Abnormalities in chronic kidney disease of ambulatory blood pressure 24 h patterning and normalization by bedtime hypertension chronotherapy

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ABSTRACT

In chronic kidney disease (CKD), the prevalence of hypertension is very high, escalating with diminishing renal function. Typically, the diagnosis of hypertension and the clinical decisions regarding its treatment are based on daytime clinic blood pressure (BP) measurements. However, the correlation between BP level and target organ damage, cardiovascular risk and long-term prognosis is greater for ambulatory than clinic measurements. Moreover, evidence is consistent among numerous studies that the elevated risk and incidence of end-organ injury and fatal and non-fatal cardiovascular events are significantly associated with blunted night-time BP decline, and that the asleep BP better predicts cardiovascular events than either the awake or 24-h BP mean. The prevalence of abnormally high asleep BP is extensive in CKD, significantly increasing with its severity. In CKD, the diagnoses of hypertension and its therapeutic control are often inaccurate in the absence of complete and careful assessment of the entire 24 h, i.e. daytime and night-time, BP pattern. Accordingly, ambulatory BP monitoring should be the preferred method to comprehensively assess and decide the optimal clinical management of patients with CKD. Recent findings indicate therapeutic restoration of normal physiologic BP reduction during night-time sleep is the most significant independent predictor of decreased cardiovascular and cerebrovascular risk, both in patients with and without CKD, and is best achieved when antihypertensive medications, mainly those blocking the renin–angiotensin–aldosterone system, are routinely taken at bedtime.

Keywords: ambulatory blood pressure monitoring, asleep blood pressure, cardiovascular risk, chronic kidney disease, chronotherapy

INTRODUCTION

Elevated blood pressure (BP) causes injury to blood vessels of the kidney and other organs through excessive mechanical and oxidative stresses [1]. In chronic kidney disease (CKD), the prevalence of hypertension is very high, increasing with diminishing glomerular filtration rate (GFR) to an estimated 86% in patients with end-stage renal disease [2]. The diagnosis of hypertension and clinical decisions regarding its treatment are typically based on a limited number of daytime clinic BP measurements obtained in the physician’s office. However, correlation between the BP level and target organ damage, cardiovascular disease (CVD) risk and long-term prognosis is greater for ambulatory BP monitoring (ABPM) than clinic BP [3, 4], including patients with CKD [5–7]. An additional advantage of around-the-clock ABPM is proper description and quantification of the predictable 24-h BP variation that results from rest-activity cycle-related alterations in behaviour (e.g. activity routine and level, meal content and timings, mental stress and posture), environmental phenomena (e.g. temperature, noise, etc.) and innate circadian (∼24 h) rhythms in neuroendocrine, endothelial and haemodynamic parameters [e.g. plasma noradrenaline and adrenaline (autonomic nervous system, ANS) and renin, angiotensin and aldosterone (renin–angiotensin–aldosterone system, RAAS)] [8, 9].
Abstract

Specific features of the 24-h BP pattern of hypertensive patients have been assessed as mediators of target tissue injury and triggers of and risk factors for CVD events—angina pectoris, myocardial infarction, cardiac arrest, sudden cardiac death, pulmonary embolism—and cerebrovascular events—ischaemic and haemorrhagic stroke [10]. Consistent findings of numerous ABPM studies show the elevated risk of end-organ injury and the incidence of fatal and non-fatal CVD events are significantly associated with blunted sleep-time relative BP decline (i.e. per cent decrease in the mean BP during night-time sleep relative to the mean BP during daytime activity), both in patients without [4, 11, 12] and with CKD [5–7, 13, 14], and that the asleep BP mean is a better predictor of CVD events than either the awake or 24-h BP mean [4, 11, 12, 15–17], including patients with CKD [6, 7, 14, 18].

