Original Article

Bedtime administration of antihypertensive medication can reduce morning blood pressure surges in hypertensive patients: a systematic review and meta-analysis

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Background: The risk of cardiovascular and cerebrovascular events is the highest during the first several hours post-awakening in patients with hypertension. This is largely due to surges in morning blood pressure (BP). The current meta-analysis explored whether morning BP is affected by the timing of antihypertensive drug administration.

Methods: Four medical databases were searched for clinical trials that examined the relationship between the timing of antihypertensive drug administration and morning BP levels. This meta-analysis compared morning BP surges in patients administered medication at bedtime versus patients administered medication during the day.

Results: The random effects model demonstrated that bedtime administration of antihypertensive drugs reduced morning systolic blood pressure (SBP) by 1.17 mmHg [with 95% confidence interval (CI): –2.47 to 0.37; P=0.08), and reduced morning diastolic blood pressure (DBP) by 0.95 mmHg (95% CI: –2.03 to 0.13; P=0.08), compared with patients who were administered medication during the daytime hours. However, the results did not demonstrate statistical significance. There was strong heterogeneity in both morning SBP (I^2 =77.9% >50%, and Q test >0.1) and morning DBP results (I^2 =77.9% >50%, and Q test >0.1). The funnel plots showed no publication bias in this study.

Discussion: Studies have shown that a 1 mmHg change was sufficient to reduce the risk of cardiovascular-related deaths by 2.1%. Therefore, changing the time of taking antihypertensive medications may significantly reduce cardiovascular-associated mortality. There were certain limitations to this meta-analysis. First, the heterogeneity of the meta-analysis was strong, with undefined reasons. Second, the sample size was relatively small, and future studies involving larger cohorts are warranted to further assess the effects of bedtime antihypertensive medication on minimizing morning BP surges.

Keywords: Hypertension; antihypertensive drugs; bedtime; morning blood pressure surge; meta-analysis

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Introduction

Hypertension is a serious condition that results in severe medical and economical burden worldwide. A recent report, the PURE study, suggested that hypertension is the greatest risk factor for cardiovascular events, contributing to 22.3% of cardiovascular episodes, and the morning peak blood pressure (BP) is an especially important factor (1). A cohort study showed that a 1 mmHg increase in morning BP was

associated with a 2.1% increase in the risk of cardiovascular-associated death (2,3). Administration of antihypertensive drugs before bedtime has been developed as a treatment strategy for BP management. In fact, some studies have demonstrated that compared with morning dosing, bedtime dosing reduced cardiovascular-related deaths by almost half (4,5). Numerous studies have examined the effects of taking antihypertensive medication before going to bed. These reports demonstrated that compared to drug administration at bedtime, administration of the medication during the daytime resulted in a significant increase in the 24-hour mean systolic blood pressure/diastolic blood pressure (SBP/DBP) in patients, especially at night, and thus, the incidence of non-dipping BP was reduced (6-8). Other studies have confirmed that taking antihypertensive drugs at bedtime exerted a beneficial effect on the 24-hour BP, especially at night. However, currently, there is no consensus on the morning peak BP-lowering effect of this strategy. Therefore, this meta-analysis was conducted to assess the influence of bedtime antihypertensive drugs on morning BP levels. We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/apm-21-1405).

Methods

Search strategy

This meta-analysis was conducted following the PRISMA guidelines (9). The PubMed, Embase, Cochrane, and ISI Web of Science databases were searched from January 1980 to December 2019 without language restrictions. Two researchers independently carried out these searches and any disagreements were resolved by discussion. The search strategy adopted in this study (10).

Selection criteria

The following selection criteria were applied to the literature: (I) the study included adult patients with hypertension as diagnosed by SBP ≥140 mmHg or DBP ≥90 mmHg (11); (II) experimental trials of antihypertensive drugs for at least 6 weeks (including calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, diuretics, and alpha-blockers); (III) patients in the experimental group were administered one or more antihypertensive drugs before going to bed (from 5:00 pm to 12:00 midnight), and patients in the control group were matched with the same medication and dose, but administered during the daytime (from 6:00 am to 12:00 noon); and (IV) the pre- and post-treatment SBP and DBP of each patient were measured by Ambulatory Blood Pressure Monitoring (ABPM), which is the gold standard for BP measurement and the most cost-effective strategy for diagnosing hypertension and evaluating the true BP levels (12).

