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The Effect of Evening *vs.* Morning Medication on Morning Blood Pressure Surge

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Abstract

Hypertension represents a significant risk factor for cardiovascular and cerebrovascular events, with the incidence of acute events peaking during the vulnerable morning hours. The morning blood pressure surge (MBPS), defined as the rise in systolic blood pressure from the nocturnal trough to the early-morning period, has been associated with increased cerebrovascular risk particularly in individuals with excessive surges, as reported in elderly hypertensive cohorts. Comprehensive searches across six medical databases resulted in the inclusion of 8 clinical trials focused on morning blood pressure surges (MBPS) and 12 trials assessing ambulatory blood pressure metrics, encompassing a total of 1239 and 1417 hypertensive patients, respectively. The findings revealed that the MBPS was significantly more reduced in patients taking medication before bedtime, averaging a decrease of 7 mmHg compared to those who took medications in the morning. Specifically, the administration of calcium channel blockers and renin-angiotensin-aldosterone inhibitors at night was associated with additional reductions in MBPS of 4 mmHg and 11 mmHg, respectively, further emphasized by a combined administration of these agents along with diuretics, which displayed an even greater reduction of 26 mmHg. Moreover, the diurnal systolic and nighttime diastolic blood pressures were found to be lower by 6 mmHg and 13 mmHg,

respectively, in the nighttime medication cohort compared to their morning counterparts. This study substantiates the concept that administering antihypertensive treatment at night is more effective in controlling the MBPS, supporting bedtime dosing as an effective strategy to attenuate MBPS and improve nocturnal blood pressure control in selected hypertensive populations. Whether these improvements translate into reduced cardiovascular events requires confirmation in adequately designed outcome-based trials.

[Keywords] hypertension; medication; morning blood pressure surge; Meta-analysis; risk factors

Hypertension is a significant risk factor for cardiovascular diseases[1]. Clinically, the primary approach to treating hypertension is through medication[2], which is usually taken once a day[3]. Blood pressure is known to exhibit a circadian rhythm, with most patients experiencing the highest blood pressure in the morning and being accustomed to taking their medication at that time[4]. However, a long-overlooked issue is that the absorption and distribution of drugs are not instantaneous; it takes a specific duration of time to achieve the maximum antihypertensive effect[5]. Therefore, if a patient takes medication during a morning spike in blood pressure, the time when the drug exerts its most pronounced hypotensive effect may not coincide with the peak time of blood pressure. This mismatch can lead to increased blood pressure variability (BPV)[6].

Morning blood pressure surge (MBPS) refers to a phenomenon wherein individuals experience an increase in their blood pressure levels as they transition from sleep to wakefulness. This shift involves an initial rise from a relatively low level to a higher one, eventually reaching the highest point. In a prospective study of elderly hypertensive patients, Kario et al. demonstrated that an excessive sleep-trough MBPS (defined as the highest decile of surge values) was associated with a higher incidence of stroke, even after adjustment for 24-hour mean blood pressure and nocturnal dipping status. Notably,

individuals with excessive MBPS in that study also showed a higher prevalence of extreme nocturnal dipping; however, when both dipping status and MBPS were included in multivariable models, MBPS remained significantly associated with stroke risk, whereas extreme dipping did not[7]. Numerous clinical meta-analyses have demonstrated a significant increase in the incidence of myocardial infarction and stroke during the morning hours, a period characterized by heightened hemodynamic and neurohumoral activity.[8]. Moreover, morning blood pressure surge has been linked to potential damage to target organs, such as the development of left ventricular hypertrophy and an increase in the left ventricular mass index. Additionally, it may lead to arterial stiffness, carotid atherosclerosis[9], and other related complications. It also may cause renal proteinuria and stroke[10]. Consequently, the management and control of morning blood pressure surge is a key objective of antihypertensive treatment strategies[11-14]. This study comprehensively analyzed the literature data in the last 15 years to discuss the relationship between medication time and morning blood pressure surge, so as to offer evidence-based medical information for doctors and patients and provide the basis for adjusting medication time and better control for hypertension.