All previous reported studies addressing the merit of ABPM for predicting CVD risk, except the Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares (MAPEC Study, i.e. Ambulatory Blood Pressure Monitoring for Prediction of Cardiovascular Events) discussed later [4, 14, 19–22], we believe are of limited value because they relied upon only a single baseline 24-h profile per participant at the time of inclusion. Thus, the design and findings of past studies can be misrepresentative because they fail to account for potential changes in the features of the baseline-determined 24-h BP pattern during long-term follow-up due to BP-lowering therapy, aging and development or progression of medical ailments and hypertension-associated target organ damage. Additionally, they are deficient due to inadequate patient assessment, i.e. either occasional daytime cuff BP measurements or only one poorly reproducible 24-h ABPM [5–7, 13], and because they entail only the traditional morning-time treatment strategy. This review presents emerging new perspectives and findings pertaining to abnormalities of the 24-h BP pattern in hypertensive CKD patients and their cost-effective normalization by bedtime chronotherapy (timing of BP-lowering medications in accordance with circadian rhythm determinants) to significantly enhance BP control and decrease CVD risk [4, 14, 19–22].

Ambulatory BP Pattern in Patients With and Without CKD

Blunted sleep-time BP decline (non-dipping, i.e. sleep-time relative BP decline <10%) is common in CKD [23–27], although its reported prevalence in the medical literature is highly inconsistent, perhaps due to disparities in studied cohorts (treated versus untreated subjects, patients of varying CKD severity, diverse criteria of CKD assessment), relatively small sample sizes, improper definition by arbitrary fixed clock times of daytime activity and night-time sleep periods and reliance, typically, upon only a single, low-reproducible, 24-h ABPM evaluation per subject at study inclusion, rather than more reliable and more reproducible longer-duration 48-h ABPM [28]. Too many investigations evaluated only the 24-h BP pattern of patients with CKD in the absence of comparison with those without CKD. For example, the reported prevalence of non-dipping in one retrospective 322-patient cohort study by Davidson et al. [25] was 57.5%, but without specification of its exact prevalence in CKD. Moreover, in the absence of information on albuminuria, patient classification was based solely on estimated GFR. The cross-sectional 24-h ABPM study of 617 patients of the African American Study of Kidney Disease Cohort Study (AASK) by Pogue et al. [26], which also only defined CKD on the basis of reduced GFR, reported a very high 80.7% prevalence of non-dipping that significantly contributed to the misdiagnosis of hypertension; indeed, among patients with controlled clinic BP, 70% evidenced masked hypertension, i.e. awake and/or asleep systolic BP (SBP)/diastolic BP (DBP) mean values greater than the recommended reference thresholds [29]. Finally, a study of 232 elderly patients with CKD [24] reported the prevalence of non-dipping increased from 60.0% in Stage-2 CKD to 80.3, 71.9 and 71.4% in Stage-3, 4 and 5 CKD, respectively (P = 0.046).

The ongoing multicentre Hygia Project [27, 30, 31], which includes patients of primary care centres of Galicia (north-west Spain), prospectively evaluates the prognostic value of ABPM and hypertension treatment time on CVD risk. ABPM assessment of the thus far recruited 10 271 hypertensive participants is done for 48 h, rather than 24 h, upon recruitment and at least annually thereafter to increase the reproducibility of findings [28]. At baseline, 3227 of these patients had CKD, defined as GFR <60 mL/min/1.73 m², albuminuria (albumin/creatinine ratio ≥30 mg/gCr) or both, at least twice with a 3-month span [32]. Diagnosis of hypertension was based on accepted ABPM criteria [29]: awake SBP/DBP means ≥135/85 mmHg and/or asleep SBP/DBP means ≥120/70 mmHg or prescribed BP-lowering treatment.

Figure 1 presents the average 24-h pattern of SBP (left) and DBP (right) for hypertensive patients with and without CKD assessed by 48-h ABPM. In CKD, ambulatory SBP was significantly elevated (P < 0.001) mainly during night-time sleep; ambulatory DBP, however, was significantly lower (P < 0.001), mainly during daytime activity. Between-group differences in SBP and DBP resulted in significantly greater (P < 0.001) ambulatory pulse pressure over the 24 h in the CKD group, even after correcting for age. The prevalence of the non-dipper BP profile was significantly greater in patients with (60.6%) than without CKD (43.2%; P < 0.001 between groups), and the sleep-time relative SBP/DBP decline progressively and significantly (P < 0.001) decreased towards the more abnormal non-dipper pattern with diminishing GFR. The prevalence of the riser BP pattern (sleep-time relative SBP decline <0) constituted the greatest difference between patients with and without CKD, respectively, 17.6 versus 7.1% (P < 0.001). The proportion of patients with CKD showing the non-dipper BP pattern significantly increased across the progressive stages of disease severity (Figure 2), and the proportion of patients with the highest CVD risk riser BP pattern significantly and progressively increased from 8.1% for Stage-1 CKD to a very high 34.9% for Stage-5 CKD (Figure 2). In actuality, elevated asleep SBP mean was the major basis for the diagnoses of hypertension and inadequacy of therapeutic BP control in CKD; indeed, among the uncontrolled hypertensive patients with CKD, 90.7% exhibited nocturnal hypertension [27].
Numerous prospective trials, comprising at least six different classes of hypertension medications—angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-II receptor blockers (ARBs), calcium-channel blockers (CCB), α-blockers, β-blockers and diuretics—evidence best safety, efficacy, duration of action and effects on the 24-h BP pattern when ingested at bedtime [33–35].