Data extraction

Basic data were collated from the included literature, including authors, year of publication, number of samples, interventions (grouping, drugs, intervention duration), and study design.

Methodological assessment

The methodological quality was independently assessed by two authors using the bias risk tool according to the Cochrane Handbook 5.1.0.

Subgroup analysis

Heterogeneity between studies was analyzed and the literature was classified according to the different sources of heterogeneity.

Risk of bias

The risk of bias was calculated according to the Cochrane Handbook for systematic review of interventions (13). The following six criteria were used: (I) the bias of selection (random-sequence generation and allocation concealment); (II) the bias of performance (blinding of participants and personnel); (III) the bias of detection (blinding of outcome assessment); (IV) the bias of attrition (incomplete outcome data); (V) the bias of reporting (selective reporting); and (VI) other bias. The three potential bias judgments were low, high, and unclear risk.

Statistical analysis

The Review Manager (RevMan, Version 5.1, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) was used to analyze the data of all included trials. Meta-analysis was based on generalized inverse variance.

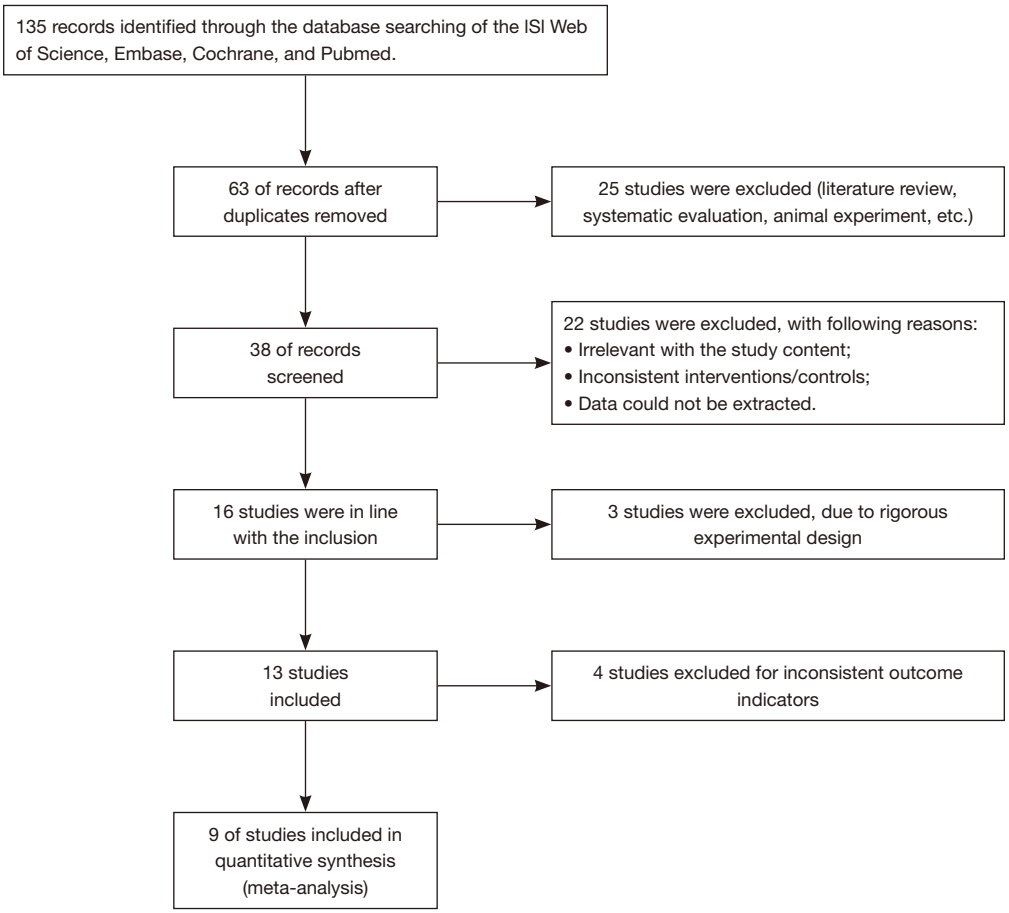

Figure 1 A flow chart showing the literature selection process.

