11 and 21**	**455**

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392**COCHRANE CENTRAL search strategy**

No.	**Query**	**Results**
#1	MeSH descriptor: [Essential Hypertension] explode all trees	145
#2	(essential NEAR hypertens*):ti,ab,kw	7356
#3	(primary NEAR hypertens*):ti,ab,kw	4319
#4	**or/1-3**	**11000**

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#5	(Chronotherapy*):ti, ab, kw	413
#6	(Chronomodulat*):ti,ab,kw	88
#7	(Chronopharm*):ti,ab,kw	192
#8	**or/5-7**	**643**
#9	(morning or daytime or day or diurnal* or awak* or am):ti,ab,kw	257625
#10	(evening or bedtime or night* or nocturnal* or pm):ti,ab,kw	36606
#11	**#9 and #10**	**22123**
#12	**#8 or #11**	**22512**
#13	**4 and 12**	**629**

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394**OVID EMBASE from 1974 to 10 April, 2020**

No.	Query	Results
#1	'essential hypertension'/exp (including related terms)	11410

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#2	(essential adj hypertens*).tw	30407
#3	(primary adj hypertens*).tw	3002
#4	**#1 OR #2 OR #3**	**33606**
#5	'chronotherapy'/exp	25616
#6	(chronophrm* or chronomodulat* or chronotherapy*).tw	1460
#7	(morning or daytime or day or diurnal* or awak* or am).tw.	1734633
#8	(evening or bedtime or night* or nocturnal* or pm).tw.	250696
#9	**#7 AND #8**	103194
#10	**#6 OR #9**	104259
#11	random* OR crossover* OR placebo* OR assign* OR allocate* OR doubl* NEAR/5 blind* OR singl*NEAR/5 blind*	10005
#12	'randomized controlled trial'/exp	10134

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#13	‘crossover procedure’/exp	17146
#14	placebo. tw	10018
#15	randomly. tw	14470
#16	**#11 OR #12 OR #13 OR #14 OR #15**	**60952**
#19	**4 and 10 and 16**	**13**

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396**Supp. 2 Subgroup analysis in the comparison of blood pressure reduction between bedtime regimen and awakening regimen**

Variable	No. of Trials	Heterogeneity (I^2)	MD/OR	95%CI	P-value
Monotherapy					
ACEIs					
Clinic SBP	4	0.0%	0.46 mmHg	[-0.94, 1.86]	P=0.52
Clinic DBP	4	94.0%	3.84 mmHg	[-2.69, 10.36]	P=0.25
24-hour or 48-hour SBP	3	0.0%	-1.85mmHg	[-3.47, -0.24]	P=0.02

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24-hour or 48-hour DBP	3	72.0%	-1.12mmHg	[-4.04, 1.81]	P=0.45
Nocturnal (asleep) mean SBP	4	48.0%	-5.97mmHg	[-8.89, -3.06]	P<0.0001
Nocturnal (asleep) mean DBP	4	65.0%	-4.49mmHg	[-7.37, -1.60]	P=0.002
Diurnal (awakening) mean SBP	4	0.0%	0.48mmHg	[-1.31, 2.27]	P=0.60
Diurnal (awakening) mean DBP	4	45.0%	-0.04mmHg	[-2.44, 2.37]	P=0.97
Awake/asleep SBP ratio *Morning*	2	0.0%	-2.79%	[-4.08, -1.50]	P<0.0001
Bedtime		0.0%	4.56%	[2.83, 6.29]	P<0.0001
Awake/asleep DBP ratio *Morning*	2	0.0%	-2.42%	[-4.13, -0.71]	P=0.006
Bedtime		0.0%	4.56%	[2.83, 6.29]	P<0.0001
Morning SBP	1	-	-7.20mmHg	[-11.05, -3.35]	P=0.0002
Morning DBP	1	-	-6.50mmHg	[-9.30, -3.70]	P<0.0001
Non-dipper (%) *Morning*	2	0.0%	OR=1.28	[0.84, 1.97]	P=0.256