1. Data and methods

1.1 Literature standard

The following selection criteria were applied to the literature: (1)The patients met the diagnostic criteria for hypertension with systolic blood pressure (SBP)/ diastolic blood pressure (DBP)≥140/90 mmHg; (2) Took the same medicines and dosage before bedtime and in the morning; (3) The study was a randomized controlled study, and blood pressure was measured by the ambulatory blood pressure monitor; (4) The morning blood pressure surge was calculated as follows[7]: it was defined as the difference between the mean SBP within 2 hours in the morning and the mean of the three blood pressure values around the lowest nighttime blood pressure; (5) Literature should report morning blood pressure surge both before and after treatment, or include 24-hour systolic blood pressure (24 h SBP), daytime systolic blood pressure (dSBP), nighttime systolic blood pressure (nSBP), 24-hour diastolic blood pressure (24 h DBP), daytime diastolic blood pressure (dDBP), and nighttime diastolic blood pressure (nDBP) after treatment.

1.2 Literature search

The hypertension, chronotherapy, morning blood pressure surge (MBPS), treatment effect, night, and morning were used as the keywords for screening in Pubmed, Web of Science, Cochrane Library, VIP database, CNKI, Wanfang database. Documents meeting the study requirements were manually searched and included as a supplement.

The literature search was conducted independently by two researchers, and the differences were determined through negotiation. The retrieval formula is as follows:

Morning blood pressure surge
#1 chronotherapy
#2 night
#3 morning
#4 #1 OR #2 OR #3
#5 MBPS
#6 morning blood pressure surge
#7 #5 OR #6

24 h mean blood pressure
#1 chronotherapy
#2 night
#3 morning
#4 #1 OR #2 OR#3
#5 hypertension
#6 treatment effect
#7 #4AND #5 AND #6

1.3 Data extraction

The information to be extracted from each study is the first author, year of publication, country, sample size, hypertension type, age, study type, drug (time of administration, treatment period), morning blood pressure surge before and after treatment, or 24 h SBP/DBP, dSBP/dDBP, nSBP/nDBP after treatment. The results were confirmed by the two researchers who independently evaluated the literature, and used the risk of bias assessment method provided in Cochrane 5.1 manual to analyze if the following bias appeared in the literatures: generation of random sequence, allocation concealment, double-blind implementer and participant, blinding in outcome assessment, incomplete outcome data, selective publication, and other bias. The study was judged to be at risk of uncertain bias when the method and

outcome details of the report were not sufficient, indicators were not relevant to the study, or the outcome assessed by the indicators were not measured in the study.

1.4 Statistical analysis

Statistical analysis was performed using the Review Manager 5.4 software provided by the Cochrane Colnetwork. For continuous variables such as mean 24 h SBP/DBP, dSBP/dDBP, nSBP/nDBP, and morning blood pressure surge, the mean and 95% confidence interval (95% CI) were used as statistics. Q test and I^2 test were used to assess heterogeneity. According to the range of I^2 values, heterogeneity was defined as mild (25%), moderate (50%), and severe (75%). To analyze the sources of heterogeneity, the different factors that may contribute to the heterogeneity were analyzed, so the subgroup analysis was performed by drug class. When $P \leq 0.05$, the difference was considered statistically significant.

The outcomes were analyzed using a random-effects model □I2 >50%□. These data were entered using a generic inverse variance. We assessed publication bias by inspecting funnel plot symmetry and using both Egger's and Begg's tests. The sensitivity analysis entailed excluding individual studies sequentially to ascertain their impact on the overall outcome. The $P \leq 0.05$ was deemed statistically significant for two-tailed tests.

There were 7 papers not provide standard deviation of the difference in morning blood pressure surge before and after treatment. To this end, we used the correction factor of 0.3 which was calculated from the Cochrane manual by Hermida[15] for a tentative analysis. The correction coefficient was selected in the range of 0.2 to 0.8, we calculated the standard deviation of the difference in morning blood pressure surge before and after treatment to verify the effect of different calibration system values on the results of morning blood pressure surge analysis.

2. Results

2.1 Results of the literature search

The study included a total of 8 morning blood pressure surge clinical trials and 12 24-hour ambulatory blood pressure clinical trials. The number of patients in each study was between 44 and 244. The morning blood pressure surge study and 24-hour ambulatory blood pressure study included 1239 and 1417 hypertensive patients, respectively. The patients were mainly essential hypertension and non-dipper hypertension, and a few were complicated with diabetes, hyperlipidemia, coronary heart disease, and other diseases. The duration of antihypertensive medication ranged from 4 weeks to 48 weeks. The literature screening process is shown in Figure 1. The basic

characteristics of the included studies are shown in the attachment.