Statistical heterogeneity and sensitivity analysis

Statistical heterogeneity was assessed using the I^2 and Q test statistics, which were defined by I^2 values of 25%, 50%, and 75%. Sensitivity analysis was performed to ensure that the included literature had no significant effect on the stability of the study.

Bias test

Funnel plots and Begger's tests were used to evaluate publication bias.

Results

Literature selection

A total of 135 articles were identified in the database search, of which, 72 studies were removed due to duplication, and 25 articles were excluded as they were literature reviews, systematic evaluations, protocols, case reports, or animal experiments. A further 22 studies were excluded due to irrelevant study content, inconsistent interventions/controls, or data could not be obtained. A total of 3 studies were excluded because of rigorous experimental designs, and 4 studies with inconsistent outcome indicators were removed. Finally, 9 studies, including 10,157 cases, were included in this quantitative synthesis (meta-analysis; *Figure 1*).

Risk of bias assessment

A total of 9 clinical trials (14-22) were included in this meta-analysis. All trials reported random sequence generation. None of the trials provided a detailed description of the allocation concealment. All included literature reported complete outcomes, without selective reporting and none of the trials reported bias (*Figure 2*).

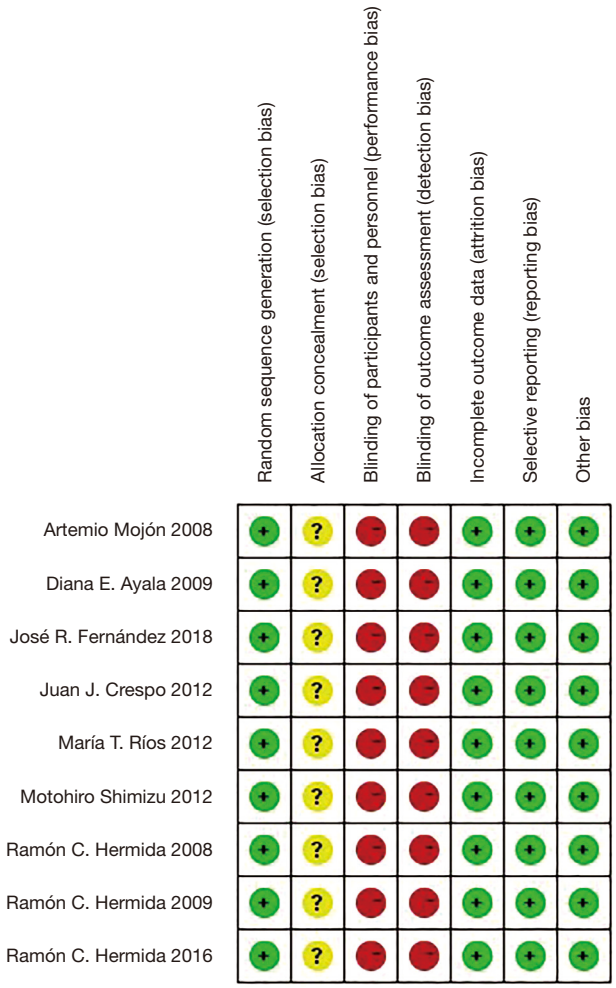

Figure 2 Risk of bias assessment. The three potential bias judgments were low risk, high risk, and unclear risk. Red represents high risk, green represents low risk, and yellow represents unclear risk.

A meta-analysis of the morning SBP

A total of 8 trials reported two outcomes, that being the SBP and the DBP from the morning BP measurements. One trial (20) only reported the SBP from the morning BP measurements.

From the 9 clinical trials included in this meta-analysis, there was a total of 10,157 hypertensive individuals. Due to the strong heterogeneity (I^2 =75% >50%, and Q test >0.1), the random effects model was used. The results demonstrated that bedtime administration of antihypertensive drugs reduced morning SBP by 1.17 mmHg [95% confidence interval (CI): −2.49 to 0.14; P=0.08] compared with drug administration during the daytime (*Figure 3*).

Sensitivity analysis on the 9 included trials showed that none had a significant impact on the stability, and the above random effects were used for an effective combination (*Figure 4*).

The funnel chart of the 9 included studies in the meta-analysis of SBP was symmetrical (*Figure 5*) and the bias test was carried out at the same time. The Begg's test showed that P=0.297 >0.05, suggesting that there was no publication bias in the included literature.

