CME MOC

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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should my patients take their blood pressure medications in the evening to enhance cardiovascular benefit?

A: No. Although the cardiovascular benefits of controlled blood pressure (BP) are clear,[1] current evidence is insufficient to recommend routinely dosing antihypertensive medications in the evening as opposed to morning for cardiovascular benefit. However, hypotension carries its own risks regardless of the time of day. Clinicians should employ shared decision-making with patients to individualize dosing practices based on risk factors and preferences.

SCENARIO 1: ELEVATED BP IN THE MORNING

A patient with primary hypertension and coronary artery disease takes antihypertensive medications in the morning. The BP is well controlled throughout the day, but the patient reports that it is elevated in the morning. The physician considers switching the patient to an evening dosing regimen for cardiovascular benefit.

BP follows a diurnal rhythm, generally lower at night (nocturnal dipping) and increasing in the morning. Because morning BP surges have been associated with cardiovascular events,[2] it follows that administration of antihypertensive medications in the evening might confer cardiovascular protection.

Patients with hypertension can be subdivided based on the nocturnal dipping pattern in systolic BP observed on 24-hour ambulatory monitoring:

- Extreme "dippers": a drop greater than 20%
- Dippers: a drop from 10% to 20%
- Nondippers: a drop less than 10%
- Reverse or inverted dippers: no change or an increase in nocturnal systolic BP.[3]

There is evidence that nondippers are at higher risk for adverse cardiovascular events. Therefore, it makes sense that evening dosing might induce dipping in the nondipper phenotype.

Hermida et al examined this hypothesis in 2 major studies[4,5]:

- The MAPEC trial[4] (Monitorización Ambulatoria Para Predicción de Eventos Cardiovasculares [Ambulatory Blood Pressure Monitoring for Prediction of Cardiovascular Events]) included 2,156 patients with untreated or resistant hypertension. Patients were instructed to take BP medications at bedtime or on awakening. The primary end point, a composite of all-cause mortality and cardiovascular events, was significantly lower in the bedtime group, with a hazard ratio (HR) of 0.39 (95% confidence interval [CI] 0.29–0.51, $P < .001$).[4]
- The Hygia Chronotherapy Trial[5] examined the risk of cardiovascular disease in patients taking BP medications at bedtime compared with on awakening. The primary outcome was a composite end point consisting of cardiovascular disease-related death, myocardial infarction, coronary revascularization, heart failure, or stroke. As with the MAPEC trial, the bedtime-dosing group had a significantly better outcome, with a reported HR of 0.55 (95% CI 0.50–0.61, $P < .001$).[5]

These results seemed to favor bedtime dosing of antihypertensive medications, but the improbable effect size led others to question the methodology

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(problematic randomization), results (no independent adjudication of cardiovascular events), and conclusions.[6] In response, the HARMONY trial[7] (Hellenic-Anglo Research Into Morning or Night Antihypertensive Drug Delivery) in 2018 randomized patients to morning or evening antihypertensive dosing and utilized a crossover design over 12 weeks. Clinic and 24-hour ambulatory BPs were compared, and no difference was detected between groups.[7]

In 2022, Mackenzie et al[8] published the results of the TIME study (Treatment in Morning vs Evening), which included more than 21,000 patients randomized to once-daily dosing of medications, daytime vs evening. Patients were followed for a median of 5.2 years. The primary outcome examined was a composite score including hospitalization for nonfatal myocardial infarction or stroke and vascular death. The primary end point was seen in 3.4% of patients in the evening dosing group and in 3.7% of patients in the morning dosing group (HR 0.95; 95% CI 0.83–1.10; $P = 0.53$). The authors concluded that patients should take their antihypertensive medications when convenient and when they experience the fewest side effects.[8]

SCENARIO 2: RISK OF FALLS AND WORSENING GLAUCOMA

A 67-year-old woman with a history of glaucoma, hypertension, and type 2 diabetes mellitus presents to establish care. Her BP is uncontrolled, and she reports that she forgets to take her medications in the morning because of her fluctuating schedule. She had been told to avoid taking BP medications in the evening, when she routinely takes the rest of her medications, to minimize the risk of falls and worsening glaucoma.

Fall risk is a major concern with dosing of nocturnal antihypertensive medications. After older studies linked low BP (systolic BP < 120 mm Hg) to an increased risk of falls,[9] many clinicians avoided prescribing evening antihypertensive medications to prevent orthostatic symptoms in the morning and to minimize fall risk. More recent data that examined intensive BP control (systolic BP < 120 mm Hg) showed a possible increased risk of syncope but not of falls.[10] The TIME study[8] (Treatment in Morning vs Evening) examined dizziness, falls, and fractures as secondary end points. Patients in the evening-dosing group reported fewer falls than their morning-dosing counterparts. The number of fractures reported was similar in both groups. The morning-dosing group reported more events of dizziness or lightheadedness.[8]

Another concern with nocturnal dosing of antihypertensive drugs is glaucoma, a debilitating disease worldwide. Nocturnal decreases in systemic BP have been postulated to lead to decreased ocular perfusion pressure, which may lessen blood flow to the optic nerve and perpetuate glaucomatous damage.[11] Studies have yielded equivocal results, but evidence is mounting that both high and low BP are associated with an increased risk of glaucoma. A meta-analysis found that a fall in nocturnal BP is a risk factor for worsening glaucomatous damage and visual field loss,[12] suggesting that evening dosing of antihypertensive medications may be inadvisable in patients with glaucoma who have a pronounced nocturnal BP dip. However, the available data are not robust enough to yield practice guidelines. Shared decision-making is key, given the potential risk of glaucoma progression with lower nocturnal BP.

Regarding the 67-year-old patient in scenario 2, her comorbidities including glaucoma suggest a need for shared decision-making to weigh the potential risks of worsening her glaucoma with nocturnal dosing of BP medications against the risk of compromising adherence if morning dosing is recommended.

BOTTOM LINE: TAKE AS DIRECTED

Current evidence does not suggest any benefit with evening vs morning antihypertensive medication dosing. The cardiovascular outcomes and overall side effects appear to be similar. Patients who take their medications in the evening do not appear to have an increased risk of falls or fractures, but they also do not appear to have better cardiovascular outcomes. The focus should be to achieve BP control and facilitate adherence, regardless of the timing of antihypertensive medications.

It is unclear whether nondippers and reverse dippers, or even patients with early morning BP surges, would have better cardiovascular outcomes with a regimen that includes nocturnal medication dosing. Data are lacking in these subgroups of patients, and identifying them remains a challenge given the limited use of ambulatory BP monitoring.

For most patients with hypertension, the act of taking the medication as directed has more significance than the timing.

DISCLOSURES

Dr. Mehdi has disclosed teaching and speaking for AstraZeneca and work as advisor or review panel participant for Fresenius. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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