A substantial number of studies (for extensive reviews see refs [34, 35]) demonstrate ingestion-time differences in effects of the ACEIs benazepril, captopril, enalapril, imidapril,
In patients taking hypertension medications at bedtime rather than upon awakening, the prevalence of the non-dipper BP pattern was much lower in participants who took some (15.7%) or all (10.6%) hypertension medications at bedtime rather than upon awakening (21.5%; P < 0.001 between groups). Additionally, the prevalence of the riser BP pattern was significantly higher in participants taking all of them upon awakening, evidenced significantly lower asleep SBP/DBP means and higher sleep-time relative BP decline (P < 0.001), thereby significantly reducing the prevalence of non-dipping from 68.3% in patients ingesting all hypertension medications upon awakening to 54.2 and 47.9% in ones ingesting, respectively, ≥1 or all of them at bedtime (P < 0.001 between groups). Furthermore, those who took all medications at bedtime showed significantly higher prevalence of controlled ambulatory BP (P < 0.001) that was achieved by a significantly smaller number of BP-lowering medications (P < 0.001) [31].

The impact of hypertension treatment-time regimen on 24-h BP patterning and BP control in CKD was recently investigated by Crespo et al. [31]; among the 2659 hypertensive participants with CKD enrolled in the Hygia Project, 1446 ingested all BP-lowering medications upon awakening and 1213 ingested the entire daily dose of ≥1 of them at bedtime. Among the latter, 359 patients ingested all such medications at bedtime, while 854 ingested the complete daily dose of some of them upon awakening and the others at bedtime. Patients taking ≥1 medications at bedtime, relative to those taking all of them upon awakening, evidenced significantly greater reduction of the asleep SBP/DBP means and significantly higher sleep-time relative SBP/DBP decline towards normal.

Clinical trials also validate ingestion-time-dependent effects of the ARBs irbesartan, olmesartan, telmisartan and valsartan [34, 35]. Independent of the considerable differences in their plasma half-life [38, 39], reduction of the awake SBP/DBP means by the awakening and bedtime therapeutic regimen was similar; however, reduction of the asleep SBP/DBP means was significantly greater with the bedtime regimen. Thus, the sleep-time relative SBP/DBP decline was slightly attenuated when the ARBs were scheduled upon awakening, while it was significantly enhanced when taken at bedtime, thereby significantly reducing the prevalence from baseline of non-dipping. Interestingly, two different studies, one involving the bedtime ingestion of valsartan [40] and the other candesartan [41], documented significant decline in urinary albumin excretion, which in the case of valsartan correlated with both decreased asleep BP mean and increased sleep-time relative BP decline. The circadian rhythm of the RAAS, with peak activity toward the end of the night-time sleep span, may explain the better BP regulation conveyed by the bedtime regimen of ACEIs and ARBs [35].

Morning versus evening treatment-time trials of the CCBs amlodipine, cilnidipine, diltiazem, isradipine, nifedipine, nilosidipine and nitrrendipine reveal dihydropyridine derivatives, in general reduce BP homogeneously throughout the 24 h, independent of timing [34]. Nevertheless, of great clinical relevance are findings of a trial conducted on 238 previously untreated hypertensive patients randomized either to bedtime or upon awakening nifedipine GITS monotherapy (30 mg once daily for 8 weeks); bedtime, relative to upon awakening, therapy resulted in significantly reduced incidence of peripheral oedema (1 versus 13%; P < 0.001) [42].

