Review

OPEN

Evening dosing versus morning dosing of antihypertensive medications for nocturnal hypertension: a systematic review and meta-analysis of 107 randomized controlled trials

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See related paper on pages 1681 and 1684

Since the effects of once-daily antihypertensive (HT) medications are more pronounced within the first few hours of ingestion, evening administration of anti-HT medications can be a feasible treatment for nocturnal HT. However, no relevant meta-analysis has been conducted in patients with nocturnal HT. This meta-analysis included randomized controlled trials involving patients with elevated mean nocturnal blood pressure (BP) and compared evening anti-HT administration with morning administration. Multiple databases, including grey literature (e.g. clincialtrial.gov), were searched. Study selection and data extraction were conducted by two independent authors. Risk of bias assessment and overall quality of evidence were conducted using Cochrane risk-of-bias tool and GRADE by two independent authors. A total of 107 studies were included, 76 of which were investigated in China and had not been identified in previous reviews. Only one trial was ranked low risk-of-bias. Evening administration of anti-HT medications was effective in reducing nocturnal systolic BP (4.12–9.10 mmHg; $I^2 = 80.5–95.2\%$) and diastolic BP (3.38–5.87 mmHg; $I^2 = 87.4–95.6\%$). Subgroup analyses found that the effectiveness of evening administration was contributed by data from the Hermida group and China. Evening administration did not provide additional nocturnal/daytime/24-h BP reduction in non-Hermida/non-China studies ($I^2 = 0$) and in meta-analyses that included studies with unclear or low risk of bias. The effectiveness of nocturnal BP reduction was similar across different types, doses, and half-lives of medications. Evening administration of anti-HT medications may reduce proteinuria, left ventricular hypertrophy (LVH), nondipping and morning surge. The overall quality of evidence was ranked as very low to low. Our results highlight the scarcity of low risk-of-bias studies and emphasize the need for such trials to evaluate the efficacy of evening dosing of anti-HT medications as a standard treatment for patients with nocturnal HT across diverse populations.

Keywords: blood pressure, evening dosing, meta-analysis nocturnal hypertension

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, beta-blocker; BP, blood pressure; CCB, calcium channel blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ESH, European Society of Hypertension; HT, hypertension/hypertensive; IMT, intima-media thickness; LVH, left ventricular hypertrophy; RCT, randomized controlled trials; SBP, systolic blood pressure; SD, standard deviation

INTRODUCTION

Hypertension (HT) is the most common chronic disease which affects around one-third of the adult population worldwide. It is the leading cause of cardiovascular diseases, chronic kidney disease and death [1]. Though traditionally, daytime blood pressure (BP) has been the sole treatment target for HT, BP during sleep (i.e., nocturnal BP) consistently emerges as a stronger predictor

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of cardiovascular outcomes and mortality, even after controlling for daytime BP [2]. Moreover, successful treatment of nocturnal HT may reduce cardiovascular risk [3]. Additionally, nocturnal HT-related BP patterns, such as nondipping (defined as a <10% reduction in BP during sleep), independently predict cardiovascular diseases and mortality [4,5]. Despite the increasing identification of nocturnal HT and abnormal BP dipping patterns due to the widespread use of 24-h ambulatory BP monitoring (ABPM), there is a lack of definite treatments, as reflected by the absence of relevant recommendations in the latest international guidelines [6,7]. Once-daily dosing of anti-HT medications is preferred to improve patients' adherence, and their BP-reducing effects are generally more pronounced within the first few hours after ingestion [8]. Thus, administering once-daily anti-HT medications in the evening may improve nocturnal BP control and reverse nondipping [9]. Additionally, some anti-HT medications may work better during sleep. For example, drugs that inhibit the renin-angiotensin-aldosterone system may work more effectively during sleep, when renin secretion is at its peak [10].

Though several meta-analyses have shown that evening dosing of anti-HT medications may provide additional nocturnal BP reduction, these studies included patients without nocturnal HT [8,9,11–13]. This distinction is important because patients with normal nocturnal BP may experience harm from evening dosing of anti-HT medications, as it can lead to excessive reduction in nocturnal BP and an associated excessive morning surge, which has been linked to cardiovascular events [14]. This may explain the highly heterogeneous results observed in these meta-analyses and relevant randomized controlled trials (RCTs) [8,9,11–13]. Besides, adequate subgroup analyses and/or meta-regressions have not been conducted [8,9,11–13]. In the latest review, data from a single center in Spain had an increased effect size and could be considered an outlier, but only one review conducted this relevant subgroup analysis [9]. Furthermore, previous reviews included trials that used different medications in the morning and evening arms, thereby providing limited clinical guidance regarding the selection of evening medications in terms of type, dose, and half-life [8,9,11–13]. Additionally, many studies published in Chinese have never been included in any meta-analysis [8,9,11–13].

METHODS

This systematic review and meta-analysis were preregistered in PROSPERO (CRD42022351553) and reported according to the PRISMA guideline (http://www.prisma-statement.org/). To put it into PICOS (Patients, Intervention, Control, Outcomes, Study design) format, this study investigates the following: "In patients with nocturnal HT (P), whether evening administration of once-daily anti-HT medication(s) (I) result in better reduction of nocturnal BP (O) compared to morning administration of the same medication(s) (C)".

Study eligibility criteria

Only RCTs were included to provide the highest quality evidence. RCTs were included if they included patients with a mean nocturnal systolic BP (SBP) of ≥120 mmHg and/or diastolic BP (SBP) of ≥70mmHg, as defined by the ESH or International Society of Hypertension [6,7]. This also included patients with nocturnal HT as defined by the American guideline (i.e. ≥110/65mmHg) [15], compared evening administration (after 6 pm) of once-daily anti-HT medication(s) with their morning administration (before noon), reported nocturnal SBP or DBP measured by ABPM, administered medications for at least 4 weeks to allow anti-HT medications exerting their fullest effects [12], and were published in either Chinese or English. Anti-HT medications included in this review were angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), beta-blockers (BBs), diuretics, and their combinations. In addition, same dosing of anti-HT medications should be offered regardless of morning or evening administration. If titration of medication(s) was allowed due to suboptimal BP control (often required in longer RCTs to ensure participants' safety), both arms should follow the same paradigm of stepwise dose titration. Studies that included patients aged <18, pregnant women, or those suffered from resistant HT were excluded. Observational studies, animal studies, commentaries, and reviews were also excluded.

Search strategy

The databases searched included Ovid MEDLINE, EMBASE, CINAHL Complete, Allied and Complementary Medicine, Cochrane Library, PubMed, Scopus, Web of Science, and Chinese databases including WanFang Data, SinoMed, Superstar Journals Database, and China Academic Journal Network Publishing Database from their inception until April 4, 2023. We used a combination of search terms and subject headings, including "hypertension", "nocturnal hypertension", "chronotherapy", "chronopharmacology", "bedtime", "evening", "blood pressure", and "controlled trial" (Table S1, Supplemental Digital Content, http://links.lww.com/HJH/C513). The searches were restricted to studies involving adults and publications in either English or Chinese. When only abstracts were available in relevant studies, the authors of those records were contacted to obtain any published report/article. In addition, reference lists of relevant systematic reviews previously published were searched [8,11–13]. The ClinicalTrials.gov was searched for unpublished trials and the respective authors were contacted whenever feasible.