2.2 Literature quality evaluation

Figure 1 shows the results of the literature quality evaluation. In the study, the investigators and the patients were double-blinded using the document-hiding method. The outcome was assessed as low risk (Figure 2).

2.3 Effect on morning blood pressure surge

Eight studies involved 1239 cases of hypertension, in which 620 cases took the medication before bedtime and 619 cases took the medication in the morning. The analysis showed that the morning peak blood pressure was reduced more effectively in the group taking medication before bedtime than one taking medication in the morning, by an average of 7 mmHg (95% CI: 3 to 12 mmHg). However, heterogeneity was detected (I^2=97%). According to the classification of anti-hypertensive drugs, the results showed that taking calcium channel blockers before bedtime had a stronger effect on reducing morning blood pressure surge than taking them in the morning (Table 1). The morning blood pressure surge was reduced by 4 mmHg (95%CI: 3 to 5 mmHg) more in the group taking calcium channel blockers before bedtime than in the group taking medication in the morning (P<0.0001). In the group taking renin-angiotensin-aldosterone inhibitor before bedtime, the morning blood pressure surge was reduced by 11 mmHg

(95%CI: 10 to 13 mmHg) more than that in the group taking medication in the morning, and the difference was statistically significant without heterogeneity (P <0.0001, I^2=0). The decrease of morning blood pressure surge in the group taking calcium channel blockers or renin-angiotensin-aldosterone inhibitor and diuretics before bedtime was bigger than that in the group taking medication in the morning, by a more 26 mmHg reduction (95%CI: 22 to 30 mmHg) (P <0.00001). The decrease of mean morning blood pressure surge in the group taking renin-angiotensin-aldosterone inhibitor and diuretic before bedtime was bigger than that in the morning, with more than 2 mmHg mean reduction, no significant difference (P=0.20). The decrease in morning blood pressure surge in the group taking renin-angiotensin-aldosterone inhibitor and calcium channel blockers before bedtime was the same as that in the group taking the above medication in the morning.

2.4 Effect on the mean blood pressure

Twelve studies involved 1417 patients, of which 709 took the medication before bedtime and 708 took the medication in the morning.

2.4.1 24 h SBP/DBP after medication

In the 12 randomized controlled experiments, the 24 h SBP before bedtime medication was significantly lower than that in the morning medication group with a maximum low of 7 mmHg. The comprehensive analysis showed that the 24 h SBP after medication before bedtime

medication group was 2 mmHg lower than that in the morning medication group, with a significant difference (P<0.001) (Table 2). The 24 h DBP before bedtime medication group was 1 mmHg lower than that in the morning medication group after medication, but without a significant difference (P=0.16) (Table 3).

2.4.2 dSBP/dDBP after medication

In the 12 randomized controlled experiments, the dSBP before bedtime medication was lower than that in the morning medication group with a maximum low of 9 mmHg. The comprehensive analysis showed that the dSBP after medication before bedtime medication group was 1 mmHg lower than that in the morning medication group, but without a significant difference (P=0.21) (Table 4). The dDBP before bedtime medication was lower than that in the morning medication group with a maximum low of 6 mmHg. The dDBP before bedtime medication group was 1 mmHg lower than that in the morning medication group after medication, but without a significant difference (P=0.14) (Table 5).

2.4.3 nSBP/nDBP after medication

In the 12 randomized controlled experiments, the nSBP before bedtime medication was significantly lower than that in the morning medication group with a maximum low of 17 mmHg. The

comprehensive analysis showed that the nSBP after medication before bedtime medication group was 6 mmHg lower (95% CI: -9 to -3 mmHg) than that in the morning medication group, with a significant difference (P=0.0007) (Table 6). The nDBP before bedtime medication was significantly lower than that in the morning medication group with a maximum low of 13 mmHg. The nDBP before bedtime medication group was 4 mmHg lower than that in the morning medication group after medication, with a significant difference (P=0.0009) (Table 7).