Other hypertension medications, including α-blocker doxazosin, β-blockers carvedilol and nebivolol and loop-diuretic torasemide, also show significantly enhanced asleep BP reduction and longer duration of BP-lowering effect with bedtime versus morning (upon awakening) therapy [34]. Combination medications—valsartan–amlodipine, amlodipine–olmesartan, valsartan–hydrochlorothiazide and amlodipine–hydrochlorothiazide—also evidence treatment-time differences in efficacy. Bedtime, in comparison with upon awakening, ingestion of every one of these combination therapies markedly reduces the asleep SBP/DBP means and significantly increases the proportion of patients converted from non-dipper to dipper patterning [34].

**CHRONOTHERAPY IN HYPERTENSIVE PATIENTS WITH CKD**

The impact of hypertension treatment-time regimen on 24-h BP patterning and BP control in CKD was recently investigated by Crespo et al. [31]; among the 2659 hypertensive participants with CKD enrolled in the Hygia Project, 1446 ingested all BP-lowering medications upon awakening and 1213 ingested the entire daily dose of ≥1 of them at bedtime. Among the latter, 359 patients ingested all such medications at bedtime, while 854 ingested the complete daily dose of some of them upon awakening and the others at bedtime. Patients taking ≥1 medications at bedtime, relative to those taking all of them upon awakening, evidenced significantly lower asleep SBP/DBP means and higher sleep-time relative BP decline (P < 0.001), thereby significantly reducing the prevalence of non-dipping from 68.3% in patients ingesting all hypertension medications upon awakening to 54.2 and 47.9% in ones ingesting, respectively, ≥1 or all of them at bedtime (P < 0.001 between groups). Additionally, the prevalence of the riser BP pattern was much lower in participants who took some (15.7%) or all (10.6%) hypertension medications at bedtime rather than upon awakening (21.5%; P < 0.001 between groups). Furthermore, those who took all medications at bedtime showed significantly higher prevalence of controlled ambulatory BP (P < 0.001) that was achieved by a significantly smaller number of BP-lowering medications (P < 0.001) [31].

The prevalence of the different BP 24-h patterns also varied by stage of CKD severity and treatment-time regimen [31]. In particular, Stage 3–5 patients who ingested all hypertension medications upon awakening (Figure 3, top panel) had greater prevalence of non-dipper and riser patterns, with 23–26% of patients evidencing the very high CVD risk riser pattern. The prevalence of non-dipping and riser BP patterns in patients taking hypertension medications at bedtime (Figure 3, bottom panel) was significantly lower than in those taking all medications upon awakening (Figure 3, top panel), with the prevalence of the riser pattern among patients of the bedtime regimen always <14%, independent of the CKD stage.

Another study [43] involving 32 uncontrolled non-dipper Italian patients with CKD reported similar significant reduction of the asleep BP mean, plus decreased urinary albumin excretion, after shifting one BP-lowering medication from morning to evening. The findings of Rahman et al. [44] entailing 151 black participants enrolled in the AASK study with controlled clinic and awake BP were somewhat different. They compared the effect on nocturnal SBP—defined according to an assumed identical fixed clock-hour span among all participants—of the
shift to bedtime of an already prescribed once-a-day hypertension medication or addition of a new low-dose medication. Both strategies reduced nocturnal SBP, but not significantly ($P = 0.08$), leading the authors to conclude bedtime chronotherapy might be of limited advantage in reducing nighttime BP in hypertensive African-American patients and/or CKD. One recent Nigerian study, however, involving 165 black hypertensives randomized to morning (10:00 h) versus evening (22:00 h) hypertension treatment for 12 weeks revealed significantly greater reductions in clinic DBP and left ventricular mass ($P < 0.001$) among those treated at night [45]. Finally, a recent study by Wang et al. [46] evaluated the advantages of awakening versus bedtime scheduling of valsartan (80–320 mg once daily for 1 year) on 60 non-dipper Chinese patients with CKD; treatment at bedtime was significantly more effective in reducing night-time BP, albuminuria and left ventricular mass ($P$ always $< 0.05$).