Study screening and data extraction

The identified studies were imported into the Covidence program (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org). Two reviewers (two members of the author team) independently conducted abstract and full-text screening followed by data extraction. Any discrepancies were compared and resolved through discussion.

The following data were extracted: details of the RCTs (e.g. country, year of publication, number of participants, length of intervention, cross-over design or parallel design), details of the participants (e.g. demographics [age/sex], baseline office or out-of-office BP [24-h/daytime/nocturnal], presence of diabetes/ hyperlipidemia/ cardiovascular disease/chronic kidney disease/sleep apnea), details of

intervention [name, dose, timing] and details of control groups. Outcome measures included mean and standard deviation (SD) of different types of BP data (out-of-office BP [including 24-h/awake/asleep BP]. Secondary outcomes included dipping status, degree of morning surge, heart rate (awake/asleep/24-h), patients' adherence rate, surrogate cardiovascular outcomes (such as proteinuria and left ventricular hypertrophy [LVH]), safety (proportion with mild/severe adverse effects and dropouts from RCT) and cardiovascular events and death in RCTs longer than one year.

Risk of bias assessment among included trials

Risk of bias assessment was conducted based on the Cochrane risk-of-bias tool [16]. In addition, as BP was the primary outcome, the quality of BP measurements was assessed, including whether the models of BP monitors were validated and whether BP measurements were conducted according to international guideline standards (e.g. ABPM should be measured every 20–30 min) [7]. A study was considered at low risk of bias only when all the signaling questions were not of concern, whereas all other studies were categorized as having "unknown risk of bias" or "high risk of bias". All assessments were conducted by two independent reviewers from the author team, and any discrepancies were resolved through discussion.

Similarly, the overall quality of evidence concerning our primary and secondary outcomes was ranked according to the GRADE framework by two independent reviewers [17].

Pairwise meta-analysis

All meta-analyses and meta-regressions were conducted using Stata (StataCorp. 2021. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC).

The primary outcomes were the weighted mean differences in nocturnal SBP and DBP on ABPM between the evening administration and the morning administration arm. Meta-analyses were also conducted for cardiovascular outcomes and the proportion with side effects and drop-outs, between both arms. Given the diversity of participants from different RCTs in terms of comorbidities and ethnicity, restricted maximum likelihood (REML, a random effects model) was used to pool weighted mean differences. Heterogeneity across the studies was assessed using the I^2 statistics. Two-tailed P-values were used and a P-value <0.05 was considered statistically significant. Publication bias was assessed using funnel plots, Eggers' test, Begg's test, and trim-and-fill tests.

Analysis was conducted for different drug classes used (ACEI/ARB/BB/CCB/diuretics and their combinations). Previous reviews considered studies from the Hermida group as outliers due to larger effect size. During our analysis, we had similar observations on studies from China. Subgroup analyses were conducted for studies from the Hermida group and China. Other subgroup analyses included dosage of medications used in the RCT (higher dose is defined as >50% of its registered maximum dose), and whether titration of medications was allowed during the RCT. When there were adequate numbers of RCTs ($n \geq 10$), meta-regressions were conducted to investigate heterogeneity or identify determinants of effects according to participant characteristics (e.g. presence of OSAS, age, sex) and intervention characteristics (e.g. half-life of the medications). The permutation method is used to adjust P-value for multiple testing in meta-regressions. Sensitivity analysis was conducted to include only larger trials ($n > 50$) and include RCTs with lower risk-of-bias.

RESULTS

Characteristics of included studies

Our search found 11,114 studies, of which 107 were eligible and included in meta-analyses (Fig. 1). The list of included studies can be found in Table S2, Supplemental Digital Content, http://links.lww.com/HJH/C513. The majority of studies were from China ($n = 76$), Spain ($n = 14$), and Japan ($n = 5$). Most studies investigated ACEI/ARB ($n = 64$), CCB ($n = 35$), and drug combinations ($n = 17$) and a few investigated BB ($n = 3$) and diuretics ($n = 1$ [Torasemide]). Our analysis included a total of 12 094 participants, of which most were male (55%), nondippers (77.76%) and did not have cardiovascular diseases (95.42%). Mean age and nocturnal BP of participants were 58.06 years and 136.63/83.73 mmHg respectively (Table S3, Supplemental Digital Content, http://links.lww.com/HJH/C513).

Only one study was ranked low-risk of bias. Most RCTs did not blind participants, who needed to know the time of taking medication(s) (Table S4, Supplemental Digital Content, http://links.lww.com/HJH/C513).

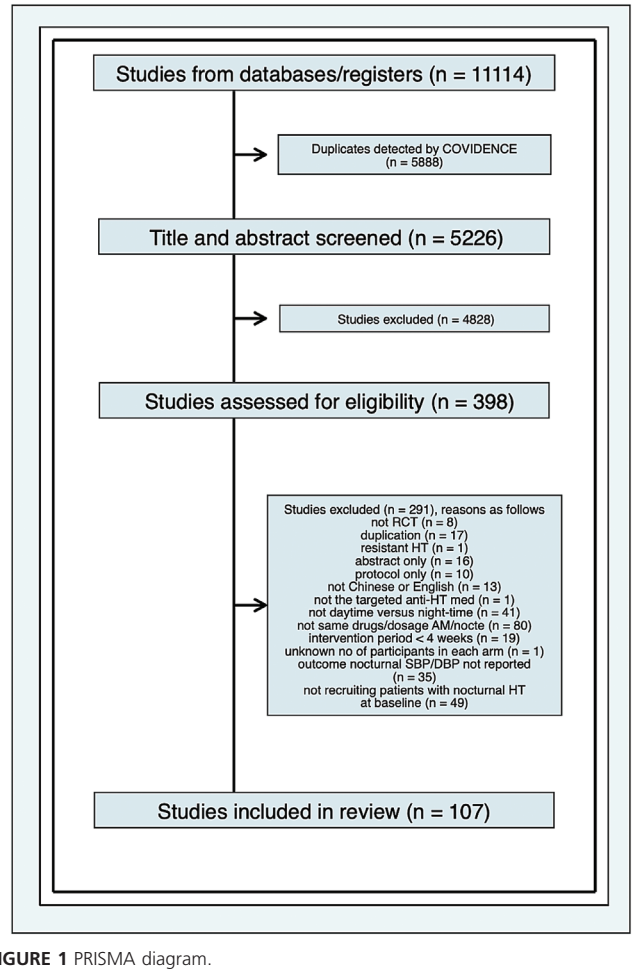


FIGURE 1 PRISMA diagram.

Primary outcome

Evening administration was more effective to reduce nocturnal SBP for ACEI/ARB (−5.10 mmHg; 95% CI: −6.51 to −3.69; I^2 90.3%), for BB (−6.42 mmHg; 95% CI: −12.77 to −0.07; I^2 80.5%), for CCB (−4.08 mmHg; 95% CI: −5.69 to −2.48; I^2 81.2%), for diuretics (−9.10 mmHg; 95% CI: −13.79 to −4.41; I^2 not applicable) and for drug combinations (−6.51 mmHg; 95% CI: −9.56 to −3.47; I^2 95.2%) (Table 1 and Fig. 2).