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Bedtime	2	0.0%	OR=0.42	[0.24, 0.72]	P=0.002
ARBs					
Clinic SBP	8	51.0%	-0.16mmHg	[-1.90, 1.59]	P=0.84
Clinic DBP	7	45.0%	-0.18mmHg	[-1.86, 1.50]	P=0.93
24-hour or 48-hour SBP	6	0.0%	-1.04mmHg	[-2.38, 0.03]	P=0.13
24-hour or 48-hour DBP	5	88.0%	-2.84mmHg	[-6.70, 1.02]	P=0.15
Nocturnal (asleep) mean SBP	4	39.0%	-6.63mmHg	[-9.07, -4.19]	P<0.0001
Nocturnal (asleep) mean DBP	4	84.0%	-2.11 mmHg	[-5.45, 1.24]	P=0.22
Diurnal (awakening) mean SBP	4	0.0%	0.77 mmHg	[-0.98, 2.52]	P=0.39
Diurnal (awakening) mean DBP	4	21.0%	0.57mmHg	[-0.96, 2.10]	P=0.47
Awake/asleep SBP ratio *Morning*	4	0.0%	-1.01%	[-1.93, -0.10]	P=0.03
Bedtime		87.0%	5.06%	[2,46, 7.65]	P=0.0001
Awake/asleep DBP ratio *Morning*	4	0.0%	-0.46%	[-1.50, 0.59]	P=0.39

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Bedtime		64.0%	5.29 %	[3.43, 7.16]	P<0.0001
Morning SBP.	2	0.0%	-2.40mmHg	[-4.77, -0.02]	P=0.05
Morning DBP	2	0.0%	-1.70mmHg	[-3.07, -0.33]	P=0.01
Non-dipper (%). *Morning*	5	0.0%	OR=0.96	[0.74, 1.24]	P=0.748
Bedtime	5	0.0%	OR=0.31	[0.22, 0.43]	P<0.0001
Diuretics					
Clinic SBP	2	0.0%	-3.10mmHg	[-8.85, 2.66]	P=0.29
Clinic DBP	2	0.0%	-3.96mmHg	[-6.92, -1.00]	P=0.009
24-hour or 48-hour SBP	2	0.0%	-7.03mmHg	[-10.38, -3.68]	P<0.0001
24-hour or 48-hour DBP	2	0.0%	-5.52 mmHg	[-8.13, -2.92]	P<0.0001
Nocturnal (asleep) mean SBP	2	51.0%	-5.78 mmHg	[-10.87, -0.70]	P=0.03
Nocturnal (asleep) mean DBP	2	13.0%	-4.36mmHg	[-7.21, -1.50]	P=0.003
Diurnal (awakening) mean SBP	2	0.0%	-7.48mmHg	[-10.89, -4.07]	P<0.0001
Diurnal (awakening) mean DBP	2	0.0%	-5.88mmHg	[-8.69, -3.07]	P<0.0001

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Awake/asleep SBP ratio *Morning*	2	0.0%	-1.09%	[-3.10, 0.92]	P=0.29
Bedtime		0.0%	-1.95%	[-4.01, 0.12]	P=0.06
Awake/asleep DBP ratio *Morning*	2	0.0%	-0.60%	[-2.64, 1.44]	P=0.57
Bedtime		5.0%	-1.24%	[-3.58, 1.09]	P=0.30
Morning SBP.	NA	NA	NA	NA	NA
Morning DBP	NA	NA	NA	NA	NA
Non-dipper (%) *Morning*	1	-	OR=1.55	[0.79, 3.03]	P=0.201
Bedtime	1	-	OR=1.47	[0.72, 3.02]	P=0.293
CCBs					
Clinic SBP	3	0.0%	-4.56 mmHg	[-6.88, -2.23]	P=0.0001
Clinic DBP	3	0.0%	-3.94mmHg	[-5.69, -2.19]	P<0.0001
24-hour or 48-hour SBP	4	0.0%	-3.44mmHg	[-5.29, -1.59]	P=0.0003
24-hour or 48-hour DBP	4	0.0%	-1.70mmHg	[-3.04, -0.37]	P=0.01

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Nocturnal (asleep) mean SBP	4	0.0%	-4.65mmHg	[-6.59, -2.71]	P<0.0001
Nocturnal (asleep) mean DBP	4	0.0%	-2.63mmHg	[-4.04, -1.23]	P=0.0002
Diurnal (awakening) mean SBP	4	0.0%	-3.14mmHg	[-5.06, -1.22]	P=0.001
Diurnal (awakening) mean DBP	4	0.0%	-0.67mmHg	[-2.08, 0.73]	P=0.35
Awake/asleep SBP ratio *Morning*	3	0.0%	-0.73%	[-1.68, 0.21]	P=0.13
Bedtime		0.0%	0.98%	[-0.15, 2.11]	P=0.09
Awake/asleep DBP ratio *Morning*	3	0.0%	-0.44%	[-1.62, 0.73]	P=0.46
Bedtime		0.0%	1.64%	[0.38, 2.90]	P=0.01
Morning SBP	1	-	-7.50mmHg	[-11.38, -3.62]	P=0.0001
Morning DBP	1	-	-4.70mmHg	[-7.10, -2.30]	P=0.0001
Non-dipper (%) *Morning*	3	0.0%	OR=1.09	[0.81, 1.46]	P=0.563
Bedtime	3	0.0%	OR=0.69	[0.50, 0.94]	P=0.019