3. Discussion

The present study comprehensively analyzed the literatures in the last 15 years and discussed the relationship between the medication time and morning blood pressure surge, which provided an effective basis for better control of hypertension. Several studies have delved into the effects of different medication times on controlling morning blood pressure surge and treatment efficacy[16, 34, 35]. While most studies were conducted in China, they adhered to internationally recognized protocols, and our quality assessment confirmed no methodological disparities compared to global studies.However, these studies still have some limitations, such as a lack of standard deviation information regarding the difference in data before and after treatment, insufficient consideration of correction coefficients' influence on

analysis outcomes, confusion between post-treatment data, and the difference data between pre-treatment and post-treatment, and an unclear definition of morning blood pressure surge in some instances. In contrast, we performed a meta-analysis that rigorously adhered to Cochrane guidelines, conducted a comprehensive literature search across multiple databases, and implemented a pre-registered protocol to minimize potential bias. Moreover, by extracting and analyzing a wide range of blood pressure parameters—including 24-hour, daytime, and nighttime SBP/DBP, beyond just MBPS—we provide a more comprehensive and nuanced assessment of the chronotherapeutic effects of antihypertensive agents.

Blood pressure has obvious circadian rhythmicity, and the peak occurs mostly in the morning. The reason may be that at bedtime, the need for blood in various organs is reduced[36, 37], so that the effective circulating blood volume and cardiac blood volume increases, thus elevating the blood pressure. Moreover, clinical investigations by Marfella and colleagues have demonstrated that the excitability of the sympathetic nervous system is significantly higher upon waking compared to pre-awakening states, a phenomenon quantified by elevated low-frequency to high-frequency power ratios (LF/HF) during morning surge periods. This sympathetic overactivity further amplifies blood pressure elevation[38]. Some studies have also suggested that the

development of morning blood pressure surge may be linked to both the reduction in baroreflex sensitivity and the regulation of hypothalamic circadian rhythms[39].For hypertensive patients, reducing the highest blood pressure in a day, such as morning peak blood pressure is more significant. According to the overall comprehensive analysis of morning blood pressure surge, the hypotensive effect of the group taking medication before bedtime was better than that of the group taking in the morning. The reason is that it takes some time to reach the peak blood drug concentration after taking drugs. For example, the peak time of blood concentration of captopril and valsartan is 3 ~ 4 hours, and the peak time of amlodipine is 6 to 8 hours. And it takes some time for the drug to get from the bloodstream to the target and then to have an effect. Therefore, the most obvious blood pressure lowering effect appears a few hours after taking the drug. Since the highest blood pressure of most patients is in the morning, taking medicine before bedtime can produce the most significant hypotensive effect in the morning time, so that patients can derive more benefits. Several studies[40-43], most notably the HYGIA Chronotherapy Trial, have reported a potential association between bedtime antihypertensive dosing and reduced cardiovascular outcomes. However, these findings have been subject to substantial methodological debate, and their generalizability remains uncertain. In

addition, comprehensive analysis of 24-hour mean blood pressure showed that the 24 h SBP, nSBP, and nDBP of the group before bedtime medication were not very different from the group in the morning, but the values of the before bedtime group were lower. Therefore, taking medication before bedtime is more effective in controlling 24-hour mean blood pressure than taking medication in the morning.

There are also limitations in our study on morning blood pressure surge. Only eight articles were included according to the inclusion criteria, seven from China and one from Spain. In 24-hour mean blood pressure analysis, except Ohishi's study, the other 11 studies didn't include SBP/DBP, dSBP/dDBP and nSBP/nDBP. We estimated the correction coefficients based on the Ohishi's study. The correction coefficients were set at 0.2 to 0.8 to calculate standard deviation change and conduct tentative analysis. There were no changes in blood pressure before and after drug treatment in the literature. In addition, due to the small number of literature and experimental cases, it is difficult to perform subgroup analysis by drug grouping. Therefore, we used the data after blood pressure treatment for a comprehensive analysis.

Morning blood pressure surge may lead to left ventricular hypertrophy[8], arteriosclerosis, carotid atherosclerosis, and other target organ damage[9]. It can also lead to renal proteinuria and

stroke[10]. Therefore, morning blood pressure surge becomes an important indicator in the treatment of hypertension. According to the analysis of our study, taking antihypertensive drugs before bedtime can significantly reduce the morning blood pressure surge and effectively control the 24-hour mean blood pressure. It works better than taking it in the morning.