Evening administration was more effective to reduce nocturnal DBP for ACEI/ARB (−3.43 mmHg; 95% CI: −4.55 to −2.30; I^2 90.1%), for CCB (−3.37 mmHg; 95% CI: −4.65 to −2.09; I^2 87.4%), for diuretics (−6.4 mmHg; 95% CI: −9.72 to −3.08; I^2 not applicable) and for drug combinations (−4.19 mmHg; 95% CI: −6.48 to −1.90; I^2 95.6%), but not for BB (−5.87 mmHg; 95% CI: −13.51 to 1.77; I^2 93.3%) (Table 1 and Fig. 3).

Subgroup analyses found that the effectiveness of evening administration was only contributed by data from the Hermida group and China. For instance, evening administration did not result in greater reduction of nocturnal BP compared to morning administration in non-China and non-Hermida studies for ACEI/ARB, CCB, or drug combination with low heterogeneity ($I^2 = 0$). Other subgroup analyses and meta-regressions did not identify consistent participant demographic factors or intervention characteristics that could predict effectiveness and did not fully resolve high heterogeneity. Moreover, the effectiveness of nocturnal BP reduction was similar across different doses and half-lives of medications within the same drug class. However, lower doses of CCB may be more effective in reducing BP (5.3/4.09 mmHg) compared to higher doses (0.66/0.08 mmHg) (Table S5, Figures S1 and S2, Supplemental Digital Content, http://links.lww.com/HJH/C513).

Other results

Evening administration also reduced 24-h SBP (ACEI/ARB, CCB, diuretics and drug combination), 24-h DBP (ACEI/ARB, diuretics, and drug combination), daytime SBP (ACEI/ARB and diuretics), daytime DBP (ACEI/ARB, diuretics and drug combination), office DBP (ACEI/ARB, CCB), nondipping (ACEI/ARB, BB, CCB, drug combination), morning surge (ACEI/ARB, CCB), and increased degree of dipping (ACEI/ARB, BB) more than morning administration. Evening administration also further reduced proteinuria (ACEI/ARB, CCB, drug combination) and LVH (ACEI/ARB) (Table 1, Table S5, Supplemental Digital Content, http://links.lww.com/HJH/C513). Evening administration also resulted in reduced participant dropouts for ACEI/ARB. However, these positive results were contributed by data from either the Hermida group or China.

Evening administration had a neutral effect on the percentage of reverse dipping (ACEI/ARB, drug combination), extreme dipping (ACEI/ARB, CCB, drug combination), awake/nocturnal/24-h heart rate (ACEI/ARB, BB, CCB), creatinine/glomerular filtration rate (ACEI/ARB, CCB, drug combination), carotid intimal media thickness (ACEI/ARB), pulse wave velocity (CCB), side effects (ACEI/ARB, CCB), adherence (ACEI/ARB, CCB, drug combination), and incidence of stroke and ischemic heart disease (only one study

TABLE 1. Summary of findings

	Subgroup	ACEI/ARB	I^2	Beta-blocker	I^2	CCB	I^2	Diuretics	Drug combination	I^2
Nocturnal SBP	Overall	−5.10(−6.51, −3.69)*	90.3%	−6.42 (−12.77, −0.07)*	80.5%	−4.08(−5.69, −2.48)*	81.2%	−9.10 (−13.79, −4.41)*	−6.51(−9.56, −3.47)*	95.2%
	Non-China, Nonhermida	−1.01(−2.57, 0.55)	0.0%	N.A.	N.A.	−2.46(−5.64, 0.71)	0.0%	N.A.	0.03(−2.10, 2.15)	0.0%
	China	−5.62(−7.39, −3.86)*	92.2%	−6.42 (−12.77, −0.07)*	80.5%	−4.46(−6.48, −2.43)*	85.1%	N.A.	−7.59(−11.13, −4.05)*	95.1%
	Hermida	−5.28(−7.08, −3.48)*	46.4%	N.A.	N.A.	−3.19(−5.18, −1.19)*	0.0%	−9.10 (−13.79, −4.41)*	−8.06(−18.84, 2.71)	94.2%
Nocturnal DBP	Overall	−3.43(−4.55, −2.30)*	90.1%	−5.87 (−13.51, 1.77)	93.3%	−3.37(−4.65, −2.09)*	87.4%	−6.40 (−9.72, -3.08)*	−4.19(−6.48, −1.90)*	95.6%
	Non−China, Nonhermida	−0.65(−1.73, 0.44)	0.0%	N.A.	N.A.	−1.19(−3.26, 0.88)	0.0%	N.A.	−0.75(−2.10, 0.60)	0.0%
	China	−3.90(−5.38, −2.42)*	92.4%	−5.87 (−13.51, 1.77)	93.3%	−3.95(−5.55, −2.35)*	89.5%	N.A.	−5.46(−8.35, −2.56)*	95.6%
	Hermida	−3.31(−4.55, −2.30)*	44.0%			−1.92(-3.17, −−0.66)*	0.0%	−6.40 (−9.72, −3.08)*	−3.16(−8.16, 1.83)	89.1%
24-h SBP	Overall	−2.48(−3.33, −1.63)*	77.4%	0.18 (−1.31, 1.67)	0.0%	−1.92(−3.05, −0.78)*	69.2%	−9.30 (−13.75, −4.85)*	−2.64(−4.70, −0.58)*	83.4%
	Non−China, Nonhermida	0.15(−1.18, 1.47)	0.0%	N.A.	N.A.	0.07(−3.28, 3.43)	0.0%	N.A.	0.82(−1.20, 2.85)	0.0%
	China	−2.94(−3.97, −1.90)*	80.8%	0.18 (−1.31, 1.67)	0.0%	−2.08(−3.43, −0.72)*	75.5%	N.A.	−2.84(−5.19, −0.48)*	84.0%
	Hermida	−1.47(−2.71, −0.23)*	0.0%	N.A.	N.A.	−2.21(−4.04, −0.39)*	7.4%	−9.30 (−13.75, −4.85)*	−4.34(−13.84, 5.16)	91.9%
24−h DBP	Overall	−1.00(−1.54, −0.47)*	61.7%	−0.52 (−2.03, 0.98)	0.0%	−0.71(−1.43, 0.01)	61.0%	−5.90 (−9.21, −2.59)*	−1.45(−2.83, −0.08)*	77.0%
	Non−China, Nonhermida	0.09(−0.92, 1.10)	0.0%	−2.00 (−10.32, 6.32)	0.0%	0.37(−1.63, 2.38)	0.0%	N.A.	0.05(−1.29, 1.38)	0.0%
	China	−1.07(−1.75, −0.39)*	69.2%	−0.47 (−2.00, 1.06)	0.0%	−0.84(−1.71, 0.04)	69.8%	N.A.	−1.50(−3.12, 0.12)	78.5%
	Hermida	−1.50(−2.38, −0.62)*	0.0%	N.A.	N.A.	−0.55(−1.84, 0.73)	0.0%	−5.90 (−9.21, −2.59)*	−2.85(−8.83, 3.12)	91.3%
daytime SBP	Overall	−0.78(−1.66, −0.10)*	73.2%	1.06 (−9.84, 11.96)	87.3%	−0.62(−1.97, 0.73)	81.6%	−9.40 (−13.83, −4.97)*	−0.96(−3.26, 1.34)	93.7%
	Non−China, Nonhermida	0.98(−0.37, 2.32)	0.0%	−13.00 (−27.39, 1.39)	0.0%	0.92(−1.94, 3.78)	0.0%	N.A.	0.23(−5.14, 5.59)	51.6%
	China	−1.17(−2.29, −0.05)*	79.4%	5.27 (−1.98, 12.52)	90.4%	−0.75(−2.37, 0.87)	85.8%	N.A.	−1.01(−3.87, 1.85)	95.1%
	Hermida	−0.03(−1.31, 1.24)	0.0%	N.A.	N.A.	−1.28(−4.37, 1.80)	25.1%	−9.40 (−13.83, −4.97)*	−1.34(−8.16, 5.48)	81.7%
Daytime DBP	Overall	−0.94(−1.83, −0.06)*	80.9%	−0.69 (−5.23, 6.60)	80.5%	−0.19(−1.29, 0.91)	83.7%	−5.70 (−9.22, −2.18)*	−1.09(−2.06, −0.12)*	53.6%
	Non−China, Nonhermida	0.59(-0.44, 1.62)	0.0%	−5.00 (−12.39, 2.39)	0.0%	1.08(−0.93, 3.10)	0.0%	N.A.	0.07(−1.34, 1.47)	0.0%
	China	−1.25(−2.43, −0.06)*	85.5%	2.60 (−3.95, 9.14)	87.5%	−0.37(-1.73, 1.00)	87.6%	−5.70 (−9.22, −2.18)*	−1.37(−2.55, −0.19)*	56.1%
	Hermida	−1.06(−1.99, -0.13)*	0.0%	N.A.	N.A.	−0.14(−1.80, 1.53)	0.0%	N.A.	−0.98(−4.48, 2.52)	68.4%