**FIGURE 3:** Prevalence of dipping classifications in terms of the sleep-time relative SBP decline—≥20% (extreme-dipper), 10–20% (dipper), 0–10% (non-dipper), <0% (riser)—of hypertensive patients with CKD in relation to stage (disease severity)—Stage 1: GFR ≥90 mL/min/1.73 m²; Stage 2: GFR 60–89 mL/min/1.73 m²; Stage 3A: GFR 45–59 mL/min/1.73 m²; Stage 3B: GFR 30–44 mL/min/1.73 m²; Stage 4: GFR 15–29 mL/min/1.73 m²; Stage 5: GFR <15 mL/min/1.73 m². Top row: patients ingesting all BP-lowering medications upon awakening. Bottom row: patients ingesting all BP-lowering medications at bedtime.

**INFLUENCE OF CHRONOTHERAPY ON CVD RISK**

The association between prognostic ABPM parameters, CVD risk and time-specified hypertension treatment strategy has thus far been investigated only in the MAPEC Study, specifically designed to test the hypothesis that bedtime hypertension chronotherapy exerts better 24-h BP control and CVD prevention than conventional morning-time therapy. Complete details of its rationale and design are described elsewhere [19]. Briefly, 3344 subjects (793 with CKD), with baseline BP ranging from normotension to sustained hypertension according to ABPM criteria [29], were prospective studied for a median follow-up of 5.6 years. Hypertensive participants at baseline were randomized to ingest all their prescribed hypertension medications upon
awakening or the entire daily dose of ≥ 1 of them at bedtime. At baseline and thereafter annually (more frequently if hypertension treatment was adjusted), ambulatory BP and physical activity (wrist actigraphy) were simultaneously measured for 48 h to accurately derive the awake and asleep BP means.

The ABPM-derived asleep SBP mean was the most significant predictor of CVD outcome [4, 12]. Interestingly, large morning BP surge was associated with significantly lower, not higher, CVD risk, consistent with the highly significant relationship between increased sleep-time relative BP decline and reduced CVD risk. Exploration of the potential combined contribution of multiple BP parameters to prediction of CVD events, revealed the best joint adjusted model included only the asleep SBP mean [hazard ratio (HR) = 1.23, 95% confidence interval (1.16–1.32); P < 0.001] and sleep-time relative SBP decline [HR = 0.98 (0.97–0.99); P = 0.019]. Moreover, when the patient asleep SBP mean was adjusted for the awake SBP mean, only the former significantly predicted CVD outcomes [4, 12]. Joint entry in the same time-dependent Cox regression model of changes in patient asleep and awake BP means during the 5.6 years of follow-up showed that attenuation only of the asleep SBP mean was significantly associated with reduced CVD risk [adjusted HR per 5 mmHg reduction in the asleep SBP mean: 0.85 (0.79–0.91); P < 0.001; adjusted HR per 5 mmHg reduction in the awake SBP: 1.00 (0.94–1.05); P = 0.849] [4, 12].

Hypertension treatment-time regimen thus significantly impacts CVD risk. Patients taking the entire daily dose of ≥1 hypertension medications at bedtime displayed significantly lower asleep BP mean, higher sleep-time relative BP decline, reduced prevalence of non-dipping (34 versus 62%; P < 0.001) and higher prevalence of controlled ambulatory BP (62 versus 53%; P < 0.001). Most importantly, routine ingestion of the full daily dose of ≥1 BP-lowering medications at bedtime, compared with routine ingestion of all medications upon awakening, resulted in a significantly lower adjusted HR of total CVD events [HR = 0.39 (0.29–0.51); P < 0.001] and major CVD events—composite of CVD death, myocardial infarction and ischaemic and haemorrhagic stroke [HR = 0.33 (0.19–0.55); P < 0.001] [19]. Greater benefits were observed for bedtime compared with awakening treatment with ARBs [HR = 0.29 (0.17–0.51); P < 0.001] and CCBs [HR = 0.46 (0.31–0.69); P < 0.001]. CVD risk was higher in patients randomized to take all their medications upon awakening, without difference between the six different classes of BP-lowering therapy tested. Patients randomized to ingest at bedtime an ARB, in comparison with any other class of medication, with or without additional hypertension medication, however, evidenced significantly lower HR of CVD events (P < 0.017) [22]. The MAPEC Study results not only substantiate that the asleep SBP mean is the most significant prognostic marker of CVD morbidity and mortality, as previously suggested [6, 7, 11, 15–18], but they also document for the first time that reduction of the asleep SBP mean by properly timed hypertension therapy significantly reduces CVD risk not only in the general population, but also in high-risk groups of patients with CKD [14], type 2 diabetes [20, 21] and resistant hypertension [47].