However, the effect of controlling 24-hour mean blood pressure was not very significant in the bedtime group. Among the currently used antihypertensive drugs, amlodipine takes 6 to 8 hours to reach its peak blood concentration, whereas most other drugs reach their peak concentration in about 3 to 4 hours. If the drug is taken before bedtime, the blood drug concentration will peak before the blood pressure peaks, resulting in a less effective overall blood pressure control.

In conclusion, our meta-analysis demonstrates that bedtime administration of antihypertensive medications provides a more pronounced reduction in the morning blood pressure surge and offers modest improvements in nocturnal and 24-hour blood pressure profiles compared with morning dosing. These findings suggest that, for hypertensive patients whose blood pressure peaks in the early morning, bedtime dosing may represent a simple and feasible strategy to improve BP control during the most vulnerable period of the day[35].

Although excessive MBPS has been associated with stroke risk in

elderly hypertensive populations, available evidence primarily pertains to individuals with extreme surge values and may overlap with abnormal nocturnal dipping patterns. Moreover, the present meta-analysis evaluates surrogate blood pressure parameters rather than cardiovascular endpoints. Therefore, clinical outcome implications should be interpreted with caution, and routine bedtime dosing for all hypertensive patients cannot be inferred solely from BP metrics.

Based on these results, future hypertension management may benefit from a more individualized approach that considers both circadian blood pressure patterns and the pharmacokinetic characteristics of different antihypertensive classes. Given the substantial variability in MBPS responses among drug categories observed in our study, further clinical trials are warranted to determine which agents and dosing schedules optimize morning BP control while maintaining stable 24-hour efficacy.

Competing interests

We declare that the authors have no competing interests.

Availability of data and materials

All the data is available from the corresponding author if requested.

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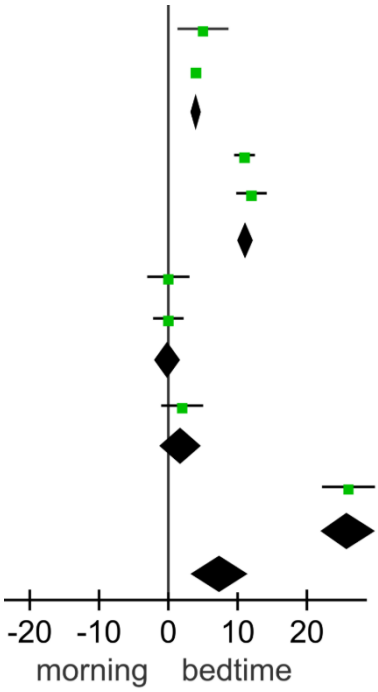
Table 1. Comparison of morning peak blood pressure reduction effect between bedtime medication and morning medication.

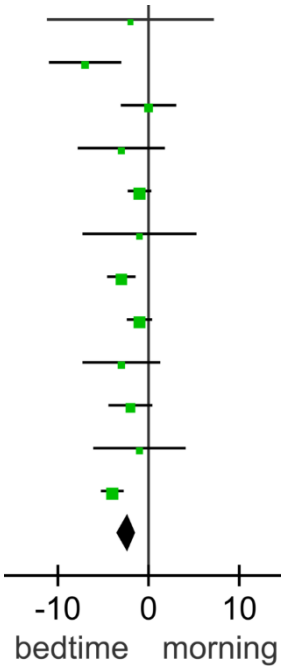
medicinal	document	Morning peak blood pressure reduction value (mmHg)				
		medication before bedtime		medication in the morning		(before bedtime - in the morning) morning peak blood pressure difference [95%CI]
		$\bar{x} \pm s$	n	$\bar{x} \pm s$	n	
CCB	Hermida2009[15]	-6±15	120	1±14	118	5[1,9]
	Zhao 2015[16]	-12±4	122	8±4	122	4[3,5]
	subtotal		242		240	4[3,5]*
RASI	Qiao 2015[17]	-13±4	54	2±5	54	11[9,13]
	Li 2016[18]	-20±5	48	8±6	48	12[10,14]
	subtotal		102		102	11[10,13]*
CCB+RASI	Fang 2019[19]	-13±10	60	13±9	60	0[-3,3]
	Zhang 2014[20]	-14±8	78	14±8	78	0[-2,2]
	subtotal		138		138	0[-2,2]***
RASI+ diuretic	Zhang 2018[21]	-18±7	35	16±7	36	2[-1,5]
	subtotal		35		36	2[-1,5]**
CCB/RASI+diuretic	Liang 2009[22]	-31±13	103	5±15	103	26[22,30]
	subtotal		103		103	26[22,30]*
	amount to		620		619	7[3,12]*