for CCB, $n = 110$) (Table S5, Supplemental Digital Content, http://links.lww.com/HJH/C513).

Sensitivity analyses

The sensitivity analyses, which included only RCTs with low or unclear risk of bias, indicated that evening dosing did not further reduce nocturnal, daytime, and 24-h SBP/DBP when using ACEI/ARB (n = 2) and CCB (Figure S3, Supplemental Digital Content, http://links.lww.com/HJH/C513). Additionally, the sensitivity analysis that included larger ($n > 50$) studies yielded similar results to the main analyses.

Small-study bias

Most statistical tests did not identify significant small-study bias, except for CCB nocturnal DBP (Egger's test $P = 0.03$). Funnel plots also did not reveal significant small-study bias because more small studies reported less nocturnal BP reduction with evening dosing (ACEI/ARB SBP/DBP, CCB DBP, combination SBP/DBP) (Figure S4, Supplemental Digital Content, http://links.lww.com/HJH/C513).

Strength of evidence

The strength of evidence for evening dosing in the treatment of nocturnal HT and abnormal BP patterns was ranked as low to very low (Table 2).

DISCUSSION

Main findings and comparing with existing literature

Our results highlighted a lack of high-quality RCTs investigating the impact of evening dosing on BP in patients with nocturnal HT. Firstly, only one of the included RCTs had a low risk of bias. Secondly, subgroup analyses which included only non-Hermida/non-China RCTs found that evening administration did not reduce daytime, nighttime, or 24-h BP, with homogeneous results ($I^2 = 0$). Data from the Hermida group have raised concerns among the scientific community and were investigated by the European Heart Journal, which also expressed concern over this data [18–21]. Hermida's data were treated as an outlier in the previous review, but data from China also contributed to our positive findings [9]. This could suggest a genuine racial difference, indicating that evening doses may be more effective in Chinese individuals. For example, Chinese people have been described as having different BP phenotypes, being more prone to nocturnal HT, nondipping, and salt-sensitive [22]. However, differences in response to anti-HT medications in Chinese have not been previously described. Besides, all RCTs from China inadequately discussed their randomization processes, and inadequate randomization is known to exaggerate effect sizes [23]. Recently, a review highlighted methodological problems associated with RCTs conducted in China [24]. In the current study, many of the included RCTs from China had the exact same number of patients in the two arms [25–33]. Additionally, a few China studies reported unusually small standard deviations for SBP (i.e. as low as 3.62 mmHg) [34] and large effect sizes for evening administration (up to 21.82 mmHg SBP difference) [35]. A recent report has suggested that false individual patient data were present in up to 44% of RCTs and up to 48% of RCTs from China [36]. Thirdly, sensitivity analyses, including RCTs with low or unclear risk of bias, demonstrated that evening dosing did not further reduce nocturnal, daytime, and 24-h SBP/DBP. Therefore, our GRADE assessment indicated that the quality of evidence supporting these findings was either low or very low. Finally, most of the included RCTs focused on ACEI/ARB, CCB, or their combinations, with only a few investigating BB or diuretics.