CONCLUSIONS

Our review of recent publications indicates BP-lowering properties of the different classes of hypertension medications are significantly improved when ingested at bedtime than upon morning awakening. The exact mechanisms underlying these observed ingestion-time differences, although not yet completely elaborated, seem to involve circadian rhythms that affect drug pharmacokinetics and pharmacodynamics [33, 34, 35, 48] relative to the staging of various other circadian rhythms, e.g. in natriuresis, nitric oxide, ANS, RAAS, etc., and day–night cycles in behaviour, ambient environment, e.g. mental and physical activity and stress, posture, meal times, air temperature, noise, etc., that affect the 24-h variation in blood vessel patency [8–10].

International practice guidelines recommend prescription of long-acting, once-daily hypertension medications having 24-h efficacy [29] based on the assumptions they improve adherence to therapy, minimize BP variability and provide smooth and consistent BP control. However, the typical morning-time habit of ingesting one or more hypertension medications with high 24-h homogeneous and sustained efficacy is unlikely to change the 24-h BP profile. Given the high prevalence of the non-dipper BP pattern in the general population [8, 30], and, particularly, in CKD [23–27, 31], the routine recommendation that once-a-day therapies be taken in the morning is inappropriate, since two newly substantiated important clinical goals of hypertension pharmacotherapy—normalization of the 24-h BP pattern and control of asleep BP—are unlikely to be achieved [33–35, 49, 50]. Findings of recently conducted long-term outcome studies indicate asleep BP normalization can be best achieved when hypertension medications are routinely ingested at bedtime rather than in the morning. The prevalence of both non-dipper and riser BP patterns increases significantly with CKD severity (Figure 2); indeed, the riser BP pattern, associated with highest CVD risk relative to all the other possible 24-h BP patterns, is reported to be 2.5-fold more prevalent in CKD [27]. Thus, among patients with CKD, an elevated asleep BP mean should be the major criterion for the diagnoses of hypertension and inadequate therapeutic BP control, provided ABPM is routinely performed for sufficient duration (48 h) and data are properly analysed according to the actual patient’s sleep and wake spans [49]. Patients with CKD who ingest hypertension medications at bedtime, versus those who ingest all of them upon awakening, show significantly reduced asleep SBP/DBP means and attenuated prevalence of non-dipping (Figure 3), i.e. lower prevalence of these sensitive markers of CVD risk [31]. Collectively, the clinical implications of new findings reviewed herein are that ABPM must be recommended for patients with CKD to accurately diagnose hypertension, assess CVD risk and establish and validate the optimal therapeutic strategy to normalize the 24-h BP profile and decrease nighttime BP that has been shown to reduce CVD morbidity and mortality [14].

Consistent with the current available information, already acknowledged by the recent recommendation by the American Diabetes Association, i.e. that all hypertensive patients with
diabetes ingest one or more BP-lowering medications at bedtime [51], bedtime hypertension treatment should also be recommended for hypertensive patients with CKD [49]. Nonetheless, to confirm the beneficial effects (reduced risk of CVD events and target tissue and organ injury) and safety of enhanced night-time BP reduction by bedtime hypertension chronotherapy, we recognize the necessity to conduct future prospective intervention trials that incorporate 48-h ABPM assessments and simultaneous diary recording of bed and wake times—to accurately and reliably ascertain asleep BP level and dipping status—at least annually during long-term follow-up evaluation, as done in the recently completed MAPEC Study and ongoing Hygia Project [27, 30, 31]. Such future investigations are warranted to confirm and supplement the published findings reviewed here and to address certain alleged problems and limitations of past investigations [4, 14, 19–21, 47]. In particular, the dipping/non-dipping BP pattern has been reported to have limited reproducibility when based solely on a single 24-h ABPM [28], which could make treatment-induced changes difficult to accurately quantify unless, preferably 48-h, ABPM is done periodically during a sufficiently long follow-up, as in the MAPEC Study [4, 14, 19–22, 47] and Hygia Project [27, 30, 31]. Additionally, future ABPM assessment studies are necessary to ensure safety of bedtime therapeutic strategies, i.e. that reduction of asleep BP does not compromise vital organ perfusion. Although further research is certainly warranted, prospective evidence of the MAPEC Study seems to answer many, if not all, of previously raised criticisms and concerns.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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