CCB: Calcium channel blocker；RASI: Renin-angiotensin system inhibitor, *P <0.00001, **P =0.20, ***P =1.00

Table 2. Comparison of 24h SBP reduction effect between bedtime medication and morning medication.

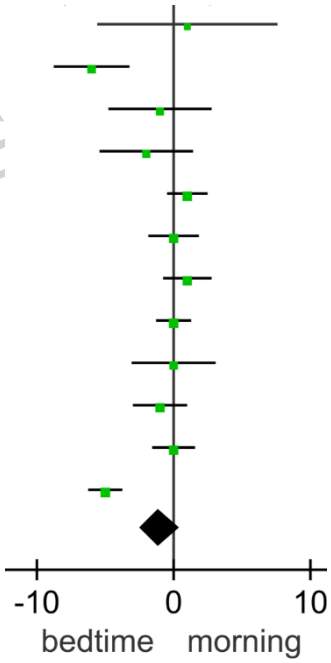
document	post-treatment 24h systolic blood pressure (mmHg)				
	medication before bedtime		medication in the morning		before bedtime - in the morning Mean difference [95%CI]
	$\bar{x} \pm s$	n	$\bar{x} \pm s$	n	
Ohishi 2013[23]	121±13	16	123±14	17	-2[-11,7]
Cai 2016[24]	121±11	64	128±12	64	-7[-11,-3]
Chen 2016[25]	122±6	35	122±7	35	0[-3,3]
Liu 2018[26]	129±15	74	132±14	66	-3[-8,2]
Ma 2021[27]	126±4	72	127±4	72	-1[-2,0]
Ma 2022[28]	126±17	56	127±17	56	-1[-7,5]
Peng 2019[29]	125±4	50	128±4	50	-3[-5,-1]
Wang 2017[30]	126±5	78	127±4	85	-1[-2,0]
Wang 2015[31]	120±11	46	123±10	46	-3[-7,1]
Zhang 2018[32]	126±5	40	128±6	40	-2[-4,0]
Zhang 2023[33]	126±13	50	127±13	50	-1[-6,4]
Zhao 2015[16]	124±5	122	128±5	122	-4[-5,-3]
amount to		703		703	-2[-3,-1]*



*$P < 0.0001$

Table 3. Comparison of 24 h DBP reduction effect between bedtime medication and morning medication.

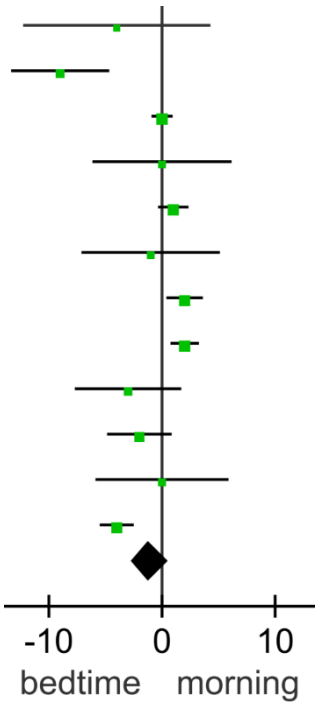
document	post-treatment 24h diastolic blood pressure (mmHg)				
	medication before bedtime		medication in the morning		before bedtime - in the morning Mean difference [95%CI]
	$\bar{x} \pm s$	n	$\bar{x} \pm s$	n	
Ohishi 2013	75±11	16	74±8	17	1[-6,8]
Cai 2016	75±8	64	81±8	64	-6[-9,-3]
Chen 2016	79±9	35	80±7	35	-1[-5,3]
Liu 2018	72±8	74	74±12	66	-2[-5,1]
Ma 2021	79±5	72	78±4	72	1[0,2]
Ma 2022	83±5	56	83±5	56	0[-2,2]
Peng 2019	79±5	50	78±4	50	1[-1,3]
Wang 2017	78±5	78	78±3	85	0[-1,1]
Wang 2015	73±8	46	73±7	46	0[-3,3]
Zhang 2018	80±4	40	81±5	40	-1[-3,1]
Zhang 2023	83±4	50	83±4	50	0[-2,2]
Zhao 2015	74±5	122	79±5	122	-5[-6,-4]
amount to		703		703	-1[-3,0]*



*P =0.16

Table 4. Comparison of dSBP reduction effect between bedtime medication and morning medication.