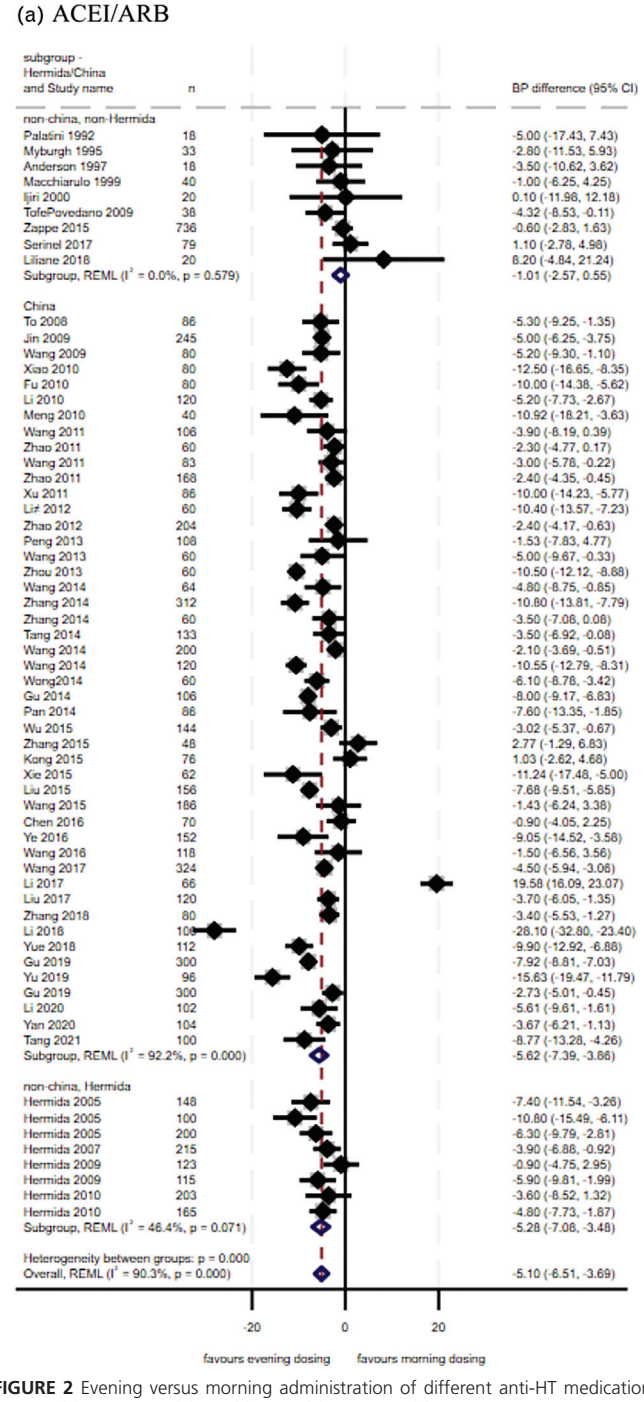
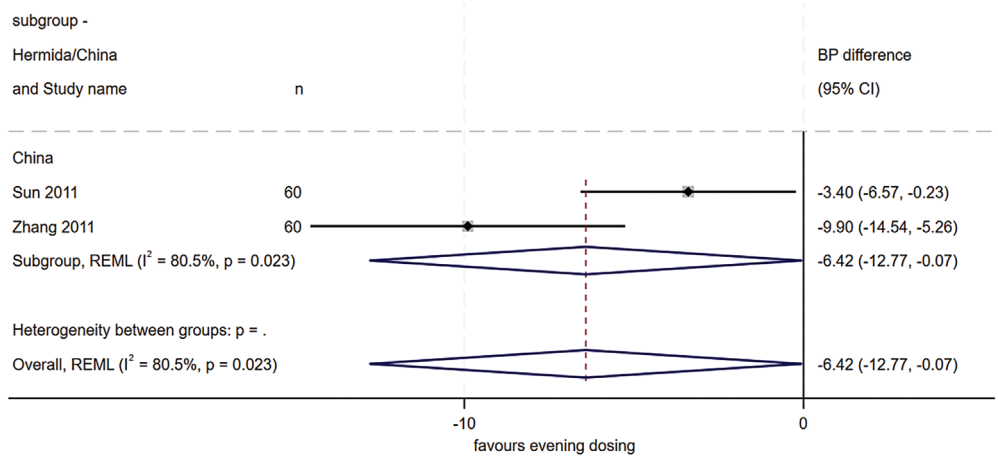
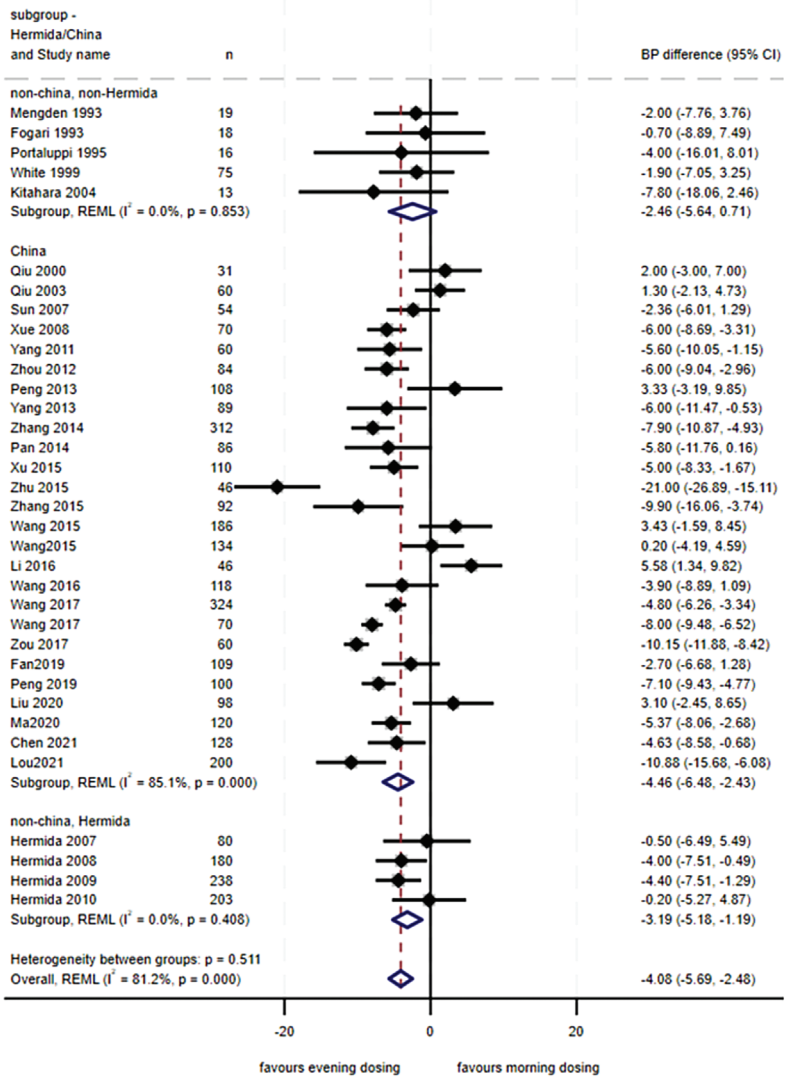


FIGURE 2 Evening versus morning administration of different anti-HT medications on SBP. (a) ACEI/ARB. (b) BB. (c) CCB. (d) Diuretics. (e) Drug combinations.

(b) BB



(c) CCB



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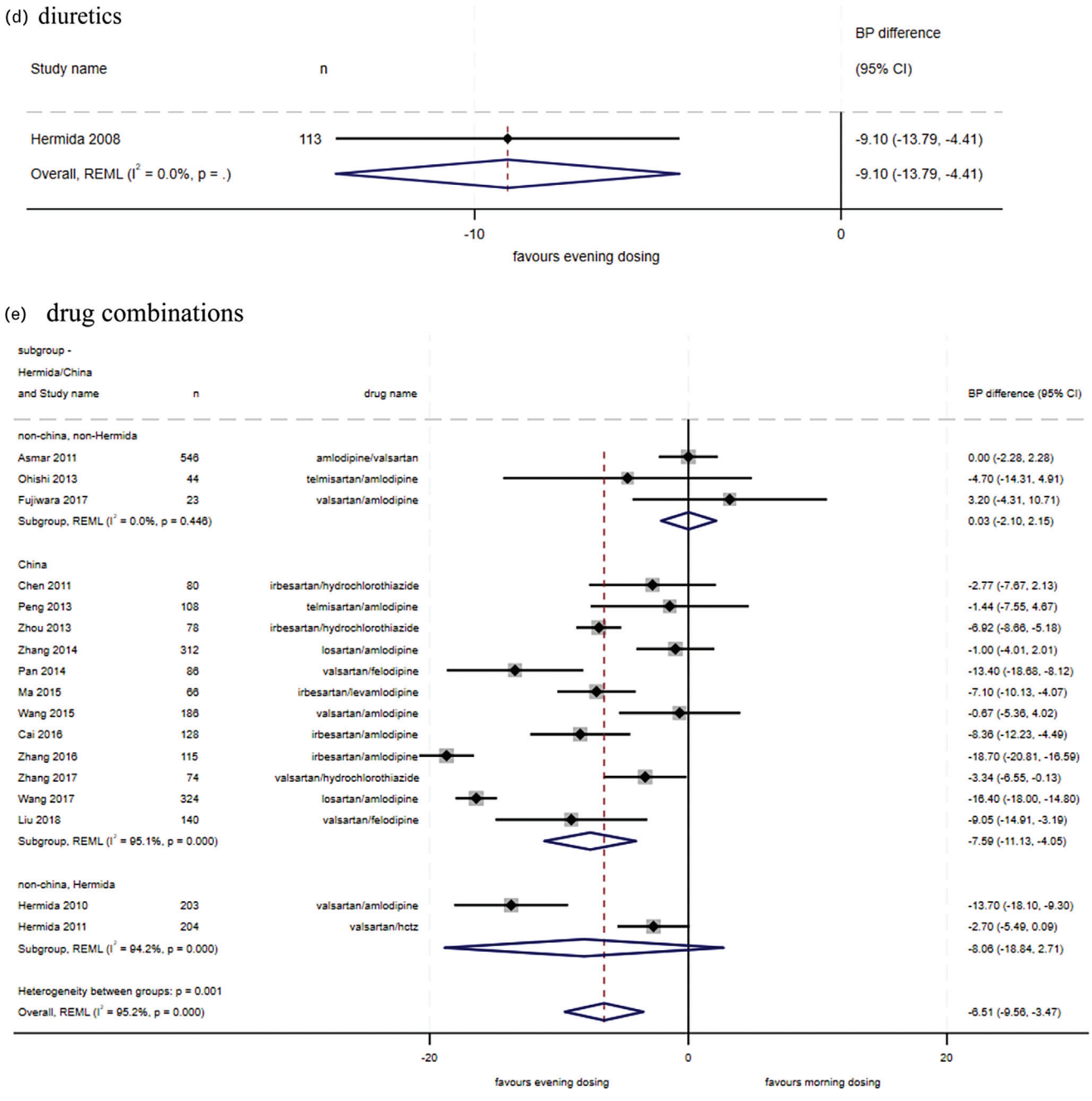