A meta-analysis of the DBP from the morning BP measurements

A total of 9,903 hypertensive individuals from 8 clinical trials were included in this meta-analysis. Due to the strong heterogeneity (I^2 =79% >50%, and Q test >0.1), a random effects model was used. The results demonstrated that bedtime administration of antihypertensive drugs reduced morning DBP by 0.95 mmHg (95% CI: −2.03 to 0.13; P=0.08) compared with patients in the daytime drug administration group (*Figure 6*).

Sensitivity analysis on these 8 trials showed that none had a significant impact on stability, and the above random effects were used for an effective combination (*Figure 7*).

The funnel chart of the included studies was symmetrical (*Figure 8*) and the bias test was performed at the same time. The Begg's test showed that P=0.805 >0.05, suggesting that there was no publication bias in the included literature.

Discussion

The random effects model demonstrated that bedtime administration of antihypertensive drugs reduced morning SBP in patients by 1.17 mmHg (95% CI: −2.47 to 0.37; P=0.08) and reduced morning DBP by 0.95 mmHg (95% CI: −2.03 to 0.13; P=0.08) compared to patients who received medication during the daytime. Although the results were not statistically significant, administration of antihypertensive drugs at bedtime appeared to have reduced morning BP surges.

The incidence of cardiovascular events, such as myocardial infarction, sudden death, and stroke, in hypertensive individuals is highest in the early hours after waking (23,24). Studies have shown that an increase in morning BP by 1 mmHg is associated with a 2.1%

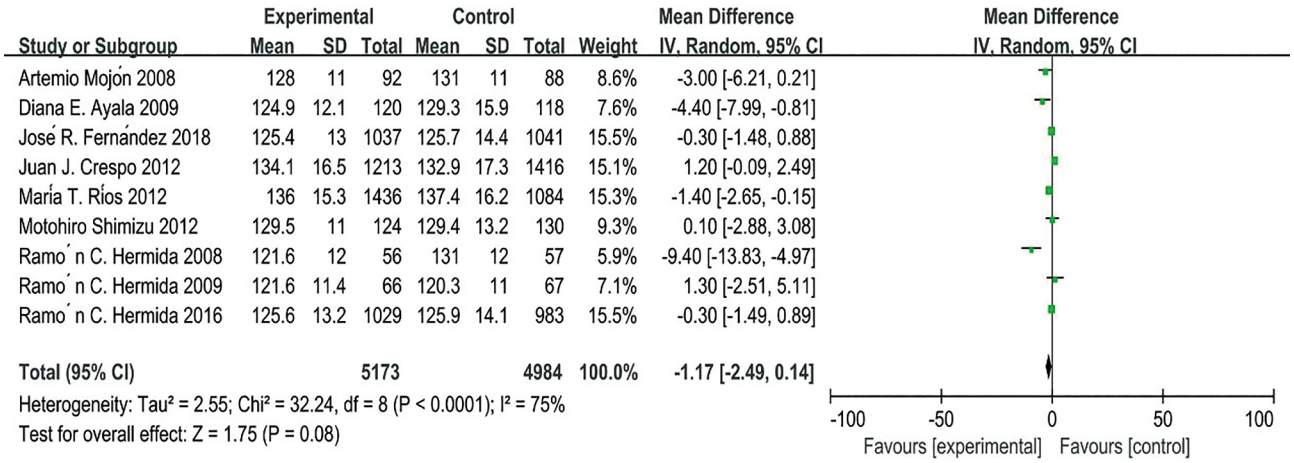

Figure 3 Statistical heterogeneity.

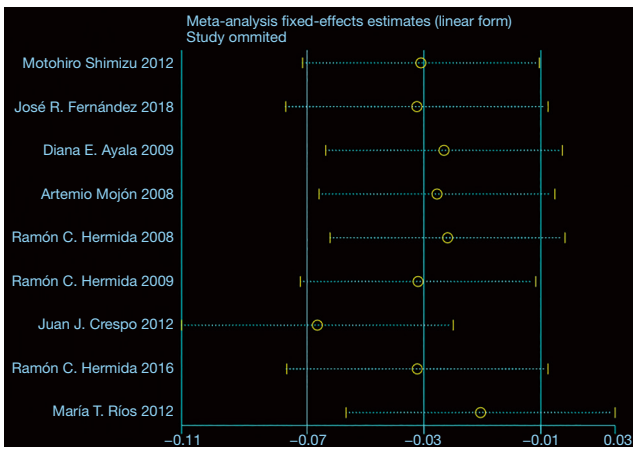

Figure 4 Sensitivity analysis.