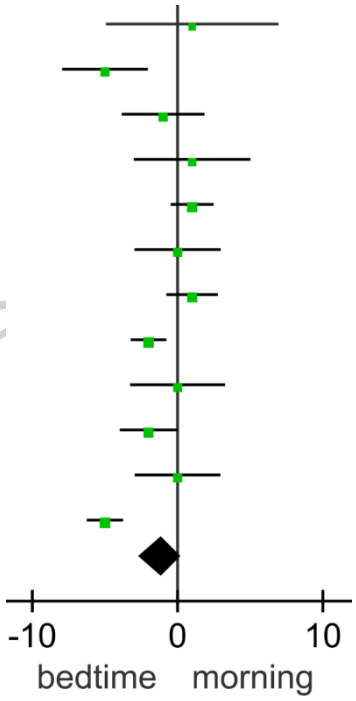
document	post-treatment daytime systolic blood pressure (mmHg)				
	medication before bedtime		medication in the morning		before bedtime - in the morning Mean difference [95%CI]
	$\bar{x} \pm s$	n	$\bar{x} \pm s$	n	
Ohishi 2013	124±13	18	128±13	20	-4[-12,4]
Cai 2016	122±12	64	131±13	64	-9[-13,-5]
Chen 2016	129±2	35	129±2	35	0[-1,1]
Liu 2018	131±18	74	131±19	66	0[-6,6]
Ma 2021	133±3	72	132±5	72	1[0,2]
Ma 2022	129±16	56	130±17	56	-1[-7,5]
Peng 2019	134±3	50	132±5	50	2[0,4]
Wang 2017	132±3	78	130±5	85	2[1,3]
Wang 2015	124±12	46	127±11	46	-3[-8,2]
Zhang 2018	127±6	40	129±7	40	-2[-5,1]
Zhang 2023	129±15	50	129±15	50	0[-6,6]
Zhao 2015	129±6	122	133±6	122	-4[-6,-2]
amount to		705		706	-1[-3,1]*



*P =0.21

Table 5. Comparison of dDBP reduction effect between bedtime medication and morning medication.

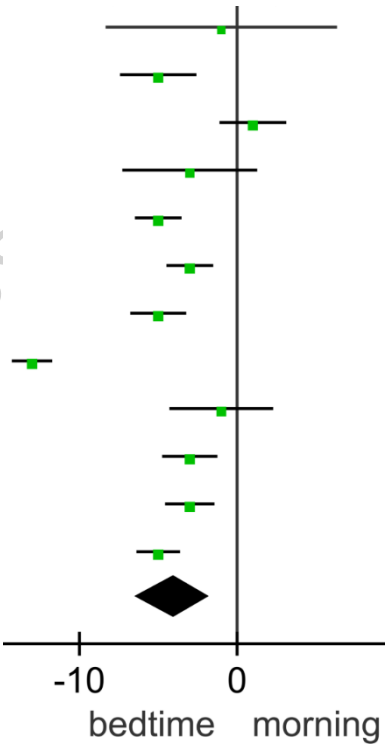
document	post-treatment daytime diastolic blood pressure (mmHg)				before bedtime - in the morning Mean difference [95%CI]
	medication before bedtime		medication in the morning		
	$\bar{x} \pm s$	n	$\bar{x} \pm s$	n	
Ohishi 2013	78±11	18	77±7	20	1[-6,8]
Cai 2016	77±8	64	82±9	64	-6[-9,-3]
Chen 2016	82±7	35	83±5	35	-1[-5,3]
Liu 2018	79±11	74	78±13	66	-2[-5,1]
Ma 2021	84±5	72	83±4	72	1[0,2]
Ma 2022	81±8	56	81±8	56	0[-2,2]
Peng 2019	84±5	50	83±4	50	1[-1,3]
Wang 2017	78±4	78	80±4	85	0[-1,1]
Wang 2015	76±8	46	76±8	46	0[-3,3]
Zhang 2018	81±4	40	83±5	40	-1[-3,1]
Zhang 2023	81±8	50	81±7	50	0[-2,2]
Zhao 2015	78±5	122	83±5	122	-5[-6,-4]
amount to		705		706	-1[-3,0]*