FIGURE 2 Continued.

Despite the very low to low quality of evidence ranked by GRADE, our findings suggested that evening administration of anti-HT medications is more effective to reduce nocturnal SBP/DBP and normalize BP patterns (e.g. non-dipping and excessive morning surge), which aligns with previous relevant meta-analyses [8,9,11–13]. Although the current review is the first to solely focus on the treatment of nocturnal HT and strictly compare the same anti-HT used in the morning and evening, the results are similar to those to a recently published meta-analysis by Maqsood *et al.* [9] Maqsood *et al.* also found a larger reduction in nocturnal BP by Hermida's studies (SBP reduction of 2.3 mmHg [95% CI:0.9,3.7]), as well as an overall reduction in nocturnal BP with evening dosing (SBP reduction of 1.41 mmHg [95% CI:0.48, 2.34]) [9]. Our results also align with two recent landmark randomized controlled trials (RCTs) that examined the timing of anti-HT drugs. These trials investigated the effect of shifting ≥1 or all anti-HT medications to the evening. However, since these trials did not use the same drug for morning and evening administrations, they were not included in our meta-analysis. The TIME trial did not measure nocturnal BP but reported lower early morning BP in patients who took anti-HTs in the evening [37]. Although the HYGIA trial reported a reduction in nocturnal BP and cardiovascular outcomes with evening ingestion, it received criticism for methodological issues [18–21]. All these

results suggested a preferential reduction of nocturnal BP by evening administration.

Research and clinical implications

Our results highlight the absence of low-risk-of-bias RCTs and emphasize the need for such studies to evaluate the efficacy of evening dosing of anti-HT medications as a standard treatment for patients with nocturnal HT across diverse populations. Currently, the reasons behind the discrepancy between China, Hermida, and other studies remain unclear and would require further investigation.

Though evening administration of anti-HT medications may reduce BP in patients with nocturnal HT, there is a lack of RCTs to prove the benefits of normalizing nocturnal BP through evening medication administration. Trials such as TIME and HYGIA, which recruited patients with HT (with or without nocturnal HT) and reported clinically relevant cardiovascular outcomes, did not specifically aim to normalize nocturnal BP (i.e. normalization of nocturnal BP was not confirmed, despite evening administration of anti-HT medications) and yielded conflicting results [20,37]. In addition, although several of the included RCTs allowed for medication titration, the titration process was based on daytime BP measurements. In the past, repeated assessment of nocturnal BP for drug titration was challenging and often poorly tolerated by patients. However, new technology, such as nighttime home BP measurements, may be more accepted to patients [22]. RCTs investigating the cardiovascular outcomes associated with normalizing nocturnal HT using evening administration of medications are needed. In this regard, our team is currently conducting an RCT to assess the feasibility of medication titration based on home nocturnal BP measurements (NCT05031637).

For clinicians treating patients with nocturnal HT, anti-HT medications may be administrated in the evening to further reduce nocturnal BP, nondipping and excessive morning surge. However, they should be aware of the limited strength of evidence (as shown in Table 2) and the reported larger BP reduction observed in studies conducted by Hermida and in studies from China. Evening administration of diuretics may increase nocturia, which should be monitored in individual patients [37]. Only one of the included studies ($n = 113$) compared evening and morning administration of a diuretic (i.e. torasemide) and found that 7% of patients in the evening administration group (versus 0% in the control group) had mild nocturia, which did not require a change of treatment [38]. Furthermore, the decision to prescribe evening doses of medications should be carefully considered in light of patients' adherence to treatment. Most of the included studies did not report on adherence, and the TIME study found an association between evening administration and medication nonadherence [37]. We agree with international guidelines that evening dosing should not be routinely used for all patients with HT, as an excessive drop in nocturnal BP can have detrimental effects [7]. Theoretically, the use of short-acting anti-HT medications in the evening may be more effective and specific in reducing nocturnal BP (e.g. in patients with isolated nocturnal HT), but our results found similar reductions in nocturnal BP regardless of medication half-life. However, all the included studies consistently did not show increased side effects or dropouts in patients allocated to the evening administration group.

Strength and limitations

The current review is the first to focus on patients with nocturnal HT, who may benefit most from evening administration of anti-HT medications, and to investigate and rank the strength of evidence for each anti-HT drug class. Our comprehensive search enabled us to identify several RCTs from China, which had not been included in previous reviews. This review also included the largest number of RCTs [8,9,11–13]. Study selection, data extraction, and quality assessment were conducted by two independent investigators. We have included various important research and clinically related outcomes, such as dropout rates and

