



BP meds: This simple change improves outcomes

For patients with uncontrolled hypertension, a switch to bedtime dosing is advisable.

PRACTICE CHANGER

Advise patients with uncontrolled hypertension to take at least one of their blood pressure (BP) medications at bedtime instead of in the morning. Nighttime dosing leads to better control and lowers the risk of major cardiovascular events.^{1,2}

STRENGTH OF RECOMMENDATION

B: Based on a well-done randomized clinical trial (RCT) and a subgroup analysis.

Hermida RC, Ayala DE, Mojón A, et al. Influence of circadian time of hypertension treatment on cardiovascular risk: results of the MAPEC study. *Chronobiol Int*. 2010;27:1629-1651.

Hermida RC, Ayala DE, Mojón A, et al. Influence of time of day of blood pressure-lowering treatment on cardiovascular risk in hypertensive patients with type 2 diabetes. *Diabetes Care*. 2011;34:1270-1276.

ILLUSTRATIVE CASES

- A 60-year-old man has struggled to get his BP under control despite the use of 3 anti-hypertensives. Is there anything you can recommend to improve his BP control and lower his cardiovascular risk?
- You prescribe hydrochlorothiazide for a 55-year-old woman with newly diagnosed hypertension. What can you tell her about how to take the medication to maximize its beneficial effects?

Management of hypertension often centers around BP measurements taken in a doctor's office during the day, although both BP and metabolism fluctuate with circadian rhythms. Most people experience an increase in pressure during the day, with peaks in the morning and eve-

ning, followed by a decline in BP while they sleep at night.³

The focus belongs on nighttime BP

Sleeping BP is getting considerable attention, particularly the phenomenon of nondipping. Commonly defined as a <10% decline in systolic pressure during sleep, nondipping is associated with an increased risk of cardiovascular events, such as heart attack and stroke.⁴ What's more, mean BP during the night is a better predictor of cardiovascular disease (CVD) risk than BP while the patient is awake.^{5,6}

Evidence suggests that taking an anti-hypertensive medication at night increases its therapeutic effect,⁷ yet most patients take it in the morning.⁸ The study detailed in this PURL was designed to investigate whether bedtime dosing significantly affects BP control and CVD risk.

STUDY SUMMARY

Bedtime dosing benefits patients, and there's no downside

The MAPEC study was an open-label RCT conducted at a single center in Spain.¹ Patients were enrolled if they had a diagnosis of either untreated hypertension (based on ambulatory BP monitoring [ABPM] criteria) or resistant hypertension (uncontrolled on ≥3 optimally dosed antihypertensive medications). Exclusion criteria included pregnancy, a history of drug/alcohol abuse, night shift work, acquired immune deficiency syndrome, type 1 diabetes, secondary hypertension, and a previous CVD diagnosis.

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Kate Kirley, MD;
Umang Sharma, MD;
Kate Rowland, MD
University of Chicago

PURLs EDITOR
John Hickner, MD, MSc
Cleveland Clinic

TABLE

Dosing of BP meds: A look at outcomes

Events/1000 patient-years	Morning dosing	Bedtime dosing	P between groups
Overall (n=2201)¹			
Total events*	27.80	11.95	<.001
CVD death	2.08	0.53	.006
Cardiovascular events	11.00	5.27	<.001
Cerebrovascular events	3.57	1.23	.001
Diabetes subgroup (n=448)²			
Total events*	54.24	19.80	<.001
CVD death	4.79	0.86	.038
Cardiovascular events	15.95	6.89	.008
Cerebrovascular events	6.38	0.86	.010

*Includes death from all causes and cardiovascular and cerebrovascular events.
 BP, blood pressure; CVD, cardiovascular disease.

➤ Mean asleep blood pressure is a better predictor of cardiovascular risk than mean BP while the patient is awake.

Patients were randomly assigned to one of 2 time-of-day dosing groups: morning dosing of all their BP medications (n=1109) or dosing of ≥1 BP medications at bedtime (n=1092). ABPM—in which patients wore a monitor that recorded their BP every 20 minutes during the day and every 30 minutes at night for 48 hours—was conducted once a year, or more frequently when medication adjustments occurred. The use of a specific drug was not required, but physicians were instructed to adjust medications according to a study-specific ABPM protocol.

Patients were followed for a mean of 5.6 years for the endpoints of CVD events and mortality. These endpoints were assessed by researchers blinded to patients' treatment assignment.

At baseline, the 2 groups were similar in age (mean of 55 years), percentage of men (48%), presence of comorbidities, and baseline clinic and ambulatory BP. Throughout the study, patients in the bedtime dosing group had lower mean asleep systolic and diastolic BP, a lower prevalence of a non-dipping pattern, and a higher prevalence of controlled ambulatory BP. The bedtime group also had a lower risk of total CVD events (relative risk [RR]=0.39; 95% confidence interval [CI], 0.29-0.51; P<.001) and major CVD events (RR=0.33; 95% CI, 0.19-0.55;

P<.001), and fewer overall deaths (4.16/1000 vs 2.11/1000 patient-years; P=.008) (TABLE). To prevent one CVD event, 63 patients would need to take their BP medication at bedtime instead of in the morning for one year. To prevent one death, 488 patient would need to adhere to the nighttime schedule for one year.

A subgroup analysis of patients with type 2 diabetes (n=448)² had similar results: For this population, too, bedtime dosing led to lower asleep BP, a lower prevalence of a non-dipping pattern, and a higher prevalence of controlled ambulatory BP, as well as a lower risk of total CVD events, major CVD events, and CVD-related death. The differences persisted after correction for the use of statins and aspirin. Among those in this subgroup analysis, 29 patients would need to take their BP medications at bedtime for one year to prevent one CVD event, and 263 patients would need to be treated for one year to prevent one death.

WHAT'S NEW

Advantages of preventing nondipping are clearly established

We've known that a nondipping pattern is associated with higher cardiovascular risks and that taking antihypertensives at bedtime

decreases the prevalence of nondipping patterns. The MAPEC study, however, is the first prospective trial to show that bedtime dosing of BP medications lowers the risk of CVD events and death.

CAVEATS

Methodology, non-US guidelines raise questions about applicability here

MAPEC was an open-label study, meaning that the physicians adjusting BP medications were aware of the treatment groups to which their patients were allocated. Physicians were given guidelines for the titration of medications, but it is unclear whether they treated patients in both treatment groups identically. Patients were also aware of their treatment group, which creates the potential for bias if one group adhered to their medications more closely than the other.

The study was a single-center trial conducted in Spain, which may limit its generalizability to the United States. Notably, Spain's medication guidelines differ from ours, with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and calcium channel blockers as first-line medications and hydrochlorothiazide as a second-line option.

While ABPM appears to be a better indicator of CVD risk compared with clinic BP monitoring, most US physicians still rely on readings taken in their office for diagnosing and managing hypertension. How ambulatory BP translates to clinic BP is somewhat unclear.

CHALLENGES TO IMPLEMENTATION

Some patients and providers may resist the switch

We see few challenges to implementing bedtime dosing of BP medications for patients with uncontrolled hypertension. It is possible, however, that patients who have a longstanding routine of taking their medications in the morning may be resistant to change. Also, pharmacists and nurses, as well as some physicians, may continue recommending morning dosing, which could be confusing for patients.

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➤ Taking an antihypertensive at night increases its therapeutic effect, but most patients take it in the morning.

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INSTANT POLL

When do you tell patients with hypertension to take their blood pressure medication?

- In the morning
- At bedtime
- Either in the morning or at bedtime
- In the morning and at bedtime
- Other _____

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