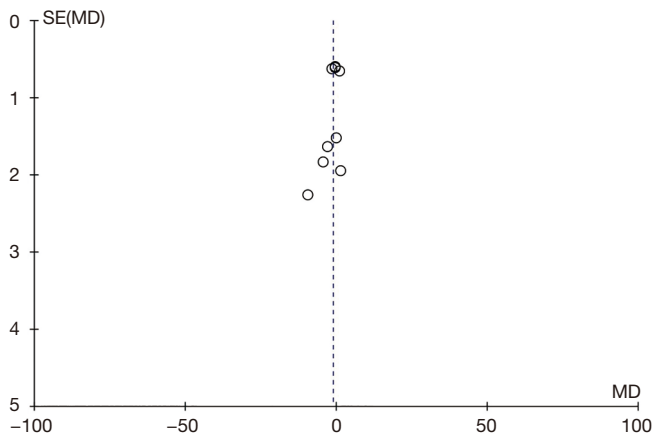

Figure 5 Bias test.

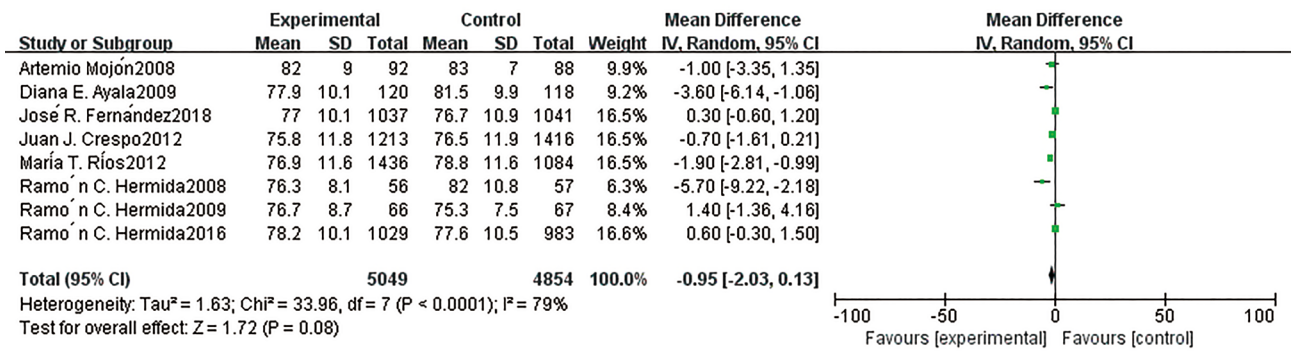

Figure 6 Statistical heterogeneity.

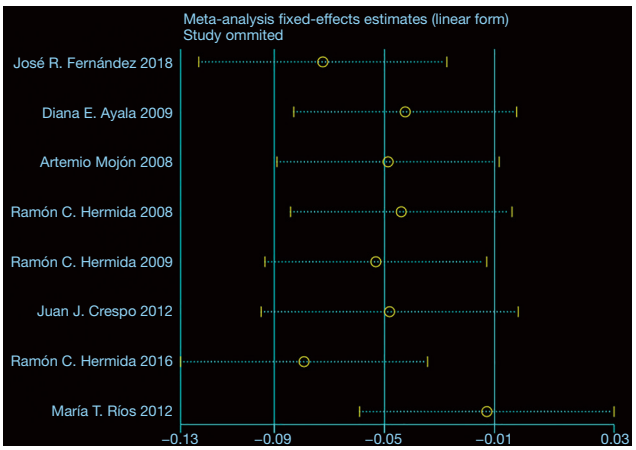

Figure 7 Sensitivity analysis.