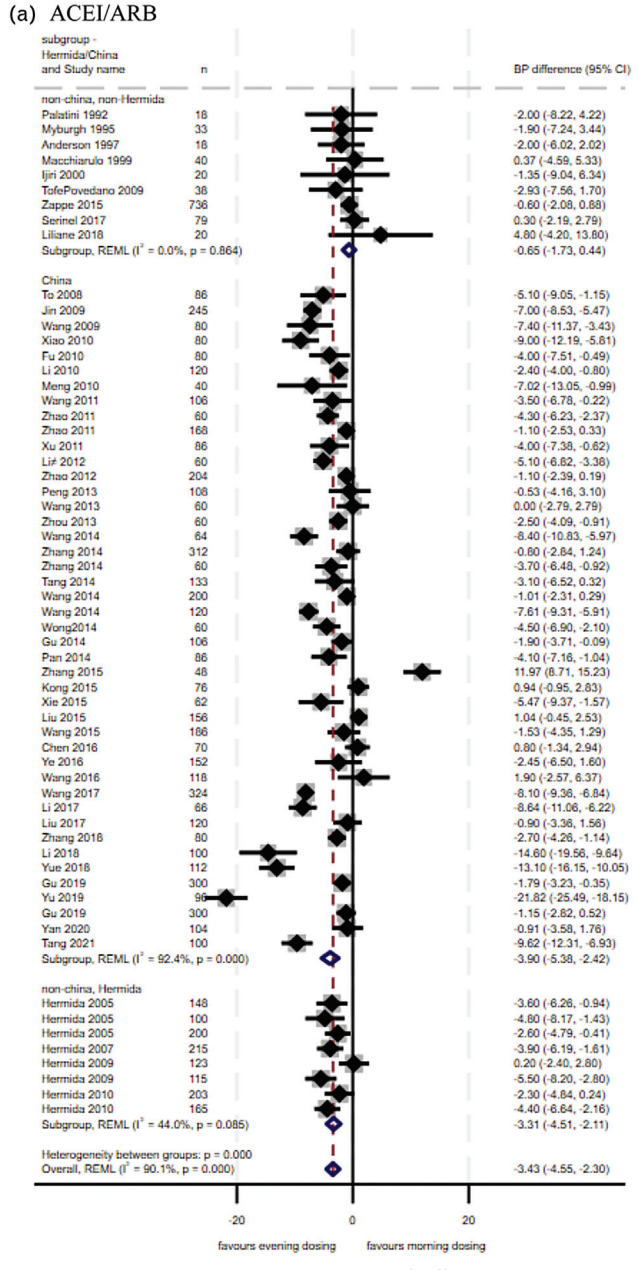
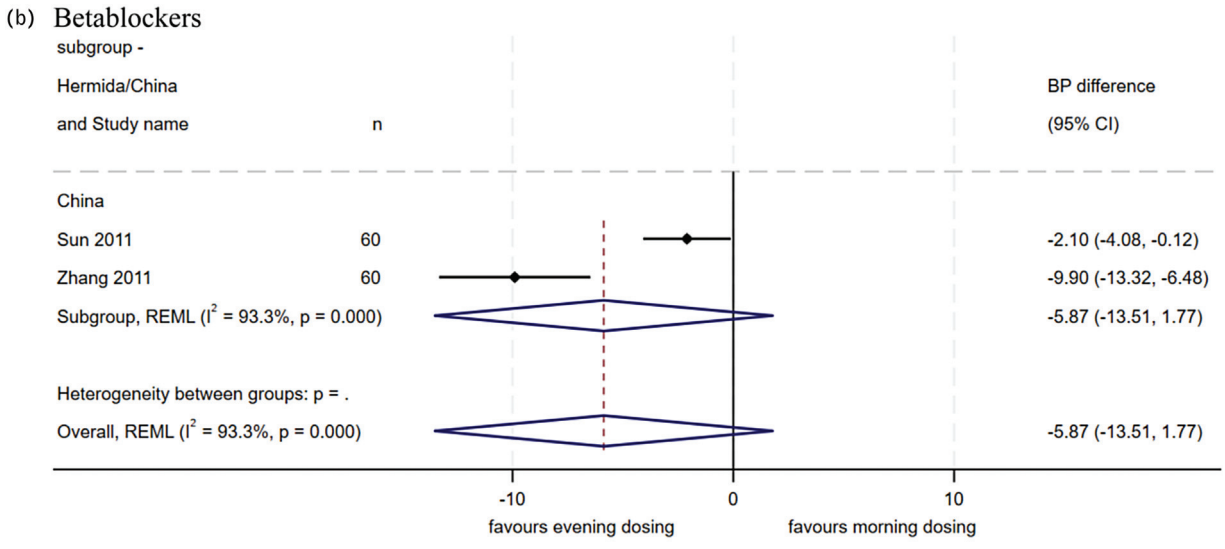
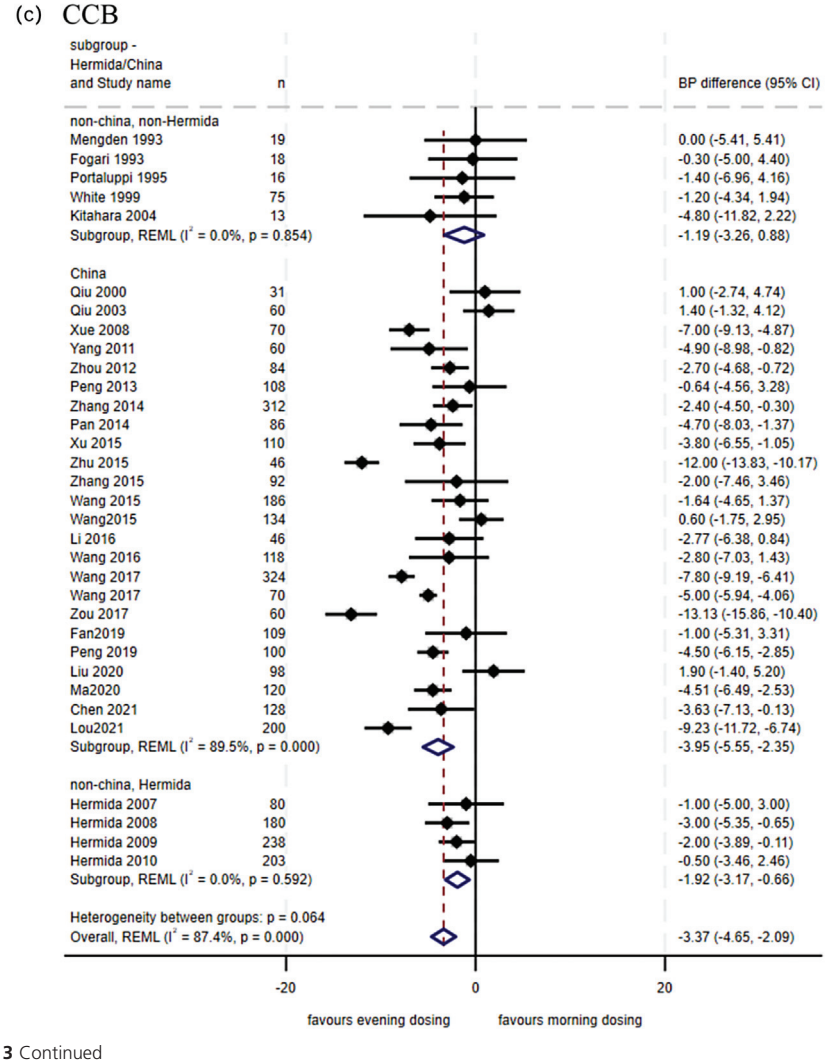


FIGURE 3 Evening versus morning administration of different anti-HT medications on DBP. (a) ACEI/ARB. (b) Betablockers. (c) CCB. (d) Diuretics. (e) drug combination.





