Is Evening Dosing of Antihypertensive Therapy Ready for Prime Time?

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Evening dosing of antihypertensive therapy has emerged as an easily implemented strategy that stands in contradistinction to the long-standing paradigm of morning administration of once-daily antihypertensive therapy. However, the morning dosing strategy was never based on clinical evidence, per se. Rather, it seems to have been chosen by default, perhaps influenced by the perceived convenience of morning dosing of once-daily drugs. The emergence of hard endpoint data suggesting clinical benefit of evening compared with morning dosing clearly brings into question which dosing strategy should be preferred.[1,2]

In this issue of the Journal, Roush and colleagues[3] present a meta-analysis of hypertension endpoint trials examining the question of the relative impact of evening vs morning dosing on cardiovascular (CV) risk reduction. They started with a universe of 175 hypertension trials including both blood pressure (BP) difference and drug comparison trials. Five trials were determined to be evening dosing trials (EDTs). A total of 35,075 participants were in EDT trials compared with 312,057 in the usual dosing trials (UDTs). In the trials included in their meta-analysis, stroke and/or coronary heart disease (CHD) events were reported. In the EDT trials, there were 2320 CV disease (CVD) events while in the UDT trials there were 18,129 events—the majority of which were CHD events. The timing of the dosing of antihypertensive drug was determined by reviewing the methods section of original publications. Any trial with greater than once-daily drug dosing was included in the UDT trial category. EDTs were those where a single daily dose of antihypertensive drug was explicitly dosed in the evening. Hazards ratios (HRs) were reported separately for stroke and CHD events; these events were also combined to create a composite HR.

The study results generally favored evening dosing. Although neither individual HR attained statistical significance, the composite HR demonstrated a statistically significant 37% lower risk in favor of evening dosing. The risk reduction favoring evening dosing appeared to be even greater with angiotensin-converting enzyme inhibitors than calcium antagonists. The authors astutely conducted sensitivity analyses to determine the impact of individual trials included in the EDT group on the reported outcomes. The Heart Outcomes Prevention Evaluation (HOPE) trial[4] had an outsized impact on the reported results as it was the only EDT trial that when excluded from the analysis resulted in a loss of statistical significance favoring evening dosing. The HOPE trial was notable in that its participants were selected for high CVD risk and it was the only EDT where the antihypertensive dose was administered prior to sleep; however, there was no direct contrast of evening to morning dosing of ramipril.

What other evidence exists to support the premise that evening dosing is superior to morning dosing of antihypertensive medications? The lines of evidence can be broken down into at least two categories: epidemiological and experimental. Experimental data include both individual trials specifically designed to determine the impact of evening vs morning dosing on pressure-related clinical outcomes as well as retrospective pooling of prospective clinical trials that determined clinical outcomes using rigorous adjudication protocols. It is an informative exercise to critically examine the strengths of these aforementioned data while simultaneously acknowledging the less understood issues related to the timing of administration of antihypertensive medications.

Ambulatory BP monitoring has been the indispensable tool of BP measurement in both epidemiological and experimental studies. Ambulatory BP data differ from clinic BP measurements in important ways. First, ambulatory BP measurement provides many more BP measurements over the recording period that can be averaged for the entire period of observation as well as for distinct time periods (eg, daytime, nighttime). The availability of a large number of BP readings provides much greater precision in determining the habitual BP level of patients than is possible with office BP readings. Accordingly, compared with office BP, ambulatory BP better predicts all-cause mortality[2,5,6] as well as CV morbidity[2,7] and mortality.[2,6,7] Importantly, within the 24-hour recording period, nocturnal BP levels predict CV risk more so than either daytime or 24-hour BP level.[5–7] The lack of the normal nocturnal decline in BP (10%–20%) has also been linked to higher CVD risk.[5–7] Also, the white-coat effect, which is potentially observed in office BP readings, is essentially eliminated with extended ambulatory BP recordings. In addition, ambulatory BP and office BP readings are not directly interchangeable. That is, 24-hour ambulatory BP readings that are much lower than office BP readings portend similar CVD risk.[7]

