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EDITORIAL COMMENT

Sleep-Time Blood Pressure

A Validated Therapeutic Target*

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The objective of treating hypertension is to reduce blood pressure (BP) in a manner that diminishes or, ideally, abolishes the cardiovascular (CV) risks associated with BP elevation. The epidemiologic relationship between BP and CV risk is consistent, whether BP is measured at random in the clinic, home, workplace, or over 24 h with intermittent or continuous BP monitoring. The salutary effect of BP reduction is likewise consistent and, to a large extent, independent of the interventions used to achieve it. Unfortunately, antihypertensive therapy as currently practiced does not eliminate the hazards associated with BP elevation. Rather, it decreases them by approximately one-third, a worthwhile but clearly suboptimal result.

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Attempts to refine estimates of risk have focused, in part, on the use of out-of-office BP monitoring to increase the sample size of BP measurements and provide an accurate estimate of the habitual pressure load to which the vasculature is exposed. Prospective studies indicate that the average of repeated BP measurements is superior to clinic BPs in predicting the development of hypertension-related structural abnormalities such as left ventricular hypertrophy and the occurrence of major CV events, including stroke and myocardial infarction (1). The long-term advantage of therapy directed at these targets has not been demonstrated, however, and the substitution of BP averages for random readings does not change the basic assumption of hypertension treatment—that lower is better so long as diastolic BP is sufficient to maintain coronary perfusion. According to the current paradigm, an effective pharmacological regimen is one that provides continuous, indiscriminate BP reduction 24 h/day. The report by Hermida et al. (2) in this issue of the *Journal*, challenges conventional wisdom and, in so doing, has the potential to effect important changes in the management of hypertension.

Their results are derived from the MAPEC (Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares) study, a prospective single-center PROBE study that enrolled 3,344 normotensive and hypertensive subjects. The rationale for the MAPEC study originates from analyses of 24-h BP recordings that indicate that the timing of BP elevation as well as the integrated BP "burden" is important in determining CV risk. In most individuals (normotensive or hypertensive), BP has a predictable circadian pattern characterized by a rapid increase at the time of awakening, with maximum levels reached during the morning hours and maintained until an evening BP decline reaches its nadir during sleep.

The normal reduction in BP during sleep is approximately 10% to 20%. In 1988, O'Brien et al. (3) coined the term "nondipper" to describe a subgroup of hypertensive patients in whom the nocturnal BP decline was <10/5 mm Hg and reported that the risk of stroke in these patients was markedly elevated. Although subsequent investigators used variable definitions of "dipping" and "nondipping," the adverse prognostic implications of reduced nocturnal BP decline has proved a durable finding. In a prospective study, Verdecchia (1) reported that "nondippers" experienced nearly 3 times as many CV events as "dippers." Other sources have confirmed an increased risk of stroke, myocardial infarction, progressive renal insufficiency, and heart failure as well as increased prevalence of left ventricular hypertrophy/diastolic dysfunction, microalbuminuria, and endothelial dysfunction in "nondippers" compared with "dippers" (4).

The MAPEC study was designed to determine the prognostic significance of pre-specified aspects of the 24-h BP profile and evaluate changes in circadian BP patterns on the frequency of CV events. The authors report that baseline ambulatory blood pressure monitoring (ABPM) parameters including mean daytime systolic blood pressure (SBP), nighttime SBP, and reduction in SBP during sleep correlated better with the occurrence of CV endpoints (n = 331) than clinic BP over a median follow-up of 5.6 years. These findings are in accordance with earlier studies. What is new is their observation that a specific alteration in the circadian BP pattern resulted in a significant reduction in CV endpoints. Thus, a 13% decrease in CV risk was observed for every 5-mm Hg decline in asleep BP ($p < 0.001$), and this risk reduction was independent of changes in other aspects of the circadian BP pattern. Reduction in the level of BP during sleep and the difference in sleep/waking BP were the most potent predictors of future events. Reduction in mean 48-h SBP was inferior as a therapeutic target and was not associated with improved outcomes in statistical models that incorporated measurements of asleep BP.