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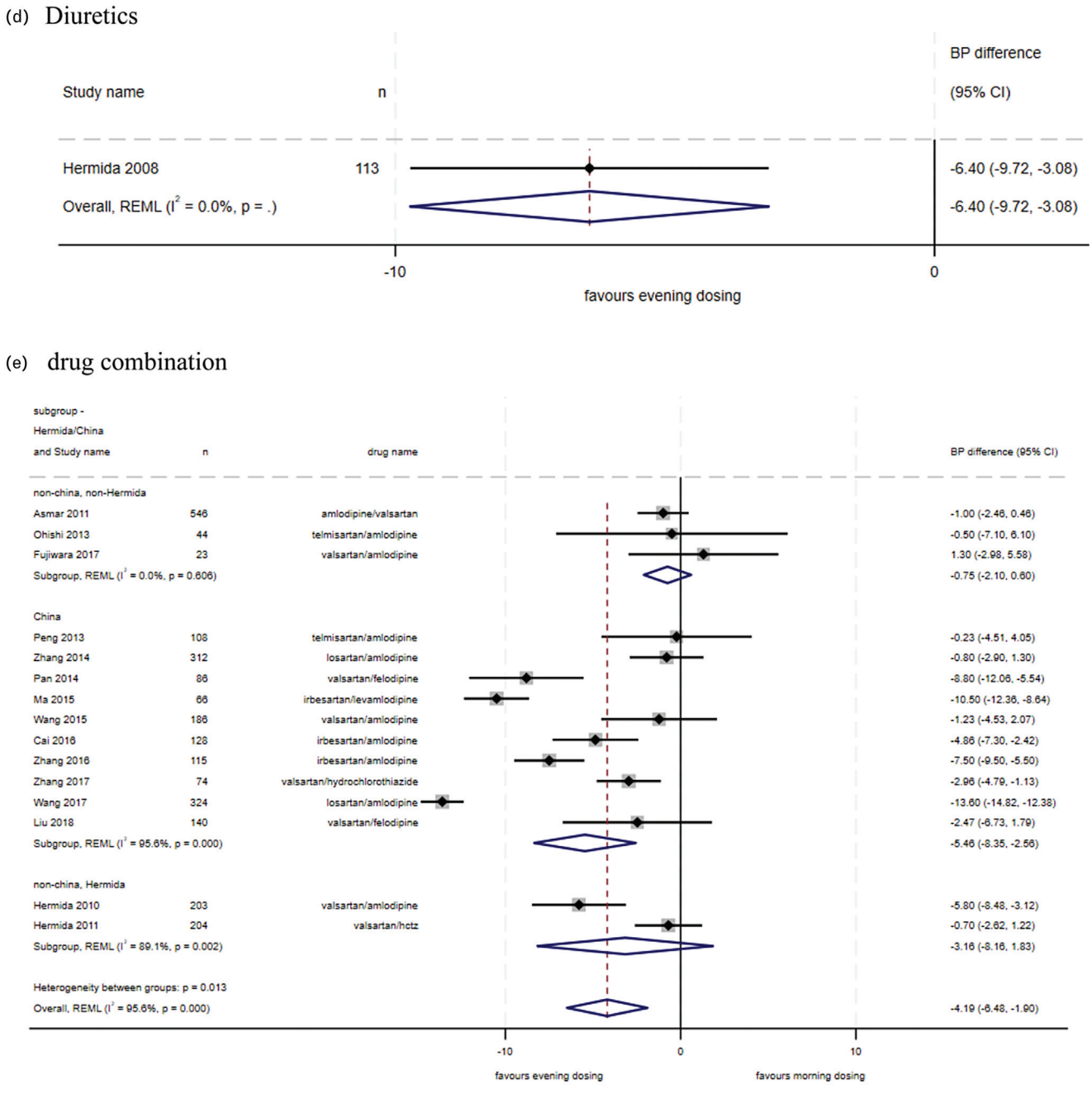

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various surrogate cardiovascular outcomes (e.g., LVH and proteinuria). The current review also included different subgroups, meta-regressions and sensitivity analyses which were most comprehensive among existing reviews [8,9,11–13].

However, despite employing these techniques, the residual heterogeneity of many results remains high. High heterogeneity may also explain the negative results in our meta-regression. However, low heterogeneity was observed in some subgroup analyses (i.e. $I^2 = 0\%$ in all subgroup analyses of non-Hermida/non-China studies). Moreover, there is a lack of long-term trials, and important cardiovascular outcomes were reported in only one of the included studies. Although we initially included alpha-blockers in our registered protocol, no eligible study was identified. Similarly, we had initially planned to conduct a sensitivity analysis using only studies with a low risk of bias. However, due to a limited number of low-risk-of-bias studies ($n = 1$), we have modified the sensitivity analysis to include studies with both low and unclear risk of bias. Systematic reviews should include languages other than English to improve comprehensiveness and explore racial or cultural differences [39]. Although the current review is the first among similar reviews to also include Chinese, we were unable to include other language due to a lack of translators. However, despite these limitations, the author's

TABLE 2. Strength of recommendation according to GRADE comparing evening administration versus morning administration[17]

Recommendation	Strength	Rationale
Evening dosing of ACEI/ARB, CCB or their drug combination to further reduce nocturnal SBP and/or DBP, and nondipping	Very Low	Evidence is generated from adequate number of RCT and participants. But high heterogeneity and vast majority of RCTs having high/unclear risk-of-bias
Evening dosing of BB or diuretics to reduce nocturnal SBP and/or DBP more than morning dosing	Very low	Evidence is generated from RCTs with totally <200 participants. There was high heterogeneity and all included RCTs having high/unclear risk-of-bias
Evening dosing of BB to reduce nondipping	Very low	Evidence from 2 RCTs, including up to 120 participants. RCTs had unclear to high risk of bias. Heterogeneity was moderate ($I^2 = 46.5\%$)
Evening dose of ACEI/ARB, CCB to reduce morning surge	Very low	Evidence is generated from adequate number of RCT and participants. But high heterogeneity and vast majority of RCTs having high/unclear risk-of-bias
Evening dose of ACEI/ARB, CCB or their combination to reduce proteinuria	Very low	Evidence is generated from adequate number of RCT and participants. But high heterogeneity and vast majority of RCTs having high/unclear risk-of-bias
Evening dose of ACEI/ARB to reduce LVH	low	Evidence is generated from adequate number of RCT and participants. But moderate heterogeneity and vast majority of RCTs having high/unclear risk-of-bias

team did not exclude any study based on language. As discussed above, although the difference can be due to the quality of the included RCT, it could also be genuine racial differences. We could not directly examine the databases of the included studies, which could have allowed further assessment of data quality and an explanation for the high heterogeneity observed across different regions. This may be achieved by individual patient data meta-analysis [36,40]. Although the authors are trained to assess the risk of bias using the Cochrane risk of bias (ROB) 1 tool, the ROB2 tool was developed with signaling questions to enhance reliability [41]. In a comparison study, both ROB1 and ROB2 provided similar results, except that ROB1 is more likely to downgrade the quality of studies for subjective outcomes in open-label studies [41]. Given that our primary outcomes are BP from ABPM, the use of ROB1 is unlikely to affect our results. For future reviews, it is worth considering the adoption of the Cochrane ROB2 tool. Finally, to combine data from crossover RCTs (18 out of 107 RCTs), we employed the same pooling method as used for parallel RCTs. Although this method has been endorsed by the Cochrane handbook (chapter 23.2.6), it may lead to an underestimation of treatment effects and yield more conservative effect sizes. Alternatively, data can be extracted solely from the initial phase of the crossover RCTs (prior to the crossover itself). Unfortunately, this option was not feasible because none of the included studies reported relevant data.

CONCLUSION

Our results highlight the lack of low-risk-of-bias RCTs ($n = 1$) and emphasize the need for such studies to evaluate the efficacy of evening dosing of anti-HT medications as a standard treatment for patients with nocturnal HT across diverse populations. The evidence regarding the effectiveness of an evening dose of anti-HT medications in reducing nocturnal BP is neutral in studies with low risk of bias, but numerous studies with unclear to high risk of bias suggest an additional hypotensive effect when compared to morning dosing. (ranked as very low to low strength of evidence by GRADE) Further research should also examine the long-term cardiovascular effects and mortality associated with the normalization of nocturnal HT through evening doses of anti-HT medications.

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Conflicts of interest

ChatGPT was employed to verify and enhance English grammar, and the authors manually reviewed the final version for accuracy.

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