

# Bedtime Chronotherapy with Conventional Hypertension Medications to Target Increased Asleep Blood Pressure Results in Markedly Better *Chronoprevention* of Cardiovascular and Other Risks than Customary On-awakening Therapy

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## KEYWORDS

- Prevention • Cardiovascular risk • Ambulatory blood pressure monitoring
- Hypertension chronotherapy • Asleep blood pressure • MAPEC Study • Diabetes
- Resistant hypertension

## KEY POINTS

- There are three bases for bedtime hypertension chronotherapy (BHCT) as superior prevention against cardiovascular disease (CVD).
- The first is the correlation between blood pressure (BP) and risk for target organ and vascular injury plus CVD events is greater for ambulatory BP monitoring (ABPM) than office BP measurements (OBPM).

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- The second is the asleep BP mean is an independent and stronger predictor of CVD risk than the daytime OBPM and ABPM-derived awake and 24-hour BP means.
- The third is the MAPEC (Ambulatory Blood Pressure Monitoring for Prediction of Cardiovascular Events) trial, which showed, with confirmation by others, targeting asleep BP by BHCT entailing one or more conventional medications versus usual on-awakening therapy reduces total CVD events by 61% and major events (CVD death, myocardial infarction, ischemic and hemorrhagic stroke) by 67%.
- BHCT thus offers the most cost-effective *chronoprevention* against adverse CVD outcomes in regular and vulnerable renal, diabetic, and resistant hypertensive patients.

**INTRODUCTION**

The most routine procedure of clinical practice is measurement of systolic blood pressure (SBP) and diastolic blood pressure (DBP), either to detect newly developed arterial hypertension or assess attainment of treatment goals of previously diagnosed hypertensive patients. This emphasis on BP assessment is intended for cardiovascular disease (CVD) risk reduction and future adverse outcomes and incidents prevention. However, of fundamental relevance to both clinicians, in terms of providing optimal care, and patients, in terms of preserving health and wellbeing, is the following question: are the limited number of office BP measurements (OBPM) made at one specific time of the day representative of BP status throughout the 24 hours and of CVD risk? A primary driver of modern medical practice is the concept of homeostasis; relative constancy of the milieu intérieur (internal environment) and thus biological indicators of health and disease. Accordingly, it is assumed that it is of little or no importance when, during the 24 hours or other time domains, diagnostic tests such as OBPM are done and medications are taken. However, a multitude of publications prove that the biology of human beings, as a heritable trait, is organized in a predictable-in-time fashion that is expressed as endogenous circadian (~24 hours) and other periods; for example, menstrual and annual rhythms.<sup>1–3</sup> Twenty-four-hour bioperiodicities, whose stagings (eg, peaks and troughs) are synchronized internally as a circadian time structure as well as externally to the environmental and social time structure primarily by the person's activity in light/sleep in darkness daily routine,<sup>4,5</sup> are especially relevant to medicine, because not only do they influence the findings of diagnostic tests but also the response to curative interventions. This is especially relevant to risk for hypertension and CVD events as shown by the great many research investigations of BP chronobiology (rhythm determinants of SBP and DBP 24-hour patterns)<sup>6–9</sup> and BP chronotherapy (rhythm determinants of hypertension medication effects according to timing: morning on

awakening versus bedtime)<sup>10–17</sup> as subsequently reviewed relative to the now well-demonstrated impact on CVD risk and prevention,<sup>18–20</sup> which the authors prefer to term *chronoprevention* to highlight the critical importance of biological time to clinical practice and prevention research.

This article first discusses the particular features of the SBP and DBP circadian rhythms, assessable only by around-the-clock ambulatory BP monitoring (ABPM), which is of the greatest importance in making the differential diagnosis of hypertension versus normotension. In this regard, this article presents evidence for the ABPM-derived asleep SBP mean as the most sensitive and independent prognostic indicator of patient CVD risk. In addition, this article reviews the findings of pertinent outcomes trials that show the attenuation of the asleep BP, most effectively achieved by bedtime scheduling of conventional hypertension medications, best *chronoreduces* and *chronoprevents* adverse CVD and other outcomes.<sup>18–22</sup>

### **AROUND-THE-CLOCK AMBULATORY BLOOD PRESSURE MONITORING VERSUS OFFICE BLOOD PRESSURE MONITORING IN THE DIAGNOSIS OF HYPERTENSION**

The diagnosis of hypertension and clinical decisions regarding its treatment are typically based on a limited number of specific time-of-day OBPM that may or may not be supplemented by occasional at-home and at-work wake-time patient self-assessments, thought to be representative of the SBP and DBP both during the day and night,<sup>23</sup> but in reality are not.<sup>24,25</sup> Thus, such casual OBPM, even when complemented by home BP measurements (HBPM), disregard the mostly predictable 24-hour patterning of SBP and DBP, which in diurnally active normotensive and uncomplicated hypertensive persons is characterized by (1) striking morning BP increase, (2) two daytime peaks (the first ~2–3 hours after awakening and the second early evening), (3) small midafternoon nadir, and (4) 10% to 20% decline during sleep

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