Therefore, sleep-time BP qualifies as a validated target of antihypertensive therapy. The authors suggest that treatment should be directed routinely at nocturnal BP and that this goal is best accomplished by nighttime administration of antihypertensive medications. In the MAPEC study, hypertensive

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patients were randomized to receive all of their medications in the morning or to ingest 1 or more at bedtime. In a previous paper, the authors reported that patients receiving at least some of their medications at bedtime had a significantly lower relative risk (RR) of total CV events, compared with those taking all of their medications upon awakening (RR: 0.39, 95% confidence interval: 0.29 to 0.51, $p < 0.001$). Reduction in the RR of major events (CV death, myocardial infarction, and stroke) was also highly significant (RR: 0.33, 95% confidence interval: 0.19 to 0.55, $p < 0.001$). No adverse effects were attributed to nocturnal drug administration (5).

The critical importance of reducing sleep-time BP might explain, at least in part, the problematic results of several earlier studies. In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study, for example, aggressive overall BP reduction did not improve CV outcomes in diabetic patients (6). In the MAPEC study, reduction of mean 48-h BP was not associated with significant risk reduction in statistical models that incorporated asleep BP. In the CONVINCE (Controlled Onset Verapamil Investigation of Cardiovascular Endpoints), a timed-release formulation of verapamil that targeted the early-morning rise in BP failed to show an advantage over conventional AM administration of atenolol/hydrochlorothiazide (7). In the present study, diminution of the early-morning rise in BP had no effect on CV events. In the HOPE (Heart Outcomes Prevention Evaluation) study, the marked reduction in CV endpoints—seemingly out of proportion to the modest changes observed in clinic BP—could perhaps be explained by the protocol-specified administration of the study drug (ramipril) at bedtime. This hypothesis is supported by the marked reduction in nocturnal BP reported in a small ABPM substudy of HOPE (8) as well as data from the present study group demonstrating that bedtime administration of ramipril results in superior nocturnal BP regulation without compromising antihypertensive efficacy during the waking hours (9).

The implications of these findings for clinical practice are substantial. A strong case can be made to accept the conclusion of the authors that bedtime administration of at least some portion of the antihypertensive regimen of the patient should become the default standard. Previous studies with a number of drugs from different pharmacological classes have compared the antihypertensive effects of nighttime versus morning dosing. For most drugs, nighttime administration produces similar changes in mean 24-h BP, compared with morning dosing, and there is little loss of daytime BP control. Bedtime administration is consistently more effective in reducing BP during sleep, increasing the magnitude of sleep-time BP reduction, and reducing the percentage of "non-dippers," irrespective of the pharmacological half-life of the agent tested (9).

It should be noted, however, that the clinical approach used in the MAPEC study was atypical in that therapy was routinely directed toward normalization of the circadian BP pattern. In addition to randomizing patients to morning versus bedtime drug administration, drug therapy was further adjusted based on analysis of repeated 48-h ABPM recordings. The benefits of this overall approach to treatment have not been documented, and application of this labor-intensive methodology to the routine management of hypertension would add considerable costs to the healthcare system.

The ideal result would be to use the insights gained from this and other studies and achieve the benefits of reducing asleep BP without performing repeated ABPM in every patient. To do so, the safety of routine nighttime drug administration must be clearly established. Bedtime drug administration raises the possibility of nocturnal hypotension, which has been reported to cause both cerebral and myocardial ischemia in susceptible patients. Although this risk seems to be small or nonexistent based on the totality of available evidence, it might be significant in certain subgroups (e.g., patients with coronary artery disease in whom coronary perfusion might be compromised by nocturnal hypotension). Further studies will be required to establish the safety of routine nighttime drug administration in such patients; alternatively, ABPM can be used in individual cases. In any event, identification of sleep-time BP as a valid therapeutic target constitutes an important milestone in the evolution of antihypertensive therapy. The mere suggestion that CV event rates in patients with hypertension can be reduced by more than 50% with a zero-cost strategy of giving existing medications at bedtime rather than in the morning is nothing short of revolutionary.

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