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Combination

ARBs/CCBs

Clinic SBP	3	2.0%	0.18 mmHg	[-4.41, 4.77]	P=0.94
Clinic DBP	2	34.0%	1.50mmHg	[-2.21, 5.20]	P=0.43
24-hour or 48-hour SBP	4	64.0%	-2.43 mmHg	[-6.29, 1.43]	P=0.22
24-hour or 48-hour DBP	4	0.0%	-0.37 mmHg	[-1.61, 0.86]	P=0.55
Nocturnal (asleep) mean SBP	4	87.0%	-4.29 mmHg	[-11.37, 2.78]	P=0.23
Nocturnal (asleep) mean DBP	4	93.0%	-3.34 mmHg	[-9.08, 2.40]	P=0.25
Diurnal (awakening) mean SBP	4	79.0%	-2.83 mmHg	[-8.14, 2.47]	P=0.30
Diurnal (awakening) mean DBP	4	0.0%	-0.23mmHg	[-1.52, 1.06]	P=0.72
Awake/asleep SBP ratio *Morning*	2	0.0%	-1.33%	[-3.35, 0.70]	P=0.20
Bedtime	2	67.0%	3.26%	[-1.24, 7.76]	P=0.16
Awake/asleep DBP ratio *Morning*	1	-	-2.20%	[-5.42, 1.02]	P=0.18

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Bedtime	1	-	5.20%	[1.85, 8.55]	P=0.002
Non-dipper (%)	NA	NA	NA	NA	NA
ARBs/diuretics					
Clinic SBP	1	-	-0.40mmHg	[-2.81, 2.01]	P=0.74
Clinic DBP	1	-	-0.40 mmHg	[-2.81, 2.01]	P=0.74
24-hour or 48-hour SBP	2	0.0%	-1.04 mmHg	[-3.77, 1.68]	P=0.45
24-hour or 48-hour DBP	2	0.0%	-0.85mmHg	[-2.69, 0.99]	P=0.37
Nocturnal (asleep) mean SBP	2	0.0%	-3.81mmHg	[-6.55, -1.07]	P=0.006
Nocturnal (asleep) mean DBP	2	0.0%	-1.50mmHg	[-3.48, 0.48]	P=0.14
Diurnal (awakening) mean SBP	2	0.0%	0.47 mmHg	[-2.46, 3.41]	P=0.75
Diurnal (awakening) mean DBP	2	0.0%	-0.30mmHg	[-2.17, 1.58]	P=0.76
Awake/asleep SBP ratio *Morning*	1	-	0.10%	[-1.13, 1.33]	P=0.87
Bedtime	1	-	3.90%	[2.39, 5.41]	P<0.0001
Awake/asleep DBP ratio *Morning*	1	-	2.30%	[0.92, 3.68]	P=0.001

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Bedtime	1	-			P<0.0001
			4.60%	[2.71, 6.49]	
Non-dipper (%)	NA	NA	NA	NA	NA
CCBs/diuretics					
Clinic SBP	NA	NA	NA	NA	NA
Clinic DBP	NA	NA	NA	NA	NA
24-hour or 48-hour SBP	1	-	-4.00 mmHg	[-11.28, 3.28]	P=0.28
24-hour or 48-hour DBP	1	-	-5.40 mmHg	[-10.59, -0.21]	P=0.04
Nocturnal (asleep) mean SBP	NA	NA	NA	NA	NA
Nocturnal (asleep) mean DBP	NA	NA	NA	NA	NA
Diurnal (awakening) mean SBP	NA	NA	NA	NA	NA
Diurnal (awakening) mean DBP	NA	NA	NA	NA	NA
Awake/asleep SBP ratio	NA	NA	NA	NA	NA

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Awake/asleep DBP ratio	NA	NA	NA	NA	NA
Non-dipper (%) *morning*	1	-	OR=0.86	[0.40, 1.85]	P=0.694
bedtime	1	-	OR=0.55	[0.24, 1.25]	P=0.152

397MD=mean of difference; OR=odds ratio; CI=confidence interval; SBP=systolic blood pressure; DBP=diastolic blood pressure; ACEI=angiotensin-converting enzyme inhibitors;

398ARB=angiotensin receptor blockers; CCBs=calcium channel blockers; NA=not available;

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