*$P = 0.14$

Table 6. Comparison of nSBP reduction effect between bedtime medication

document	post-treatment nocturnal systolic blood pressure (mmHg)				
	medication before bedtime		medication in the morning		before bedtime - in the morning Mean difference [95%CI]
	$\bar{x} \pm s$	n	$\bar{x} \pm s$	n	
Ohishi 2013	114±15	17	118±18	18	-4[-15,7]
Cai 2016	118±11	64	126±11	64	-8[-12,-4]
Chen 2016	114±6	35	115±7	35	-1[-4,2]
Liu 2018	122±19	74	131±17	66	-9[-15,-3]
Ma 2021	118±7	72	125±5	72	-7[-9,-5]
Ma 2022	115±9	56	119±9	56	-4[-7,-1]
Peng 2019	118±7	50	125±5	50	-7[-9,-5]
Wang 2017	106±5	78	123±5	85	-17[-19,-15]
Wang 2015	114±13	46	115±10	46	-1[-6,4]
Zhang 2018	117±5	40	120±5	40	-3[-5,-1]
Zhang 2023	115±8	50	119±9	50	-4[-7,-1]
Zhao 2015	113±8	122	118±7	122	-5[-7,-3]
amount to		704		704	-6[-9,-3]*

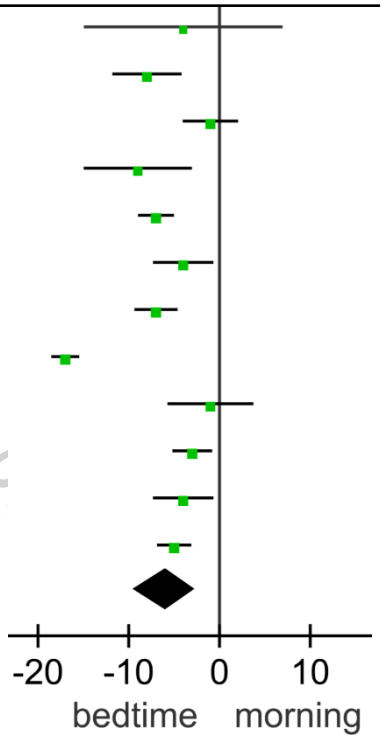


*P = 0.0007

and morning medication.

Table 7. Comparison of nDBP reduction effect between bedtime medication

document	post-treatment nocturnal diastolic blood pressure (mmHg)				before bedtime - in the morning Mean difference [95%CI]
	medication before bedtime		medication in the morning		
	$\bar{x} \pm s$	n	$\bar{x} \pm s$	n	
Ohishi 2013	69±12	17	70±10	18	-1[-8,6]
Cai 2016	74±7	64	79±7	64	-5[-7,-3]
Chen 2016	74±4	35	73±5	35	1[-1,3]
Liu 2018	69±10	74	72±15	66	-3[-7,1]
Ma 2021	72±5	72	77±4	72	-5[-6,-4]
Ma 2022	73±4	56	76±4	56	-3[-4,-2]
Peng 2019	72±5	50	77±4	50	-5[-7,-3]
Wang 2017	66±5	78	79±3	85	-13[-14,-12]
Wang 2015	68±9	46	69±7	46	-1[-4,2]
Zhang 2018	74±4	40	77±4	40	-3[-5,-1]
Zhang 2023	73±4	50	76±4	50	-3[-5,-1]
Zhao 2015	64±5	122	69±6	122	-5[-6,-4]
amount to		704		704	-4[-6,-2]*



*$P = 0.0009$

and morning medication.

Figure 1: Quality evaluation chart of blood pressure literature.

Upper: Morning peak blood pressure; Below: 24-hour mean blood pressure

A~G: Generation of random sequence, allocation concealment, implementer and participant blind, blinding in outcome assessment, incomplete outcome data, selective publication, other bias.