The experimental data comparing evening vs morning dosing of antihypertensive drugs have, however, been mixed, depending on the endpoint(s) actually measured. Hermida and colleagues[2] reported an intriguing study in hypertensive patients that favored nocturnal (bedtime) dosing of ≥1 antihypertensive medication compared with administration of all antihypertensive medications being

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administered in the morning (upon awakening). The Ambulatory Blood Pressure Monitoring for Prediction of Cardiovascular Events (MAPEC) study was a prospective, open-label, blinded endpoint study that enrolled 2156 hypertensive men and women aged 56 years who were randomly allocated to the aforementioned two dosing regimens. Over a median follow-up of 5.6 years, total CVD events were 61% lower ($P<.001$) in the evening dosing group; a 67% reduction ($P<.001$) was also noted for the risk of major events including CVD death, myocardial infarction, ischemic stroke, and hemorrhagic stroke). Forty-eight–hour ambulatory BP monitoring was performed at least annually. Participants in the evening dosing group also had lower nocturnal BP, a greater relative nocturnal decline in BP from daytime levels, fewer nondippers, and greater ambulatory BP control. Interestingly, the average 48-hour ambulatory systolic BP was only marginally lower in the evening dosing group (142.6 mm Hg vs 144.4 mm Hg, $P=.065$) while the diastolic BP was virtually identical (81.1 vs 81.4 mm Hg, $P=.693$). Adverse events, however, were not reported. In an open-label, randomized crossover study, bedtime compared with morning dosing of the combination of amlodipine-olmesartan significantly reduced the morning BP surge as well as urine albumin: creatinine excretion.[1] Nocturnal BP, however, was significantly lowered only in participants characterized as nondippers at baseline. On the other hand, in former participants in the African American Study of Kidney Disease (AASK) study cohort with chronic kidney disease (CKD), Rahman and colleagues[8] did not find that bedtime dosing of antihypertensive drugs significantly reduced nocturnal BP compared with morning ingestion of antihypertensive medications. Nevertheless, an open-label trial[9] in 661 hypertensive patients with CKD and median follow-up of 5.4 years found that total CVD events were 69% lower ($P<.001$) in patients randomized to bedtime dosing of ≥1 antihypertensive medication vs ingestion of all medications in the morning upon awakening. Also, there was greater ambulatory BP control and lower sleeptime BP in the bedtime dosing group.

A Cochrane review of 21 randomized controlled trials in 1993 patients with hypertension found a slightly lower systolic BP (~2 mm Hg) with evening dosing.[10] In the 5 studies reporting adverse events, there was no difference in overall adverse events despite favorable trends in overall adverse events and study withdrawals due to adverse events. However, none of these studies included in this analysis reported all-cause or CV mortality, CV morbidity, or serious adverse events. Importantly, the potential safety issues related to nocturnal dosing of antihypertensive medications have been incompletely explored. Accordingly, a rigorously conducted randomized controlled trial 36 to 42 months in duration comparing morning dosing of all antihypertensive medications vs administration of all nondiuretic medications at bedtime is currently being planned.[11]

The analysis by Roush and colleagues[3] reported in this issue of the Journal adds important new information to the growing body of evidence that CVD risk reduction is more impressively lowered with evening compared with morning dosing of antihypertensive medications. Thus, the preponderance of evidence, at present, has aligned in favor of nocturnal dosing of once-daily antihypertensive medications. Nevertheless, there are important issues related to the timing of antihypertensive medication dosing that we simply do not know enough about. When selecting any therapeutic strategy, it is important to not only determine the benefits but also the risks. At present, not enough is known about the risks of nocturnal compared with morning dosing of antihypertensive drugs. However, despite the potential for nocturnal hypotension to precipitate ocular ischemic events, there does not appear to be any substantive signal of major risk in the data thus far accumulated. The most convincing way to determine the RR-benefit ratio is to undertake an adequately powered, prospective, double-blind trial of sufficient duration with adequate characterization of the patient cohort not only at baseline but during the course of the trial to determine the impact of the timing of drug administration on clinical outcomes and safety endpoints. The trial cohort should enroll a broad enough patient cohort to be able to make inferences regarding important hypertensive cohorts who theoretically are at risk for nocturnal dosing. Until such a trial is performed, our current body of knowledge is tilted in favor of nocturnal dosing of ≥1 once-daily hypertension drugs.

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