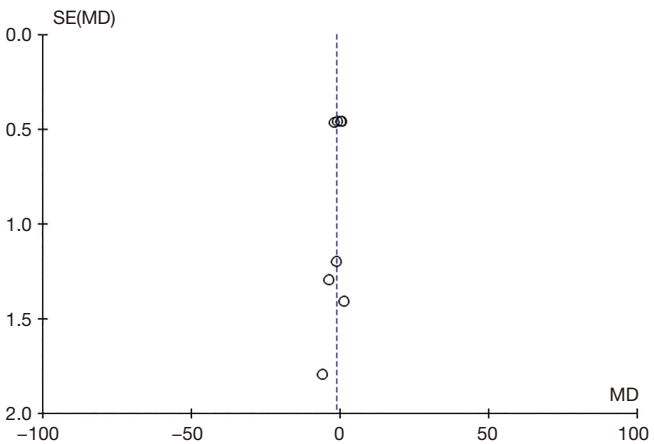

Figure 8 Bias test.

increase in the risk of cardiovascular-related deaths (2,3). Increasingly, investigations have demonstrated that the elevation in morning BP is an important factor in cardiovascular events, renal function damage, and stroke (25-27). Clinical guidelines suggest that long-term use of 24-hour BP stabilizing antihypertensive drugs can control the large fluctuations of BP in the mornings and reduce the early peak BP rises caused by the failure to take drugs on time or a lack of medical care. Indeed, bedtime administration of nifedipine has been shown to significantly reduced the morning BP surge, which is a significant risk factor for stroke (14). At present, most patients with hypertension, especially those with primary (grade 2) or secondary hypertension, require the use of combination therapy to achieve satisfactory BP control (28). A report examining the effects of combination therapy on the antihypertensive efficacy of different administration time showed that compared with twice or multiple administration, once daily administration had the highest patient compliance. Hypertension is a chronic disease and most patients will require life-long medication. There is increasing evidence that compliance with antihypertensive drugs of 80% or more can improve BP control and reduce the risk of BP complications (29). The traditional regimen of antihypertensive drugs involves administration in the morning, usually with breakfast, which can reduce the rate of omission. An optimal once-a-day treatment of hypertension can not only reduce BP, but can also facilitate the normalization of the circadian rhythm of BP (30,31). Studies by Farah others (6) have found that changing the timing of drug administration to bedtime can improve BP control and avoid non-spoon rhythm without increasing drug dosage.

This present study summarized and analyzed 9 RCTs, including 10,157 cases of hypertensive individuals. The data suggested that bedtime administration of antihypertensive drugs may be more beneficial compared to drug administration during daytime. The differences in the amplitude of hypotension was only 1.17 mmHg in the morning SBP and 0.95 mmHg in the morning DBP. However, studies have shown that a 1 mmHg change was sufficient to reduce the risk of cardiovascular-related deaths by 2.1%. Therefore, changing the time of taking antihypertensive medications may significantly reduce cardiovascular-associated mortality. Furthermore, bedtime administration of antihypertensive medication may improve patient compliance as administration of other commonly used cardiovascular drugs, such as statins, are recommended before bedtime. Bedtime administration also provides protection against hypertension in target organs at night. Some reports have suggested that as a result of social aging, many elderly people live alone and have adapted to a lifestyle of early exercise, and these patients tend to be affected by morning BP surges. However, this is controversial. Others believe that a sharp drop in BP at night will adversely affect organ blood supply. Zeng and colleagues (32) examined a group of patients who were administered a single tablet containing 5 mg amlodipine and 20 mg atorvastatin at bedtime (10 pm), and another group of patients who were

administered 5 mg amlodipine and 20 mg atorvastatin as separate tablets in the morning at 7 am. Although there was no significant difference in the adverse reactions between the two groups, the compliance of patients given the single pill was significantly better than that of the patients taking the two drugs as two separate tablets. The study showed that taking antihypertensive drugs before going to bed can be more effective at controlling morning BP fluctuations. In addition, the antihypertensive drugs that are widely used in the clinics tend to have a short half-life and action time, and thus if administered in the morning, the drugs may not provide complete 24-hour coverage, especially by early next morning. Therefore, taking antihypertensive drugs before going to bed can reduce the morning BP, reduce the incidence of cardiovascular events, and improve the compliance of patients.

There were certain limitations to this meta-analysis. First, the heterogeneity of the meta-analysis was strong, with undefined reasons. Second, the sample size was relatively small, and future studies involving larger cohorts are warranted to further assess the effects of bedtime antihypertensive medication on minimizing morning BP surges.

Conclusions

Although there was no statistical significance, bedtime administration of antihypertensive medication tended to reduce morning BP surges, and thus, this treatment regimen may reduce the risk of cardiovascular events in patients with hypertension.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-1405

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-1405). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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